

Critical Evaluation of Pharmacy: Truth, Control and Application

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Abstract

Pharmacy is one of the most important subdisciplines of the vast fields of health sciences. It is usually conceived as both a science and profession for developing, producing, formulating and dispensing safe and effective drugs. The dissertation analyses pharmacy from the perspectives of philosophy and social sciences. The epistemic foundation of pharmacy as a science specializing in making products dedicated to the better-being of society is critically evaluated. Knowledge in pharmacy is paradigm dependent, pragmatic and communal. It is never absolute, and therefore pharmaceutical products undergo strict regulations and risk control strategies to mitigate disasters and minimize direct and broader side-effects. The main objective of control in pharmacy is to counterbalance the inherent uncertainty in decision-making intended to deliver safe and effective products. Yet recent global events brought attention to the social acceptability of such approved products; acceptance of pharmaceutical products has recently been challenged and the reasons are beyond safety and effectiveness. Social factors as well as cultural, psychological and environmental differences ought to be accommodated so as not to reduce patients into their ailments rather treat them as active participants in the therapeutic journey. This study aims to stimulate a broad, interdisciplinary debate on the implications of pharmacy and bridge any existing gap between pharmacy and social sciences.

Zusammenfassung

Die Pharmazie ist eine der wichtigsten Teildisziplinen im weiten Feld der Gesundheitswissenschaften. Die Dissertation analysiert die Pharmazie aus den Perspektiven der Philosophie und der Sozialwissenschaften. Das epistemische Fundament der Pharmazie als Wissenschaft, die sich auf die Herstellung von Produkten zur Verbesserung des gesellschaftlichen Wohlergehens spezialisiert, wird kritisch bewertet. Wissen in der Pharmazie ist paradigmatisch, pragmatisch und gemeinschaftlich geprägt. Es ist niemals absolut, daher unterliegen pharmazeutische Produkte strengen Vorschriften und Risikokontrollstrategien, um Katastrophen zu verhindern und Nebenwirkungen zu minimieren. Das Hauptziel der Kontrolle in der Pharmazie ist es, die inhärente Unsicherheit bei Entscheidungen, die sichere und wirksame Produkte liefern sollen, auszugleichen. Jüngste globale Ereignisse haben jedoch die soziale Akzeptanz solcher zugelassener Produkte in den Fokus gerückt; die Akzeptanz pharmazeutischer Produkte wird zunehmend infrage gestellt, wobei die Gründe über Sicherheit und Wirksamkeit hinausgehen. Soziale Faktoren sowie kulturelle, psychologische und umweltbedingte Unterschiede müssen berücksichtigt werden, um Patienten nicht auf ihre Krankheiten zu reduzieren, sondern sie als aktive Teilnehmer im therapeutischen Prozess zu behandeln. Diese Studie zielt darauf ab, eine breite, interdisziplinäre Debatte über die Implikationen der Pharmazie anzuregen und mögliche Lücken zwischen Pharmazie und Sozialwissenschaften zu überbrücken.

Résumé

La pharmacie est l'une des sous-disciplines les plus importantes des vastes domaines des sciences de la santé. Cette thèse analyse la pharmacie sous les perspectives de la philosophie et des sciences sociales. Les bases épistémiques de la pharmacie en tant que science spécialisée dans la création de produits pour le bien-être de la société sont évaluées de manière critique. Les connaissances en pharmacie sont dépendantes des paradigmes, pragmatiques et communautaires. Elles ne sont jamais absolues, c'est pourquoi les produits pharmaceutiques sont soumis à des réglementations strictes et à des stratégies de contrôle des risques pour éviter les catastrophes et minimiser les effets secondaires directs et plus larges. L'objectif principal du contrôle en pharmacie est de contrebalancer l'incertitude inhérente à la prise de décisions visant à fournir des produits sûrs et efficaces. Cependant, des événements mondiaux récents ont attiré l'attention sur l'acceptabilité sociale de ces produits approuvés; l'acceptation des produits pharmaceutiques a récemment été remise en question pour des raisons dépassant la sécurité et l'efficacité. Les facteurs sociaux ainsi que les différences culturelles, psychologiques et environnementales doivent être pris en compte pour ne pas réduire les patients à leurs maladies, mais les traiter en tant que participants actifs au parcours thérapeutique. Cette étude vise à stimuler un débat large et interdisciplinaire sur les implications de la pharmacie et à combler les éventuelles lacunes entre la pharmacie et les sciences sociales.

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List of Abbreviations

ABC:	Abacavir
ACS:	American Chemical Society
AD:	Anno Domini
ADH:	Alcohol dehydrogenase
ADR:	Adverse drug reaction
AI:	Artificial intelligence
Allo:	Allopurinol
AMX:	Amoxicillin
APC:	Antigen presenting cell
API:	Active pharmaceutical ingredient
ARE:	Antioxidant response element
BC:	Before Christ
BP:	Blood pressure
BP:	British Pharmacopoeia
cGMP:	Current good manufacturing practices
CO:	Cardiac output
CZB:	Carbamazepine
DiHS:	Drug-induced hypersensitivity syndrome
DJ Distinction:	Discovery and justification distinction
DNA:	Deoxyribonucleic acid
DOI:	Digital object identifier
DRESS:	Drug reaction with eosinophilia and systemic symptoms
DTP:	Drug take back program
EMA:	European Medicines Agency
EP:	European pharmacopoeia
EU:	European Union
FDA:	Food and Drug Administration
Flux:	Flucloxacillin
FP:	Filling pressure (kidney)
GAPDH:	Glyceraldehyde 3-phosphate dehydrogenase
GHS:	Ghana health services
HBM:	Health belief model
HHS:	Hypersensitivity syndrome
HLA:	Human leukocyte antigen
HR:	Heart rate
HAS:	Human serum albumin
IBE:	Inference to the best explanation
ICH:	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IUPAC:	International Union of Pure and Applied Chemistry
JP:	Japanese pharmacopoeia
LTP:	Long-term potentiation
MIT:	Monoiodothyrosine
MoA:	Mechanism of action or mode of action
MPT:	Manuscript processing time
MRE:	Metal response element

MT:	Metallothionein
MTF-1:	Metal response transcription factor 1
NDEA:	<i>N</i> -Nitrosodiethylamine
NDMA:	<i>N</i> -Nitrosodimethylamine
NMDA:	<i>N</i> -methyl-D-aspartate
NMR:	Nuclear magnetic resonance
OS:	Oxidative stress
OTC:	Over the counter medication
OUP:	Oxford University press
P4R:	Post publication public peer review
PVR:	Peripheral vascular resistance
QbD:	Quality by design
RAA System:	Renin-angiotensin-aldosterone system
RCT:	Randomized controlled trial
RNA:	Ribonucleic acid
RWE:	Real world evidence
Rx:	Prescription medication
SCAR:	Severe cutaneous adverse reaction
SC:	Stages of Change
SDT:	Self-determination theory
SEM:	Socio-ecological model
SLEP	Shelf-life extension program
SNS:	Sympathetic nervous system
SOC:	Sence of coherence
SP Model:	Self-publishing model
SV:	Stroke volume
T3:	Triiodothyronine
T4:	Levothyroxine
TBG:	Thyroxine binding globulin
TLC:	Thin layer chromatography
TM:	Transtheoretical Model
TPB:	Theory of Planned Behavior
USP:	United States pharmacopeia
USSR:	Soviet Union
WHO:	World Health Organization

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“When I consider the short duration of my life, swallowed up in the eternity before and after, the little space which I fill, and even can see, engulfed in the infinite immensity of spaces of which I am ignorant, and which know me not, I am frightened, and am astonished at being here rather than there; for there is no reason why here rather than there, why now rather than then. Who has put me here? By whose order and direction have this place and time been allotted to me? Memoria hospitis unius diei prætereuntis.”

Blaise Pascal (1623-1662), *Pensées*

Chapter One

1. Introduction: Why Do We Need a Philosophy of Pharmacy?

Answering such a question in an intelligible manner, demands exploring how, and if, one can distinguish pharmacy from the vast and different sciences which constitutes it and why cannot pharmacy simply be philosophically scrutinized from already established perspectives. Let's inaugurate this discussion with an appetizing example. Imagine being served a slice from a delicious, homemade strawberry cake¹. Your taste buds tingle, and curiosity leads you to ask for the recipe. Upon being done with shopping, you get to the kitchen and lay out the flour, sugar, eggs, oil, cream, and strawberries on your counter. You quickly realize, however, that this is not the cake which delighted you. The creamy *gateau* was simply more than just a collection of these ingredients. The heat from the oven, the vigorous blending, and the knowledge, care and passion invested into making it, together with the quality and quantity of the ingredients gave that cake its mouth-watering look, firm texture and enjoyable flavour. The cake manifests emergent properties which its individual ingredients are indeed lacking.

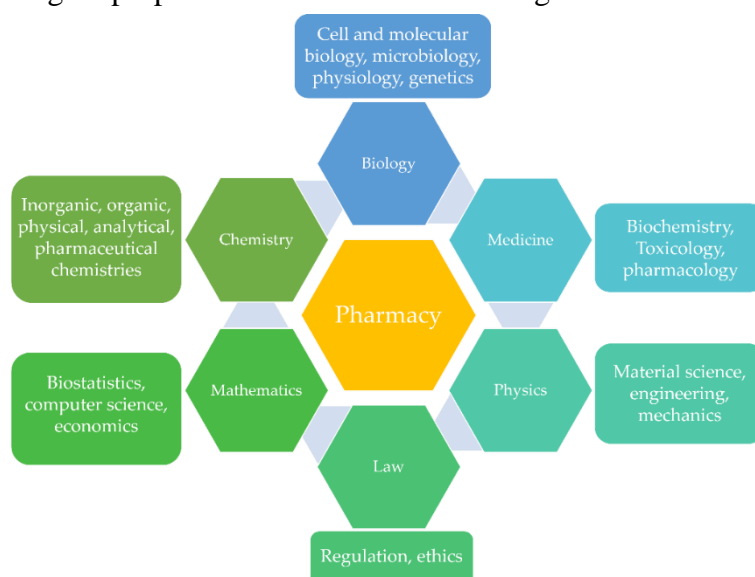


Figure 1. Examples of the different scientific fields which form pharmacy.

Similarly, pharmacy is an applied science consisting of a mix of different scientific disciplines such as chemistry, biology, biochemistry, toxicology, physiology and many other sciences, Figure 1. When such parts combine to form pharmacy, however, they produce a discipline which is much more than just the sum of these parts. The pharmacological effect of a drug is rooted in biology, chemistry and their specialized sub-disciplines, but the journey of such a drug from bench to bedside, its regulation and role in public health, economy, politics

¹ The cake may be vegetarian, vegan, halal, kosher, without strawberries or not even a cake at all. The readers are encouraged to further stimulate their imagination by substituting the strawberry cake with what is to their liking.

and the environment introduces emergent properties which neither constituting scientific discipline can fully encapsulate. Against this backdrop, philosophical issues arising within the realm of pharmacy cannot also be fully captured from accounts pertaining to its constituting scientific fields. Discussions within the philosophy of chemistry, philosophy of biology, even the philosophy of medicine and bioethics may indeed inform and guide the discourse within a philosophy of pharmacy. Yet, this is almost akin to discussing the importance of flour or eggs to the cake without considering the role of the baker, the oven, or the occasion for which it is baked. Therefore, to fully account for the “pharmaceutical phenomena” and their implications, a specialized philosophy is a must, *i.e.* philosophy of pharmacy.

Unfortunately, this phenomenological aspect of pharmacy is rather undermined and overshadowed in the literature. Apart from a few valuable contributions, the current discourse in pharmacy seems too specialized and focused within subdisciplines [1,2]. Despite the great progress and success, pharmacy has been disconnecting from its broader implications in economy, politics, society, and environment. While there is ample discourse on the ethical and moral dimensions of medical practices in the philosophy of medicine and bioethics, profound interrogations into epistemological, metaphysical, or ethical substrates unique to pharmacy and pharmaceutical phenomena appear scant. This gap demands an interdisciplinary and philosophical approaches so to characterize the depth and breadth of pharmacy. It is, therefore, crucial to re-anchor pharmacy by revisiting its theoretical foundations and philosophical heritage so to develop and secure a holistic, interdisciplinary approach equipped to address the complex challenges of today.

Constructing a coherent philosophy of pharmacy, however, is beyond an easy task. Any attempt will probably be heavily challenged by both philosophers as well as scientists². As a cornerstone for initiating this project, however, one must begin by identifying what makes pharmacy, whether as a science or a profession, so unique. Essentially, pharmacy is about substances, drugs, medications, remedies or pharmaceutical products. Such substances are the *stuff*³ of pharmacy. Pharmacy is the art, science and profession of medications. Generally, it involves the research and development of substances into regulated, safe and effective pharmaceutical products intended to respond to societal needs. Subsequently, one ought to

² Stimulating such discussions represents one of the main objectives of this dissertation.

³ “Stuff” represent an ontological category of entities which cannot be subsumed under the category of *individual* such as individual particles in physics interacting with each other [3].

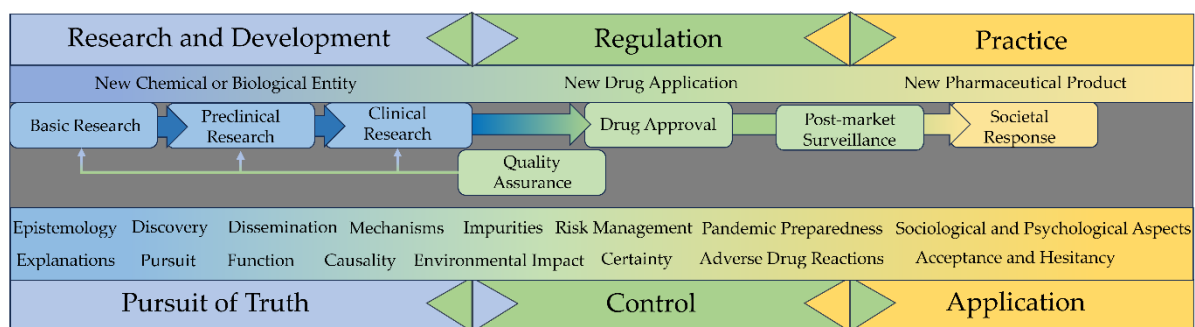


Figure 2. The lifecycle of a pharmaceutical product from bench to bedside. The journey begins with the discovery of new chemical or biological entities through basic research which often involves initial synthesis and *in-vitro* testing. Promising candidates progress to translational research, encompassing both preclinical and clinical studies so to establish safety and effectiveness. Subsequently, a new drug application is submitted to regulatory authorities for evaluation and potential licensing. Notably, such regulatory mechanisms are not only limited to assessing new submissions; they also dictate standards for manufacturing and quality assurance so to maintain consistency, safety, and effectiveness of pharmaceutical products. Upon approval, the drug enters the market, yet it is continually monitored for adverse reactions. Simultaneously, societal response plays a role, determining acceptance levels or hesitations regarding the application of the drug. The relevant philosophical issues to each phase are also illustrated.

thoroughly comprehend a range of foundational issues and elements around pharmaceutical substances and products which grant structure and depth into pharmacy. In this context, three main aspects are rendered conspicuous when approaching pharmacy: the pursuit of truth through research and development in scientific practice, the careful control exerted by governing bodies and stringent regulations on various practice and drug related issues, and the widespread application of such products in terms of dispensing, recommendation and societal response. These three aspects pertaining to the journey of pharmaceutical products are demonstrated in Figure 2.

To address these three aspects, one may look to establish an epistemological foundation, which would contemplate the nature of knowledge, questioning how it is acquired, validated, and conveyed within pharmacy. It is crucial to concede on the dynamic and evolving nature of knowledge in pharmacy which is also inherent with uncertainties and inevitable limitations. Simultaneously, this requires spelling out the relevant criteria for scientific practice in terms of evidence, inference, causality and justification. Furthermore, tracing the origins of key concepts, practices, and breakthroughs in pharmacy might also provide important insights which may guide research, regulation or application of drugs. This includes recognizing focal episodes or paradigm shifts which have transformed current understanding or practice. Alongside these epistemic concerns are the metaphysical considerations. This could involve accounting for the inherent nature of drugs, their regulation and application.

On the ethical front, not only the practice of pharmacy but also research are both steeped in a set of values and duties. Being an applied science, a philosophy of pharmacy should

inherently emphasize the tangible, yet careful, application of pharmaceutical knowledge. It is essential to delineate the primary responsibilities of practitioners inside the community or clinical pharmacies, as well as, researchers in academia or industry. This could include addressing concerns of regulation, access, equity, and fairness, which in pharmacy translates to issues related to drug availability, pricing structures, the inviolable rights of patients and animals and indeed the impact on the environment. Furthermore, guidance on potential moral conflicts which arise in practice is indispensable. The dynamics between practitioners and a plethora of stakeholders, ranging from patients to regulatory bodies and industries, ought to be meticulously understood. The *societal and cultural* context in which pharmacy operates cannot be overlooked. The field must be evaluated in light of its role within the broader social fabric, taking into account the influence of diverse cultural beliefs and practices. Equally significant is understanding the multifaceted relationships between pharmacy and other disciplines, emphasizing its interdisciplinary nature. A continual dialogue with overarching philosophical debates and traditions within this context will ensure a vibrant and dynamic evolution of pharmacy.

Therefore, the discourse of this dissertation has elected to pose two main questions at each step represented in Figure 2. Firstly, what philosophical issues unique to pharmacy can be identified? And secondly, how can the account developed be wielded to yield practical benefits to pharmacy? The general nature of these two questions may indeed provide a wealth of issues to tackle. But again, the aim here is to lay a foundation which could guide or enrich future debates. Therefore, at each step in this pharmaceutical journey, fundamental issues have been discerned as follows.

At the ‘Research and Development’ step which corresponds to ‘Pursuit of Truth’, issues related to scientific practice in pharmacy are concerned. Does the distinction between discovery and justification, renowned in the philosophy and history of science, hold in the scientific practice in pharmacy? Or are scientists on a constant pursuit? How is knowledge embedded within this intricate relationship? Does the definition of knowledge as justified, true belief hold here? What truly defines the relationship between ‘truth’ and ‘knowledge’ in pharmacy? Pharmaceutical research frequently oscillates between explanatory models. Is reducing complex systems to boxes and arrows the most comprehensive approach? Or does a more encompassing, holistic approach render a deeper understanding? Are mechanistic explanations necessarily reductionist? Or are there different types of mechanisms which could account for

the complexity inherent in pharmaceutical phenomena? Additionally, where does the idea of function and purpose, with its teleological dimension, fit within these narratives? In terms of the relationship between a cause and an effect, how does one deal with drawing inference in pharmacy? What philosophical and conceptual tools one may utilize to resolve such issue? What about the distribution and exchange of knowledge? Do current practices in the advent of open access factor in the anthropocentric aspects of peer-review in the context of dissemination?

At the regulation step which is best captured through the concept of ‘Control’, intriguing epistemological and ethical dilemmas emerge: How to understand the concept of control in pharmacy? And subsequently, how do governing bodies navigate the delicate balance between ensuring that pharmaceutical products are both effective and safe? What principles underpin the complicated regulatory landscape of today? Where does risk and its management fit in this picture? What role can philosophy play in informing and refining these regulatory decisions? Is there room for the environment and the ecology in pharmaceutical regulations? Does the existing regulatory framework possess the agility to adapt to swiftly changing scientific and societal needs? And if not, could philosophical tools provide the lens needed to critically examine and adapt these structures? How can philosophy guide the balance between advancing scientific and technological breakthroughs, maximizing the benefit in responding to societal needs, and minimizing potential detriments?

As pharmaceutical products enter the market, their ‘Application’ is subject to societal response, leading to the emergence of a series of compelling inquiries. What is the current understanding of the concept of application in pharmacy? How is the acceptance, hesitancy towards or refusal of pharmaceutical products navigated within the intricate interplay between orders or recommendations from healthcare experts and individual or societal responses? Why, in an era rich with cutting-edge approaches such as personalized medicine and pharmacogenomics, might patients still be positioned as secondary players, overshadowed by a pathology-focused understanding of disease? Does this current approach, which is heavily anchored in handling and treating disease, sufficiently regard the patient’s unique socio-cultural and psychological particularities? If the goal is a more holistic, patient-centric application, could philosophy refine the conception of drugs and disease to subsequently transition from merely combating disease to truly promoting health? How can philosophy and interdisciplinary research assist in ensuring the patient remains central, not just receiving

treatment but actively participating in therapeutic decisions? Setting a comprehensive and exhaustive account of a philosophy of pharmacy, however, remains outside the scope of this dissertation. The main objective here is to lay a debate-stimulating foundation through critically identifying and evaluating issues within the threefold aspect of pharmacy. Essentially, the discourse of this dissertation may be interpreted as an attempt to reduce the gap between philosophy and pharmacy and highlight the great benefits yielded by adopting such an approach.

Hence, the subsequent chapters progress as follows: Chapter Two, “Pharmaceutical Research and Development: The Pursuit of Scientific Truth”, is dedicated to evaluating the philosophical foundations of scientific inquiry in pharmacy. The chapter scrutinizes the nature of truth, knowledge, and different modes of inference and reasoning. Three examples are presented: an exploration of mechanisms in pharmacy and pharmacology via the lens of new mechanist philosophy of science, a philosophical reflection on methodological distinctions in biochemical research, and a refined mechanistic approach assessing causal hypotheses in pharmacovigilance. Chapter Three, “Science Communication in the 21st Century”, underscores yet another aspect of scientific inquiry in pharmacy related to the dissemination and sharing of knowledge. Issues related to transparency, peer-review and the context of dissemination are explored. The discourse emphasizes the anthropocentric nature of scientific practice by adopting a constructivist approach representing science as a human endeavor and focuses on the importance of this construction in peer-review and the exchange of knowledge in alignment with social and environmental goals.

Chapter Four, “Controlling the Pharmaceutical Product: Decisions, Regulations and Consequences,” unpacks the aspect of control in pharmacy. Here, topics range from impurities in drug products to the environmental repercussions of pharmaceutical waste. Additionally, the chapter provides a critical analysis into the approval procedure of drug products and the challenges of risk assessment and decision-making during global emergencies. Chapter Five, “Application of Pharmaceutical Products: Beyond Pathology and Medicating,” elucidates the concept of application within pharmacy. A historical account of the concept of application in pharmacy sets the stage, followed by an interdisciplinary approach to understanding the particularities for accepting, hesitating or refusing pharmaceutical products. Chapter Six is a general discussion and Chapter Seven is dedicated to the tentative conclusions. Within this

dissertation, analyses and discussions derive their authority from 13 scholarly manuscripts, all published and recognized in international, peer-reviewed journals between 2019 and 2023.

Chapter Two

2. Pharmaceutical Research and Development: The Pursuit of Scientific Truth

Scientists immerse themselves in pursuing truth through researching and developing safe and effective pharmaceutical products. This pursuit is directed towards the needs of society through a path heavily controlled and standardized by regulatory bodies, Figure 3. The focus of this chapter is to detail and exemplify the philosophical implications of pharmaceutical research and development from an epistemological perspective with the aid of recent discussions in the philosophy of science. Subsequently, the theoretical frameworks developed are applied into tangible action⁴.

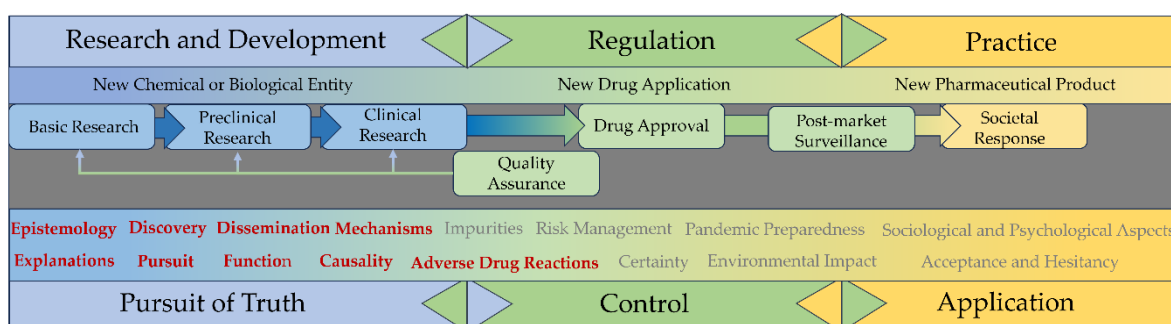


Figure 3. The first step in this endeavor is research and development in pharmacy which accounts to the pursuit of truth. The relevant topic in this chapter is illustrated in red.

The main theme of this chapter is the pursuit of truth and its philosophical implications within research and development in pharmacy. The aim is to characterize and lay down a philosophical foundation which grounds scientific practice in pharmacy and subsequently explore how developing such an account may aid scientists and help them in their pursuit. In this context, issues related to research methodologies for acquiring and synthesizing knowledge in pharmacy is addressed; the main topic of research here is research or scientific practice itself. The tune of the chapter is set by briefly recounting the relevant philosophical underpinnings and concepts. A distinction between truth and knowledge in scientific practice is presented. Here, the focus will be on recent discussion of the context of pursuit, the new mechanist philosophy of science and approaches to reasoning and inference in scientific practice. Subsequently, three cases related to scientific practice in pharmacy are identified and discussed in more detail: 1). the topic of mechanisms in pharmacy and biochemistry is examined from

⁴ The discussion in this chapter is supported and based on three manuscripts published in international peer-reviewed journals: **Abdin, A.Y.**; Auker-Howlett, D., Landes J.; Mulla, G.; Jacob, C.; and Osimani, B., Reviewing the Mechanistic Evidence Assessors E-Synthesis and EBM+: A Case Study of Amoxicillin and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), *Curr. Pharm. Des.* 2019; 25(16). <https://dx.doi.org/10.2174/1381612825666190628160603>, **Abdin, A.Y.**; Jacob, C.; Kästner, L. Disambiguating “Mechanisms” in Pharmacy: Lessons from Mechanist Philosophy of Science. *Int. J. Environ. Res. Public Health* 2020, 17, 1833. <https://doi.org/10.3390/ijerph17061833> and **Abdin, A.Y.**; Jacob, C.; Kästner, L. The Enigmatic Metallothioneins: A Case of Upward-Looking Research. *Int. J. Mol. Sci.* 2021, 22, 5984. <https://doi.org/10.3390/ijms22115984>.

the perspective of the new mechanistic philosophy of science, 2). building on the philosophical account developed for mechanisms, several methodological distinctions are highlighted and applied in the contexts of discovery and pursuit in biochemistry, and 3). the mechanistic account together with several philosophical notions are developed further in assessing causal hypotheses in pharmacovigilance.

2.1. Scientific Inquiry in Pharmacy: A Philosophical Account

Scientific inquiry is a multifaceted activity, surpassing empirical and logical considerations to include methodological, epistemological, and socio-epistemic aspects [4,5]. A rich philosophical tradition has engaged with these facets of science, aiming to expose the process of knowledge generation and the pursuit of truth. This tradition is particularly relevant in applied fields such as pharmacy, where science directly influences human health and wellbeing.

Early 20th-century philosophers of science, such as Hans Reichenbach (1891-1953), distinguished by their allegiance to logical empiricism⁵, often formulated their account of the scientific activity within a two-way distinction: the “context of discovery” and the “context of justification” (also known as the DJ distinction⁶) [7]. Logical positivists championed the *Verification Principle*, arguing that statements are meaningful only if they are logically true or empirically verifiable. The context of discovery is concerned with the origin of scientific ideas—the spark of insight, the creative process of formulating hypotheses, in pharmacy, this could involve the discovery of a new molecular pathway or a pharmacological target implicated in a disease or the identification of a potential therapeutic compound. The context of justification is concerned with the rational or logical reconstruction of discoveries. It has generally been viewed as the realm of empirical testing and logical verification. Hypotheses undergo rigorous scrutiny through systematic experiments and data analysis. In pharmaceutical research, this might involve a series of *in-vitro* preclinical and clinical trials to establish the safety and efficacy of a novel therapeutic compound.

Discovery and justification in pharmacy, however, seem to go hand in hand. The discovery stage is not simply an ‘Aha’ or a ‘Eureka’ moment; it is indeed a rigorous process [8]. Consider the discovery of new drugs in pharmacy—extensive exploratory research and compound screening are performed before a potential drug candidate is designated. Apart from computer

⁵ Logical positivism, later called logical empiricism, is a philosophical movement adopted by elite philosophers and scientists who grouped within the Vienna Circle. This approach is attributed with a heavy emphasis on epistemology whose central thesis is the verification principle. This stance faced criticisms, notably its potential self-defeating nature and its strict criteria which seemingly excluded meaningful statements in ethics, aesthetics, and metaphysics. Furthermore, their emphasis on direct observability appeared to conflict with the prevalent use of unobservable entities in science and overlooked the influence of theoretical commitments on observation [6].

⁶ The distinction between “discovery” and “justification” dominated and shaped the discussions about discovery in 20th-century philosophy of science. The context distinction marks the distinction between the generation of a new idea or hypothesis and the defense (test, verification) of it. Advocated of this distinction such as the logical positivists hold that discovery in an activity which cannot be analyzed philosophically rather the focus should be on justification which can be scrutinized based on its logical structure.

modeling and *in-silico* experiments, high-throughput screening, for instance, represents an important step in drug discovery. It allows robots to rapidly screen millions of compounds in search of potential leads.

While this dichotomy might seem clear and convincing, many philosophers such as Karl Popper (1902—1994) and Thomas Kuhn (1922—1996) among many others challenged its adequacy and argued for a more polarized understanding of scientific practice⁷ [9,10]. They noted that discovery and justification cannot be easily distinguished as they are often intertwined, with each phase informing the other in a continuous cycle of scientific inquiry. Consider for instance the process of drug development, initial findings about the therapeutic potential of a compound might trigger new questions about its mechanism of action or its efficacy in various patient populations.

Building upon this evolving debate, Larry Laudan (1941—2022) proposed an additional context to broaden the scope of philosophy of science: the “context of pursuit”⁸ [11,12]. For Laudan, the notion of “research traditions” highlights the interconnected set of beliefs and practices in science, each of which is tied to specific problems and their solutions. Here, the essence of scientific advancement lies not just in theory or rational reconstructions of discovery but in the theory’s adequacy to resolve more problems than it generates. He believed that a truly progressive scientific traditions not only outperforms its rivals in problem-solving but also introduces fewer difficulties than it settles. Hence, Laudan sets scientists on a constant pursuit to find the *better* solution to the problems of their fields with the employment of different research traditions⁹.

The context of pursuit has been conceptually understood to serve as an intermediary phase between discovery and justification. Here, researchers decide whether a particular hypothesis or idea is worth further investigation and also how to do so. A variety of criteria may influence the decision to pursue a scientific theory or tradition. The presence of a significant explanation of the phenomenon in question, the inferential density which relates to the internal coherence

⁷ Such philosophers also argued against the adequacy of the verification principle emphasized by logical positivists as a demarcation criterion of science and introduced their own ideas as will be discussed in the ensuing section.

⁸ There are other conceptual distinctions in the scientific activity. The context of acceptance, for instance, is represented when a hypothesis, theory or research tradition which has matured and became widely accepted within a scientific community. Here, the epistemic commitment is at its maximum while the pragmatic commitment is minimum which is in contrast to a hypothesis, theory or research tradition at the stage of pursuit. Furthermore, the context of dissemination, explored in Chapter Three, is yet another possible distinction.

⁹ For an enlightening discussion of models in pharmacy, specifically QSAR (Quantitative Structure–Activity Relationship), and their pursuitworthiness see [13].

of a theory composed of several connected hypotheses and the external coherence with established and accepted theories, the pragmatic character when dealing with anomalies and the theoretical and pragmatic growth, represent four important criteria to consider when evaluating the pursuit-worthiness of a theory or a research tradition [14]. Other factors might include the potential implication of the research question, applicability of the proposed study, resources available such as funding and accessibility to equipment, and alignment of the approach with prevailing research traditions. The concept of pursuit is especially salient in pharmacy, where decisions to pursue a particular therapeutic strategy involve careful consideration of the potential impact on patient health, resource implications, and alignment with the current understanding of disease mechanisms.

The context of pursuit proposed by Laudan indeed captures the pragmatism, dynamism and complexity of scientific practice and offers a more accurate representation of the pursuit of truth and the generation of knowledge in science and pharmacy in particular [15,16]. In recognizing these contexts, one acknowledges that scientific knowledge is not simply the result of logical processes applied to empirical data. Instead, it is a complex, cyclic and iterative process which is heavily intertwined with practical, methodological, and socio-epistemic factors. This is exemplified in the development of the Exeter Method which is a flexible and constantly evolving four-step “iteration method” that is based on philosophy, as well as, biochemistry [17].

Philosophers like Imre Lakatos (1922—1974) and Paul Feyerabend (1924—1994) further emphasized this complexity associated with scientific enquiry, as well as, the role of methodological pluralism and the social and cultural influence on scientific practice (more on this below). These perspectives serve as a reminder that the path to truth in science, and particularly in an applied field like pharmacy, is not a linear progression but a dynamic process, shaped by a multitude of scientific and non-scientific influencing factors. Recognizing the complexities of scientific practice, particularly in a field as consequential as pharmacy, offers a deeper understanding of how knowledge is generated, and truth is pursued. It underscores that scientific pursuit in pharmacy is constant and shaped by a variety of empirical, logical, practical, and socio-epistemic factors.

2.2. The Pursuit of Knowledge vs. Truth

Another central topic of debate in philosophy of science is the interplay between truth and knowledge. The epistemological contours surrounding these concepts have witnessed several shifts, leading to both harmonious and contentious relationships. Traditional view posits knowledge as justified true belief, thus clearly linking truth to knowledge. This classical Platonic view emphasizes that, for any proposition to be considered as knowledge, it should not only be believed and justified, but crucially, it also needs to be true. Truth is, hence, established as a condition for knowledge, and conversely, all knowledge is necessarily true.

This simple correspondence theory of truth has, however, faced challenges. The twentieth century witnessed the emergence of influential philosophical movements such as logical positivism and later, post-positivism, which placed the emphasis on logical verification and then on falsifiability as demarcation criteria for the “scientificity” of a proposition, thereby subtly altering the relationship between truth and knowledge. In this context, a proposition could be considered scientifically valid, that is, part of scientific knowledge, even if its truth status remained provisional and open to falsification.

Popper, who introduced the falsification criterion, hinted at an estrangement of truth from knowledge in science. He found the *verification principle* to be self-defeating and, therefore, inadequate to be applied to assess scientific knowledge. Popper maintained that scientific theories could never be proven true definitively but only corroborated to varying degrees until they are eventually falsified or proven wrong. In this sense, knowledge accrues through a process of conjectures and refutations, while the pursuit of truth remains a tantalizing, ever-receding horizon.

Willard Van Orman Quine (1908—2000) put forward a holistic perspective which emphasizes the deep interconnectivity of beliefs. This in turn cast doubt on the clear-cut distinction between analytic and synthetic statements¹⁰ [18]. He proposes that the collective “web of belief,” encompassing both scientific theories and the linguistic tools framing them, undergoes empirical scrutiny [19]. Instead of seeking foundational statements as the bedrock of knowledge, Quine suggests that the entire belief system in science faces adjustment when

¹⁰ Analytic statements are true based on their linguistic or logical properties alone, such as "All bachelors are unmarried," which is a tautology and the truth is inherent in the terms used. Synthetic statements, conversely, derive their truth from facts about the world, exemplified by "The cat is on the mat," requiring empirical verification. This distinction, which is essential in philosophical discourse, demarcates truths arising from language alone from those necessitating worldly empirical validation.

any segment is tested, a stance diverging from Logical Positivist views on observation-based foundations.

Kuhn's seminal work "The Structure of Scientific Revolutions" advanced the idea of paradigm shifts, suggesting that what is considered 'knowledge' and 'truth' in one paradigm might not hold in another, a concept known as "incommensurability" [20]. Rather than a linear and cumulative growth, Kuhn posited that science progresses in nonlinear manner, influenced by social, political and economic factors of the era. Each paradigm entails a distinct worldview, but over time, anomalies, *i.e.* contradictions or observations unexplainable within the theories, methods, tools and approaches adopted, may prompt a revolutionary change to a new paradigm. For Kuhn, knowledge is paradigm-relative. Thus, he emphasizes a historicist and relativistic epistemology, questioning the notion of a universally "objective" scientific stance, *i.e.* truth. This suggested a degree of relativity into the relationship between truth and knowledge, implying that they are not absolute but contingent on the prevailing scientific paradigm.

Furthermore, several other philosophers from the late 20th and 21st centuries developed a similar account for the relationship between knowledge and truth. In this context, Paul Feyerabend contested the existence of a singular scientific method, suggesting instead that science thrives in methodological "*anarchy*." He critiqued dominant scientific philosophies such as Popper's falsifiability, emphasizing that in the vast history of science, exceptions to any prescribed rules thrive and flourish, leading to his claim that in science, "*anything goes*" [21]. Imre Lakatos sought a compromise between Popper and Kuhn, introducing the concept of "research programs," sequences of theories in a specific scientific realm with a shared core but varying auxiliary hypotheses. Contrary to Popper's direct falsification approach, Lakatos believed that faced with opposing evidence, scientists often tweak auxiliary hypotheses while maintaining the core [22].

Feminist philosophers of science, represented by figures such as Sandra Harding (1935—) and Helen Longino (1944—), accentuate the influence of societal and gender values in crafting scientific knowledge, positing that a holistic understanding of science demands recognizing its social underpinnings [23,24]. This perspective highlights the often-overshadowed social contextuality in traditional philosophical accounts such as those of Reichenbach, Popper and Kuhn. In a similar vein, social constructivists, including Bruno Latour (1947—2022) and Steve Woolgar (1950—), advocate for the idea that scientific facts emerge from intricate social processes. Instead of picturing science as a mere mirror to nature,

they emphasize the importance of sociopolitical negotiations, instrumentation, and institutional dynamics in molding scientific comprehension.

The pragmatist perspectives, echoing the thoughts of Charles Peirce (1839—1914), Willham James (1842—1910), John Duwy (1859—1952), Isaiah Berlin (1909—1997) and Richard Rorty (1931—2007), prioritize the practicality of beliefs over their alignment with external truths, suggesting that the value of a scientific theory hinges on its practicality or utility, not truth in the conventional sense [25–28]. To the pragmatists, metaphysical debates about truth, reality or knowledge are games without rules. These thinkers focus on the utility of knowledge. This is very similar to the problem-solving theory of knowledge proposed by Laudan which views knowledge as ever changing and that scientists are on a constant pursuit, as discussed above.

The relationship between truth and knowledge in philosophy of science can be seen as both cooperative and contentious. It reflects the enduring tension between the static, definitive nature of ‘truth’ and the dynamic, evolving character of ‘knowledge’ in the sciences. Truth can be considered the end goal of scientific practice, while knowledge is a provisional construct, shaped by various factors including technological advancements and socio-cultural contexts to solve problems.

This distinction between knowledge and truth is indeed evident in the special sciences such as pharmacy. Knowledge in pharmacy mirrors the ongoing progress in scientific understanding. It is a science concerned with complex, sometimes unpredictable, phenomena irreducible to a set of physical laws. As research advances, technology evolves, and societal needs shift, the body of knowledge in pharmacy continuously grows and refines. This dynamic aspect contrasts sharply with the unchanging, definitive nature of truth, which is the ultimate objective of scientific practice.

2.3. Reasoning in Pharmacy: A Dive into Modes of Inference and Explanation

Modes of reasoning render a crucial set of tools in the dynamic and evolving knowledge-generation process in pharmacy, guiding scientists in producing hypotheses, validating models, and subsequently reaching informed, evidence-based conclusion and decisions. The ultimate objective is to unveil truth about mechanisms of drug actions, interactions, and clinical outcomes in the pursuit of effective, safe, and patient-centered healthcare solutions.

Therefore, modes of reasoning represent the core principles of how scientists interpret and infer from data. These principles, including deduction, induction, abduction, inference to the best explanation, and Bayesian inference, serve as the foundation of cognitive processes, enabling the scientist to make meaningful discoveries and decisions and generate new knowledge in their pursuit of truth. Each mode of reasoning carries its distinct character and holds significant relevance in various fields of study, including pharmacy, where they help in assimilating and interpreting complex drug-related phenomena.

Deductive reasoning, one of the most well-known and fundamental reasoning processes, operates under a logical structure where conclusions are drawn based on certain given premises; the conclusion is entailed in the premises. Such mode of reasoning moves from the general to the particular, *e.g.*, Aristotle is a man and all men are mortal, therefore, Aristotle is mortal. In its purest form, deductive reasoning assures certainty, assuming that the initial or given premises are true, *i.e.* if the premises are true then the conclusion is true [29–31]. Such reasoning might be applied, for example, in the calculation of drug dosages. Given the premises that a specific drug dosage has been established safe and effective for adults at 10 mg/kg, and that an adult patient weighs 70 kg, a pharmacist can deduce that a 700 mg dosage would be suitable for this individual. Here, the process of deduction plays a vital role in ensuring the safety and efficacy of administered drugs.

Inductive reasoning, on the other hand, begins from the specific and moves to the general. It involves taking individual, often empirical, ideally repeated, observations and forming a generalized conclusion. This kind of reasoning, although generates its conclusions that seem likely, does not provide certainty [32,33]. If a medication is observed to improve symptoms in a number of patients, for example, one might utilize inductive reasoning to claim that the medication will have the same effect on all similar patients. It is possible, however, that there are unobserved instances where the medication does not improve symptoms, which makes the conclusion less than certain.

Abductive reasoning, abductive inference or retroduction, is yet another important mode of reasoning. It is employed when picking the most plausible explanations from a set of possibilities. The main objective of employing this mode of inference is to generate plausible explanations for further testing [34,35]. Within the context of pharmacy, abductive reasoning might be applied in diagnosis or to infer causal relationships between medication and side-effects. If a patient develops a certain set of symptoms after initiating a new treatment, for instance, and this medication is known to potentially cause such side effects, one might abductively infer that the medication is indeed the cause of the symptoms.

Inference to the Best Explanation (IBE) shares many similarities with abductive reasoning. It involves inferring a hypothesis which appears to best explain a set of data or observations. IBE is often used in the interpretation of experimental data. The main difference with abductive reasoning is that IBE aims to single out an explanation rather than providing a range of testable hypotheses [34,36]. If a clinical trial reveals that a new antihypertensive drug reduces blood pressure more effectively than existing medications, for instance, one might infer, via IBE, that the new drug is superior in treating hypertension.

Bayesian inference, a probabilistic method of reasoning, differs from the previous modes in that it works on principles of probability to update the likelihood of a hypothesis as more evidence becomes available. This mode of reasoning has gained significant traction in health sciences, including pharmacy. The Bayes' theorem, named after Reverend Thomas Bayes (1701—1761), is central in this mode of reasoning [37–39]. This theorem calculates the probability of an event occurring based on prior knowledge of conditions which might be related to the event. Bayesian inference helps to revise beliefs while considering new evidence, rendering this mode a dynamic approach to understanding uncertainty. It allows for a level of flexibility in amalgamating medical evidence, especially in cases where a clear relationship between cause and effect is missing. In the setting of clinical trials, for instance, Bayesian inference can be employed to update the probability of a new drug's efficacy as more patient data accumulates over time.

Each of these modes of reasoning carries distinct strengths and limitations. Deduction offers certainty but it is limited by the truth of its premises and indeed their general applicability. Conclusions reached by inductive reasoning provide generalizability but lack definitive certainty. Abduction and IBE are potent tools for formulating hypotheses but depend

on the range and quality of considered explanations. Bayesian inference, meanwhile, relies heavily on the quality and quantity of data available.

It should be noted that this list is neither complete nor exhaustive. Other modes of reasoning also exist. *Analogical reasoning*, for example, involves utilizing the knowledge of one domain (the source) to make inferences about another domain (the target). In drug development, for instance, scientists often apply analogical reasoning to draw conclusions about a new drug based on its similarity to known chemical structure or biological activity of another. This is indeed the case in bioisoteric replacement where scientists seek strategic changes to molecules by swapping specific atoms or groups, ensuring they function similarly in a biological context. Through this process, one may subtly alter a molecule's effects, its interaction with the body, or even its potential side effects. Furthermore, *counterfactual reasoning* involves thinking about what could have happened in a situation, had the circumstances been different. A pharmacist may use counterfactual reasoning, for instance, to consider the possible outcomes if a patient had taken a different medication.

These modes of reasoning are not mutually exclusive, and in fact, most complex tasks involve a mix of different types of reasoning. In pharmacy, a balanced and thoughtful utilization of these reasoning modes can aid in reaching robust and comprehensive interpretations, further advancing current understanding of pharmaceutical research. Each mode provides a unique perspective and aids in answering different types of questions, ultimately contributing to a richer and more nuanced understanding of the scientific world within pharmacy.

2.4. The New Mechanist Philosophy of Science

The twentieth-century philosophy of science has been predominantly influenced by logical empiricism and the pursuit of truth as rational or logical reconstructions of scientific practice. It emphasized abstract, epistemic aspects of science, particularly in physics. In the twenty-first century, however, philosophy of science is experiencing a shift towards the “new mechanical philosophy” which represents a more suitable account to scientific practice in the special sciences. Unlike logical empiricism, this framework focuses on actual scientific practice and is dedicated to the application in biological sciences through spelling out and searching for mechanisms. Advocates of this tradition aim to succeed the logical empiricist’s approach to numerous scientific philosophical issues such as causation, laws of nature, reductionism and scientific discovery and pursuit.

The new mechanical philosophy diverges from the tradition of examining scientific inferences with logical tools and instead leans towards scrutinizing historical scientific episodes. Scholars noticed that the search for mechanisms predominantly drove contemporary scientific practice, and this approach underpinned numerous historical scientific breakthroughs.

This new philosophy takes root in the late 1960s, with theorists like Wesley Salmon (1925—2001), Jerry Fodor (1935—2017), Robert Cummins (1939—), William Wimsatt (1941—), and Nancy Cartwright (1944—) presenting their contribution which critiques logical empiricism and highlights the need for understanding mechanisms in scientific explanations [40–44]. Salmon, for instance, focused on causality and the structure of explanation, emphasizing the necessity of causal processes and interactions. Fodor, in his discourse, championed the modularity of the mind, suggesting that mental processes operate in integrated, specialized systems. Cummins introduced the analytical approach of “*functional analysis*”, highlighting the importance of understanding a system’s components in the context of their contribution to the overall function. Wimsatt addressed the heuristic nature of scientific practice, noting that errors, approximations, and redundancy are often integral to scientific progress. Cartwright, on her part, underscored the patchwork nature of scientific laws, suggesting they often hold true only under specific conditions. Collectively, these philosophers of science shed light on the multifaceted nature of scientific explanations, advocating for a deeper understanding of mechanisms rather than relying solely on empirical findings.

By the 1990s, these theories began to merge into a comprehensive perspective, aptly demonstrated in Bechtel and Richardson's work "Discovering Complexity" [45]. This period also saw Glennan propose mechanisms as the secret connections between cause and effect, and Thagard placed emphasis on the search for causes and mechanisms in medical sciences [46,47]. Peter Machamer (1942—2023), Lindley Darden (1945—), and Carl Craver's work, "Thinking about Mechanisms," further bound these concepts together, suggesting that the philosophy of biology, and potentially the entire philosophy of science, should be organized around the pursuit of mechanisms [48]. According to the new mechanistic approach, scientists—especially in the life sciences—explain phenomena by discovering and pursuing the mechanisms *responsible* for them. A range of different accounts of mechanisms has been offered, but a consensus may be expressed as follows¹¹ [48,50–52]:

"A mechanism for a phenomenon consists of entities (or parts) whose activities and interactions are organized such that they are responsible for the phenomenon to be explained".

This unifying characterization neatly conveys the central tenets of the new mechanist philosophy¹². It does, however, leave important issues underspecified. There is, for instance, considerable discussion about what exactly "phenomena" are [16,17,18]. In the context of this dissertation, phenomena are to be understood as the explananda of mechanistic explanations, *i.e.*, phenomena are what a mechanistic explanation or a mechanism seeks to explain. It is assumed that mechanistic explanations can explain phenomena from various scientific domains which transcends reducing them to a set of physical laws. Accordingly, the explananda of mechanistic explanations may range from electrons and chemical reactions mechanisms to higher emergent cognitive capacities. Here, the notion of a mechanism being "responsible for" a phenomenon requires further inspection [56–59]. One ought to delve deeper into the different types of mechanisms put forward by the new mechanist philosophy.

¹¹ The view of mechanisms presented here is comparable to the popular view of systems as an interconnected set of elements which is coherently organized in way so to achieves a goal or objective. The elements represent the mechanistic components, the interconnectedness is echoed in their interaction and the goal or objective is the phenomenon which they together underly. Similar to systems, such mechanisms experience feedback loops, *i.e.* stabilizing or reinforcing, resilience, are self-organizing and part of a hierarchy. This systemic outlook of pharmacological mechanisms is indeed worthwhile exploring [49].

¹² It should be noted that the metaphysical commitment here whether these mechanisms are part of reality or simply a beneficial representation which guides problem solving in the sciences is dependent on the user. In this dissertation mechanisms are treated as the best possible representation and approach to scientific inquiry in pharmacy.

2.4.1. Three Types of Mechanisms

Generally, there are three types of mechanisms [60]: mechanisms which produce, underlie, and maintain their phenomena, Figure 4. The difference between the three can be understood in a metaphysical sense. Yet, it is more beneficial to view it as a triad of three kinds of mechanistic explanations. Thus, being “responsible for” can take at least three different forms of explanations. Firstly, it can refer to a causal relation where the phenomenon is the effect of a preceding mechanism’s operation, *i.e.* a producing mechanism. Secondly, “being responsible for” can designate a constitutive relation where the phenomenon is the overall behavior of the mechanism (its organized parts, their activities and interactions), *i.e.* an underlying mechanism.

Thirdly, “being responsible for” can describe some set of regulatory relations which keep a certain state stable or continuous process going, *i.e.* a maintaining mechanism. Hence, the mechanisms which produce, underlie, or maintain their phenomena are suited to explain different kinds of phenomena; To explain how a product, an effect or an end-result is generated or reached, scientists will search for the producing mechanism; to explicate a process, they will focus on the mechanism underlying it; and to explain how a system’s stable state or continuous behavior is maintained, they search for the mechanism maintaining it [61]. The idea that different kinds or types of explanations serve to answer different research questions is not new. In fact, many philosophers of science have assumed this [62–64]. Besides, this assumption is also inherent in the mechanistic view: mechanistic explanations are always mechanistic explanations for a specific phenomenon.

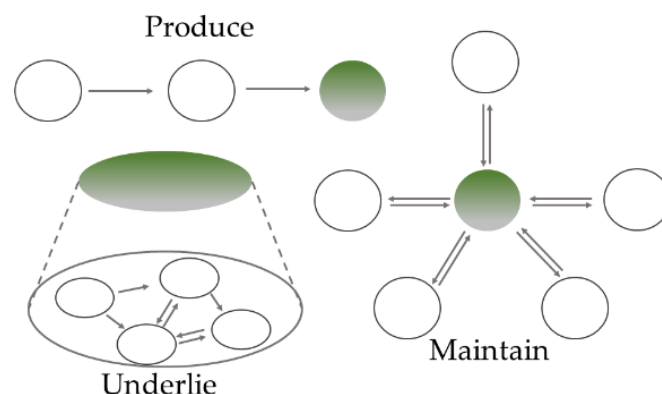


Figure 4. Three kinds of mechanisms; green circles depict the phenomenon to be explained (adapted from [65], p. 66).

The difference between producing and underlying mechanisms mirrors the familiar distinctions between etiological and constitutive explanations [64]. In this context, etiological

explanations are focused on the causal chain of events leading to the phenomenon to be explained, such as attributing a disease to a virus. In diagrams or illustrations such relationships are represented by an arrow or a series of arrows. Constitutive explanations describe the underlying mechanism constituting the phenomenon to be explained, such as attributing the act of reaching one’s arm to interactions among brain regions, muscles, and joints. Such relationships are conveyed in Figure 4 in underlying mechanisms as dotted lines stemming from bottom-up towards the phenomena to be explained. Still, there is more to this distinction than assuming a different phenomenon–mechanism relation: explanations describing producing and underlying mechanisms, respectively, have different explananda, *i.e.*, end-products or overall processes. There are two straightforward rationalizations/descriptions as to how underlying and producing mechanisms relate.

Firstly, a producing mechanism may be located within an underlying mechanism Figure 5. In examining the productive aspects within an underlying mechanism, scientists temporarily switch the explanandum: they focus on how a certain state or activity of a given component within the mechanism is produced.

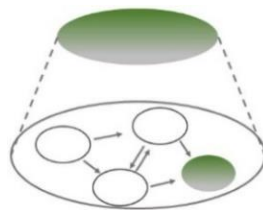


Figure 5. Production within an underlying mechanism. Note that any component of the underlying mechanism shown in white may itself also be an explananda of another, even deeper underlying mechanism.

Secondly, each step in the causal sequence of a producing mechanism may be spelled out further by identifying the underlying mechanisms at each stage, the top circles shaded in green in Figure 6. As in the first case, scientists here change the explanandum. To investigate the underlying mechanisms at each stage, *i.e.*, “phenomenon to be explained”, they must ask how each of the processes occurring within a productive chain is implemented rather than what is produced at the end of the sequence.

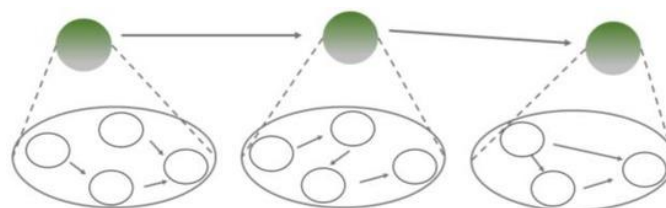


Figure 6. Mechanisms underlying components of a productive mechanism.

The major difference between these scenarios is how the information is placed together in a coherent picture to reach an explanation. The first scenario provides an analysis of some causally productive mechanism responsible for relations within another mechanism recognized to underlie a phenomenon, Figure 5. By contrast, the second scenario spells out how the contributing productive mechanisms are themselves being mechanistically responsible for, *i.e.*, which mechanisms underlie them, Figure 6. This complexity of multilevel mechanisms is demonstrated in Figure 7.

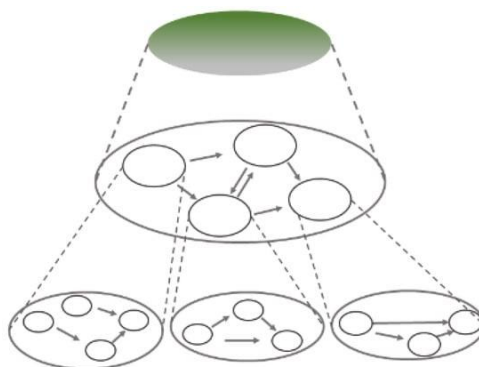


Figure 7. Schematic representation of a multi-level mechanism.

Consolidating different available mechanistic insights about production and underlying mechanisms equips scientists with the capacity to develop multilevel mechanistic understanding, Figure 7. The interplays amid mechanistic components can be construed as the emergence of production mechanisms within an inherent underlying mechanism. Concurrently, each component of an underlying mechanism is susceptible to further mechanistic scrutiny, signifying its own inherent constitutive mechanism comprised of components open to additional mechanistic exploration; the process continues in a similar manner. Ultimately, the mechanism culminates in reaching its intended structure, at which point it no longer constitutes a ‘black box’ and the research question is answered [60].

In subsequent sections, a demonstration of how in pharmacology and related disciplines, underlying and producing mechanisms are often superimposed on a single “box and arrow” representation of a mechanism of action (MoA). An analysis in terms of different kinds of mechanisms may usefully guide the interpretation of such traditionally “flat”, *i.e.*, non-hierarchical, diagrams to assist in transforming them into more powerful multilevel Baumkuchen models. It is proposed that Baumkuchen models provide an amenable, alternative, practical, and more powerful tool to represent “mechanisms of action” in pharmacology as they render different kinds of “being responsible for” relations more explicit.

2.5. Disentangling Mechanisms in Pharmacy: Insights from the Mechanist Philosophy of Science

The philosophical underpinnings of research and development in pharmacy emphasizes the prevalent notion of “mechanisms” is taken into consideration. Embedded deeply in the practices of biochemistry and pharmacy, this concept represents a pivotal axis around which a large portion of pharmaceutical research revolves. A fundamental attribute of natural sciences, particularly biochemistry and pharmacy, lies in their prowess to dissect complex interactions among entities, encompassing small-molecule compounds, biopolymers, organelles, cells, and organisms. The scales, levels or layers of these complex interactions span from the atomic and molecular to the biological, psychological, and even sociological levels. In pharmacy, complex molecular interactions, such as those between natural products or chemically synthesized drugs and biomolecules, are elucidated to comprehend physiological or psychological changes. Such relevant “lower-level” processes lead to “higher-level” phenomena or effects, commonly described in terms of “mechanisms”. These are typically represented graphically through diagrams or schemes, where entities are depicted as structures and boxes, and activities or interactions are portrayed as arrows. While these mechanisms are appealing due to their explanatory potential, understanding what precisely they convey, however, remains challenging¹³.

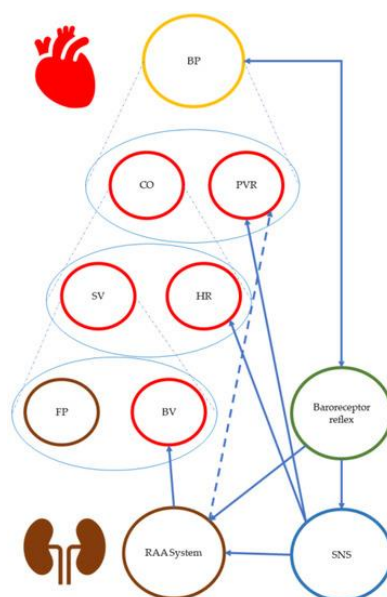


Figure 8. Schematic representation of the “mechanisms” regulating the blood pressure in the human body. BP: blood pressure, CO: cardiac output, PVR: peripheral vascular resistance, SV: stroke volume, HR: heart rate, BV: blood volume, FP: filling pressure (kidney), BV: blood volume, SNS: sympathetic nervous system, RAA System: renin-angiotensin-aldosterone system. This scheme has been adapted from a pharmacology textbook namely, Brenner and Stevens’ Pharmacology 5th edition p. 105 [66,67].

¹³ It should be noted that in the ensuing discussion the notion of level and layer will be used interchangeably to highlight or relate to the degree of complexity involved in the discussion.

A primary challenge in interpreting these mechanistic diagrams is deciphering the implications of these representations accurately. In Figure 8, interconnected control and feedback loops regulating blood pressure are demonstrated with arrows bridging different aspects of blood pressure regulation. Each arrow in these diagrams, however, stands for diverse relations, with some indicating causation and others being less explicit. This ambiguity provides a potent platform for the application of insights from the new mechanist philosophy, an insightful perspective from philosophy of science, to scrutinize and disambiguate such diagrams.

In this discourse, the mechanist philosophy of science is leveraged to provide a refined perspective on such “mechanisms” in pharmacology. The hypothesis that these complex diagrams superimpose different types of mechanisms onto one another is, therefore, examined.

Sections 2.4. and 2.1.4. have already provided a brief introduction to the concept of mechanisms from the perspective of contemporary philosophy of science. The focus is shifted in Section 2.5.1. to investigate in which sense and to which extent the so-called “mechanisms of action” in pharmacy resemble the mechanisms as discussed in philosophy of science. It is shown that at least two kinds of “mechanisms of action” (MoA) - pharmacokinetic and pharmacodynamic ones - must be differentiated. This dichotomy interestingly mirrors a distinction recognized in the philosophical debate: the differentiation between productive causal and underlying constitutive mechanisms, respectively. The implications of this observation are further probed.

Section 2.5.2. provides a detailed examination of ‘arrows’ in pharmacological diagrams. Given that these representations superimpose different kinds of mechanisms, the metaphysical relations that each arrow represents are of interest. Among several other examples, the biosynthesis of thyroid gland hormones and their actions in the human body are considered as a case study. It is highlighted that some arrows denote causal connections, others represent temporal, transitional or operational orders, and some function as shorthand for entire constitutive mechanisms. Section 2.5.3. introduces the Baumkuchen model and Section 2.5.4. concludes.

2.5.1. Mechanisms of Action in pharmacology

Pharmacology is a pillar for pharmacy and an intricate scientific discipline. It centers on unraveling the complex interactions between substances—predominantly drugs—and living systems [68]. Given its breadth and depth, pharmacology encompasses two closely intertwined

subfields: pharmacokinetics and pharmacodynamics, each with its unique focus and methodological approach.

Pharmacokinetics is defined according to the IUPAC as: “the process of the uptake of drugs by the body, the biotransformation they undergo, the distribution of the drugs and their metabolites in the tissues, and the elimination of the drugs and their metabolites from the body over a period of time” [69]. It focuses on the interactions occurring between the body and a drug, meticulously tracing the journey of a drug within the biological system, starting from absorption, following through distribution and metabolism, and finally to elimination. This sequence of events is often represented with traditional mechanistic diagrams, featuring a series of boxes and arrows, effectively summarizing the process in a supposedly causal chain. Such chains can even be symbolized by mathematical formulae, reflecting the quantitative nature of these interactions.

In pharmacokinetics, the drug itself is the primary subject of interest, and the mechanisms of action (MoAs) describe the transformation of the drug as it navigates the biological system. A notable example is spironolactone, a potassium-sparing diuretic administered in the management of hypertension and chronic heart failure. The drug’s journey is traced from its oral absorption, where it reaches its peak plasma concentration in 2.6–4.3 hours, to distribution, where about 90% of it binds to plasma proteins. It then undergoes extensive metabolism in the liver, transforming in the process to mostly inactive metabolites, and is eventually excreted in urine and bile [70,71].

Pharmacodynamics, on the other hand, studies the interactions between the drug and the body. This subfield focuses on how drugs function within the human body, investigating their physiological activities and unraveling the underlying MoAs from binding to membrane receptors to conducting changes on the organ level. While pharmacokinetics concerns “body–drug” interactions, pharmacodynamics is preoccupied with “drug–body” interactions. Nonetheless, both subfields resort to the concept of MoAs to explicate their observations yet from different perspectives.

It should be noted that the term MoA is not confined to pharmacology; it is applied in various scientific disciplines, each interpreting it within its context. In systems biology, for instance, a mechanism typically encapsulates the interactions between different parts and processes within a larger overall system. In contrast, in chemistry, reaction mechanisms might

pertain to abstract models or hypothetical constructs proposed to explain or predict certain processes or products.

Pharmacodynamics primarily employs MoAs as underlying mechanisms to investigate the resultant pharmacological effects at higher levels of phenomena, such as blood pressure. The International Union of Pure and Applied Chemistry (IUPAC) defines pharmacodynamics as the “study of pharmacological actions on living systems, including the reactions with and binding to cell constituents, and the biochemical and physiological consequences of these actions” [72]. This definition underscores the multi-level nature of pharmacodynamics, illustrating its broad scope spanning from microscopic cellular interactions to macroscopic physiological effects.

Exploiting Spironolactone as an illustrative example again, the drug’s pharmacodynamic MoA can be dissected. Excess levels of mineral corticosteroids lead to the retention of sodium and water, culminating in edema. Spironolactone acts mechanistically by competitively blocking aldosterone from binding to its receptors in the nephron’s late distal tubule and collecting duct, thus reducing sodium reuptake by obstructing the DNA expression of genes for sodium channels and pumps. This seemingly simple mechanism traverses at least three different levels of complexity, illuminating the multilayered nature of pharmacodynamics [67,70,71].

Pharmacokinetic MoAs are primarily productive chains often formulated mathematically, providing quantitative insights about various drug parameters such as half-life. In contrast, pharmacodynamic MoAs delve into the processes underlying higher-level physiological effects of the drug in question. These effects hinge on “reactions with and binding to cell constituents,” *i.e.*, lower-level processes responsible for the MoA’s operation. As will be elaborated in later sections, these mechanisms are best understood as combinations of producing and underlying mechanisms to fully comprehend these intricate interdependencies.

This brief exposition introduces the main theme that will be developed in the following sections. It acknowledges the multilevel nature of mechanisms investigated by biochemical scientists, and while the commonplace representation for MoAs is non-hierarchical, there lies a well-hidden multilevel picture beneath. As will be elaborated in the subsequent section, the key to transforming such flat pharmacological schemes to multilevel representations lies in recognizing that the arrows contained in traditional “box and arrow” diagrams denote different kinds of “being responsible for” relations. Upon disentangling these arrows, a

multilevel/multilayered representation of pharmacological MoAs, consisting of a variety of interconnected producing and underlying mechanisms, will naturally emerge.

2.5.2. Unraveling Arrows: Interpreting Pharmacological Diagrams

Standard diagrams utilized in pharmacology seek to encapsulate the vast complexity of various processes into easily digestible two-dimensional depictions, often consisting of numerous boxes and arrows. These boxes sometimes symbolize the mechanistic components involved, while the arrows suggest the presence of causal activities or interactions. This simplification can, however, mislead or obscure the true intricacies of the processes represented.

As an exemplification, consider the case of biosynthesis and the subsequent activity of the thyroid hormones triiodothyronine (T3) and thyroxine (T4) within the healthy human thyroid gland. This process is typically represented through a diagram, Figure 9, a common sight in current biochemistry or pharmacology textbooks. In these diagrams, several arrow types can be distinguished, each representing a different aspect of the process, such as producing, underlying and maintaining mechanisms, time flow, substance transfer, modificatory influences, and so forth.

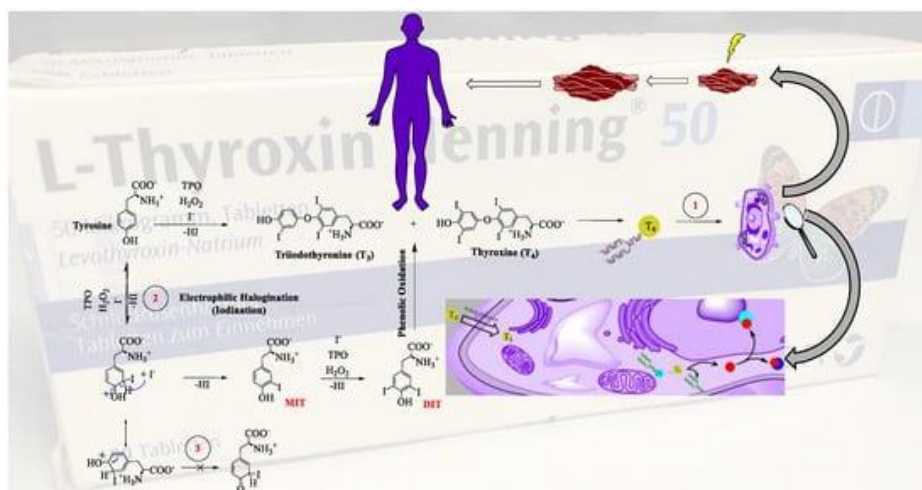


Figure 9. The biosynthesis of thyroid hormones and their impact on healthy muscle growth [67,73,74,74]. This scheme is adapted from two standard pharmacology textbooks, namely, Brenner and Stevens' Pharmacology 5th edition p. 368 and Basic & Clinical Pharmacology 14th edition p. 688, and purely for illustration purposes, has been expanded to include some additional formulae and conversions.

For the time being, the spotlight will be on identifying and differentiating the arrows that symbolize producing and underlying relations in Mechanisms of Action (MoAs). These two categories of arrows are essential for understanding the distinct mechanistic processes and

how they come together to produce or underlie the overall effect of a particular pharmacological interaction.

In the context of the new mechanist philosophy of science, the distinction between producing and underlying relations becomes particularly relevant. As previously mentioned, this perspective views mechanisms as inherently multileveled, each contributing different but interconnected functionalities to the system as a whole. Thus, flat diagrams with their boxes and arrows can be thought of as simplifications of this complex, hierarchical view of mechanisms.

The ‘box and arrow’ diagrams widely used in pharmacology are effective at providing an at-a-glance understanding of complex processes. To truly appreciate the complexity and interconnectedness of pharmacological mechanisms, however, one must delve deeper. This involves understanding that the arrows in these diagrams represent not just simple causality, but a whole array of relations, including producing and underlying mechanisms, time and transfer, amongst others.

Moving forward, the focus will be on unraveling this complexity, beginning with distinguishing between arrows indicating producing and underlying relations in MoAs. Understanding these relations is a crucial step toward a deeper insight into pharmacological mechanisms and their multileveled nature.

2.5.2.1. The Straight Arrow

In pharmacological depictions, the straight arrow or the forward arrow is among the most ubiquitous. Exhibiting an array of variations such as unidirectional or bidirectional, a solid line (a standard in chemistry) or a block arrow (a norm in biochemistry and physiology), these arrows generally point towards a causal relationship. Moreover, they frequently encapsulate supplemental information in or around them. The diagram in Figure 9 demonstrates this exhaustive utilization of various types of arrows. In this example, block arrows signify some form of linkage between biochemical and physiological systems, like the connection between the thyroid gland and the muscular system. Here, the nature of causality is complex and rather unclear, as the thyroid gland is certainly not directly “causing” the muscles; instead, certain processes within the thyroid gland are influencing processes within the muscular system (arrow tagged with 1 in Figure 9).

To elaborate, this type of arrow subtly communicates that the products created within the thyroid gland circulate and reach the muscles, where they modulate or govern muscle mass through intracellular modification. T3 and T4 hormones, being the intermediaries between these two organs, should be correctly positioned inside or adjacent to the arrow.

In the field of chemistry, the straight black arrow carries a different significance, connecting reactants of a chemical reaction with the corresponding products. This arrow delineates a causal relationship between chemical compounds, either unidirectional or in equilibrium, and links chemical symbols that usually—though not invariably—denote elements, ions, molecules, and the like. In Figure 9, such arrows link the representations of the reactants, tyrosine and iodine, with the ones for T3 and T4, and also encompass some information about the reaction conditions and products positioned next to them. These arrows represent a fundamental component of the chemical language [75]. Consequently, their usage adheres to a specific syntax and they represent chemical substances and observable events.

Beyond simple straight arrows, there also exist arrows that point towards products that are theoretically expected. Due to various reasons, however, these anticipated products may or may not be obtainable in a laboratory setting. A “crossed out” straight arrow emphasizes that the expected substance is not formed under the given reaction conditions, that is within the biological system. An example of this special case of a “crossed out” straight, producing arrow is tagged with 3 in Figure 9, where a theoretical or expected product is not achieved in the laboratory. Chemists tend to direct such a producing arrow towards a non-product, possibly to emphasize an element of surprise or the possibility that future endeavours may yield a different outcome.

2.5.2.2. **The Hidden and Transitional Arrows**

Within Figure 9, certain straight arrows can be noted which appear to direct attention towards the “intrinsic chemical reaction mechanism”. These straight arrows, at first glance, seem strikingly similar to those which link reactants or reagents and products. Within the confines of the reaction mechanism, however, they serve a distinct function by pointing towards a differing level of complexity. They might also indicate various chemical aspects such as intermediates, excited states or transition states. Such entities may correspond to tangible substances, or they may not, as suggested in the lower-left segment of Figure 9.

Indeed, when arrows connect depictions of compounds with transition states - states which fail to provide any identifiable components within mechanisms - they pose a challenge.

Transition states frequently remain purely hypothetical and resist further mechanistic decomposition given available technologies and the research traditions of chemistry. It is also impossible to tie them to any specific chemical compound or mechanistic component. A classic example of this is present in Figure 9, where the transition state follows tyrosine to generate monoiodothyrosine (MIT) (denoted by arrow number 2). This highlights the process of a chemical reaction, progressing from reactants through specific intermediate transition states, finally resulting in the products. In this instance, the direct arrow connecting tyrosine and iodine to T3 and T4 should be interpreted as a producing, causal relationship. By contrast, the arrow that travels through the intermediate and transition state encapsulates the intrinsic chemical mechanism.

Such representations are crucial within these schemes as they elucidate specific reactions and the pathways they follow. They also help in predicting the trajectory and progression of a chemical reaction, attempting to explain why certain products are formed while others are not. Interestingly, arrows which target transition states often penetrate the underlying mechanics of the reaction, thus moving into a separate layer within the multi-tiered scheme.

Interestingly, within the chemical reaction sequence depicted in Figure 9, one may identify several types of seemingly similar arrows. Early in their studies, students of biochemistry and related fields are educated to differentiate between straight black arrows and the rather unusual double-pointed arrows, which signify mesomerism. These arrows do not indicate causal, generative, or underlying relationships. The double-pointed straight arrows demonstrated in Figure 10, for example, show that perchlorate has four contributing structures, each resulting from a symmetrically delocalized electron pair [76].



Figure 10. Resonance structures of perchlorate (ClO_4^-) connected by arrows indicating mesomerism. The hooked arrows point towards “delocalized” electron pairs which are “moving” in the representation to generate four distinct structures. In contrast, this “movement” cannot be observed experimentally, as there is only one perchlorate molecule. The hooked arrows serve solely the purpose of explanation and to connect the four resonance structures required to describe perchlorate, its properties, acidity of perchloric acid, spectroscopy and reactivity more completely.

One can also uncover yet another arrow type within Figures 9 and 10, concealed within or adjacent to the chemical structures: the hooked arrow. This indicates the “movement” of an electron (single-headed hooked arrow) or an electron pair (double-headed hooked arrow),

either within a given molecule or between molecules. This type of arrow is frequently found in mesomeric structures and in reaction mechanisms.

The hooked arrow provides insight into the electronic movement or resonance involved in the chemical reaction mechanism, crafting a nested situation that parallels the one depicted in Figure 8. The arrows connecting mesomeric structures and transition states might be viewed as components within an intrinsic chemical reaction mechanism which progresses from reactants to products, indicating that they occupy the same layer. In contrast, the electron movement signified by the hooked arrow appears to underly these mechanisms, meaning they exist on the next lower level.

In the following section, we will elucidate that the mechanism underlying the intrinsic mechanism of the chemical reaction is believed to reside at the lowest level in the current case of T3 and T4. It is imperative to note, however, that this represents a practical choice within the realm of scientific practice in pharmacy rather than an ontological commitment. This approach is widely utilized within many practical illustrations (for instance, Figure 9). Nevertheless, the scheme can, in theory, be expanded further as we delve deeper into the mechanistic hierarchy, potentially reaching as far as protons, neutrons, electrons, and even quarks.

2.5.3. The Baumkuchen Model

Thus far, the discourse has illuminated that such conventional pharmacological diagrams, colloquially referred to as “box and arrow” diagrams, are inherently constituted by an assortment of diverse mechanisms. These mechanisms are represented within a “flat” or non-hierarchical scheme, characterizing a multitude of biochemical processes which traverse different investigative levels. To elucidate the potential ambiguities ensuing from such compression of a multi-level hierarchy into flat diagrams, a triad of tasks is necessitated [77]:

- A. Differentiation must be made among various levels or layers of analysis, from the “Resonance Level” of electron movements in molecules to the “Health Level” of medical conditions.
- B. Diverse types of mechanisms, especially those producing and underlying, must be distinguished.
- C. Clarification must be achieved regarding the various kinds of arrows and the relations of “responsible for” they portray.

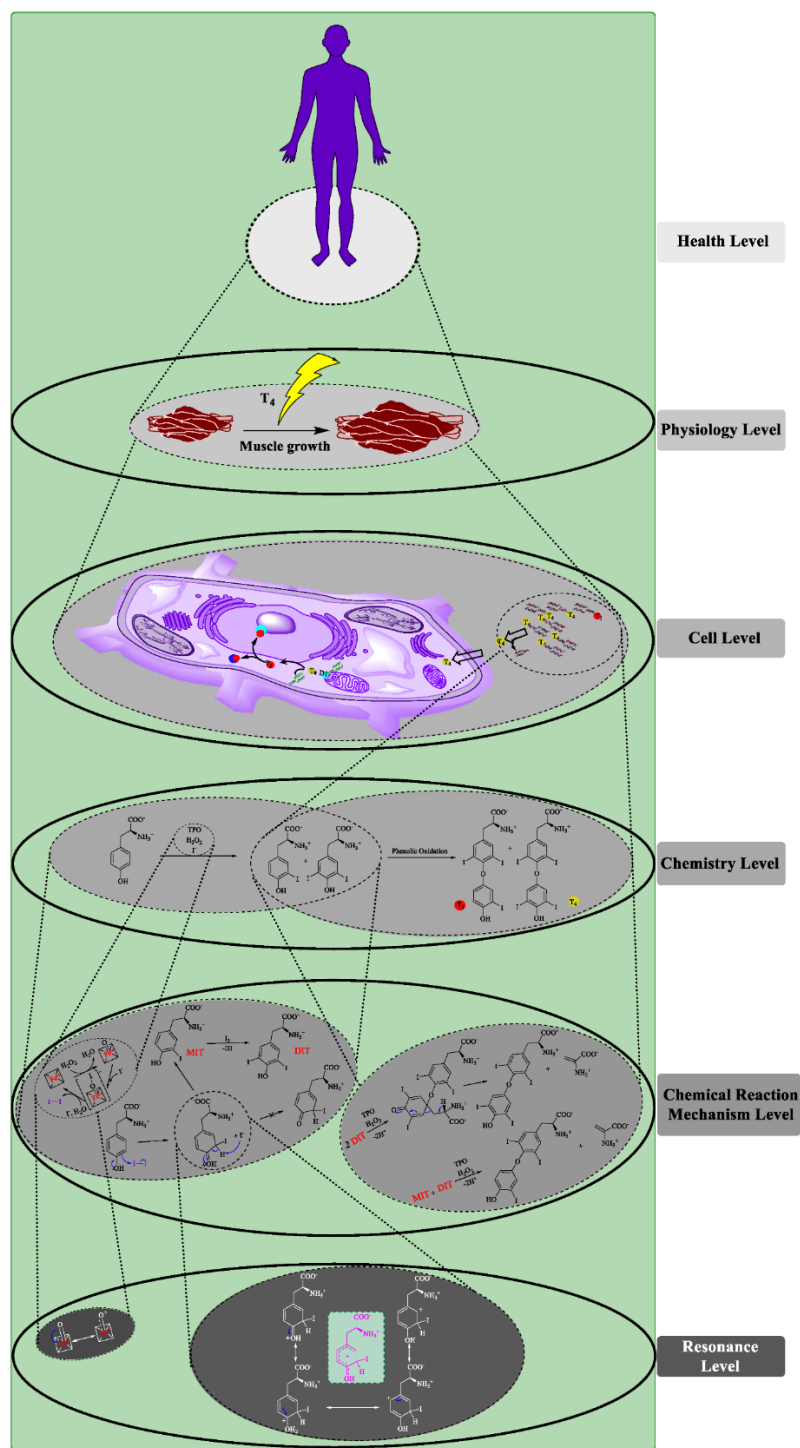


Figure 11. The Baumkuchen model of the initially “flat” biochemical scheme depicted in Figure 9. Here, the different layers are clearly separated. Producing mechanisms within layers are shown in straight arrows, and underlying mechanisms depicted with cones, similar to the model in Figure 8. As discussed before, the straight arrows within the same level represent causal relationships, while the inter-level constitutive relationships are represented with dotted lines. Hence, the Baumkuchen model avoids arrows between layers. If shown, these rather lines may serve as heuristic tools rather than indicators of interlevel causation.

Attentive adherence to these tasks allows the construction of a multi-layered Baumkuchen model from non-hierarchical pharmacological diagrams. This model serves as a practical and efficacious tool to delineate mechanisms of action (MoAs) in pharmacology. Figure 11

provides a Baumkuchen model of the biosynthesis of thyroid hormone and its operation in the human body [67,73,74,78–82]. As an enhanced and more precise iteration of Figure 9, the Baumkuchen model clearly segregates different layers, each coinciding with a unique scientific discipline. Within each layer, producing mechanisms are operational, and connections between different layers are facilitated by underlying mechanisms.

An instance of this is the arrow connecting monoiodothyrosine (MIT) and thyroid hormones T3 and T4 at the “Chemistry Level”, distinctly indicating a causal mechanism. Conversely, the apex of the cone stemming from T3 and T4 supports the formation of their biochemical complex with Thyroxine-binding globulin (TBG) in the bloodstream.

Importantly, effective clarification of various relations, symbolized by most of the straight black arrows in Figure 9, is achieved in the Baumkuchen model. Arrows representing producing relations are situated within each given layer, while those indicating constitutive relations, characteristic of underlying mechanisms, are superseded by cones. Upon closer examination of the Baumkuchen model, a stratified structure is revealed. The basal level comprises resonance or electron pair movements. These structures encompass moving electrons and hooked arrows, constituting the fundamental electronic mechanisms of the chemical reaction as it transits stepwise from reactants to products.

Ascending the Baumkuchen model in Figure 11, the second level houses the underlying reaction mechanism, explaining the chemical reaction itself and including the intermediate MIT. Advancing further, the third level, designated as the “Chemistry Level”, encapsulates the chemical reaction progressing from tyrosine and iodine to T3 and T4. At the next level, the “Cell Level”, illustrates how these hormones complexed with TBG (Thyroxine-binding globulin) interact with the cellular membrane and eventually enter the cell to bind to their cytoplasmic and nucleic targets and initiate a cellular response. The Physiological Level demonstrates how alterations on the Cellular Level instigate the muscle growth effect of T3 and T4. This tiered structure of the Baumkuchen model, spanning from electron movement to health level, affords a more detailed understanding of the interconnectedness of biological mechanisms, biochemical interactions, and physiological changes, culminating in health or disease states.

The Baumkuchen model, in comparison to traditional non-hierarchical models, boasts several advantages. It renders a richer and more accurate depiction of different dependency relations and permits researchers to delve into individual layers and concentrate on specific

aspects of the overall scenario. Despite its merits, the Baumkuchen model presents certain limitations. A few arrows and relations remain unidentified, clear allocation of all entities and activities at specific levels is not always possible, and determining the optimal level in each case is a challenge. Additionally, the integration of maintaining mechanisms into the Baumkuchen model remains unexplored. The Baumkuchen model transcends being a mere representation of mechanisms. It embodies a conceptual framework with profound philosophical implications, serving as an efficacious instrument for representing and comprehending the multilayered nature of biological phenomena and the various levels of mechanisms at work.

2.5.4. Concluding Remarks

The analysis undertaken in this section has illuminated the potential benefits of a meticulous dissection of the traditional “flat” pharmacological diagrams. The introduction of the Baumkuchen model, a derivative of concepts from the burgeoning mechanist philosophy of science, is presented as a robust alternative to conventional diagrams. The utility of this model lies in its ability to distinguish between multi- and interlevel-relations and clarify various associations inherent in the traditional “box and arrow” schemes.

The practicality of the Baumkuchen model is evident in its compatibility with familiar tools and resources, and its capacity for further development into interactive, electronic versions. Such a transformation of mechanistic representation, while building upon its “flat” predecessor, opens the potential for a more comprehensive communication of complex phenomena. Thus, it can be postulated that the adoption of multi-level Baumkuchen models may aid scientists in achieving a more profound understanding of how various MoAs interlink and provide direction for future research.

A note of caution must be, however, inserted here. The objective of this section is not to draw definitive metaphysical or ontological conclusions about the nature of the entities involved in the Baumkuchen model. A commitment to a form of realism is acknowledged, yet it is understood that empirical evidence may not definitively endorse one Baumkuchen model over another. The importance lies in the fact that even hypothetical or imprecise multi-level models can advance pharmaceutical research. Such multilevel depictions may begin by identifying a phenomenon and breaking it down into its constituting components and their interactions or find a component and link it to a function or purpose. These aspects of research strategies are explored further in the next section.

2.6. The Quest for Purpose: Research Strategies for Scientific Pursuit in Pharmacy

Historically, the discourse of scientific explanations has been punctuated by various paradigms, but two methodologies have often come to the fore: mechanistic explanations rooted in mechanical philosophy, and teleological explanations with a rich philosophical lineage [83]. Teleological explanations hark back to ancient times, with philosophers such as Aristotle positing which things in nature act towards a “purpose”, “telos” or “goal” [84]. Over the centuries, this concept has evolved and expanded, finding relevance in diverse fields from biology to psychology, albeit with varying degrees of endorsement and acceptance. It is this teleological perspective, intertwined with the mechanistic viewpoint, which will form the crux of the following exploration.

Often, research in biochemistry, and its offshoots such as pharmacology and toxicology, commences with a defined function. Scientists might, for instance, observe the conversion of light into energy by certain plants, the regulation of blood pressure, or the control of muscle growth in an organism, and strive to understand the mechanisms behind these phenomena. In all these scenarios, the scientific process flows from an explanandum—a phenomenon to be explained—towards its elucidation. Such inquiry typically involves dissecting the system under consideration, identifying the precise roles of its various components, and deciphering how they synergistically contribute to the phenomenon observed. The contours of this analysis may assume diverse forms and necessitate numerous iterations. The quintessential logic underpinning any version of this ‘downward-looking’ approach, however, can perhaps be encapsulated by the battle cry, “Divide and Conquer!” Researchers dissect the system into distinct units, each unit associated with a specific function [77,85]. As the following sections will emphasize, such methodological approach to research does not tell a full story and there are other relevant approaches scientists may apply in their pursuit of truth and knowledge generation. To demonstrate such a relationship, the enigmatic function of the metalloproteins, metallothionines (MTs), is explored.

In the following section, a brief introduction to the discovery and significance of MTs is presented. Section 2.6.2. delves into the features of initial MTs research and how it contrasts with prevailing research strategies in biochemistry and related disciplines, such as pharmacology, from a philosophy of science viewpoint. The aim is to systematically evaluate the research methodologies applied thus far and propose novel strategies based on the *status quo*. Section 2.6.3. discusses more recent research on vertebrate MTs and reviews specific

hypotheses about their potential biological functions. Section 2.6.4. proposes to change direction and explore alternative research strategies to comprehend MTs' biological and evolutionary roles, as supported by recent hypotheses in mollusk MT research. The aim is to open up new avenues for understanding the function(s) of MTs in vertebrates and beyond. Section 2.6.5. is a conclusion.

2.6.1. The Enigmatic Metallothionines

In the aftermath of the Second World War, an intense scientific interest was directed towards the metabolic pathways of various metals, prominently iron, zinc, and copper, in biological systems. Among the leading figures in this exploration was Dr. Bert Lester Vallee (1919—2010), who divided his time between Harvard Medical School and the Massachusetts Institute of Technology (MIT). Having obtained his medical degree from New York University in 1943, Vallee recognized the potential of spectroscopy for the detection of metals in biological systems [86].

Vallee, known for his intellect and rigorous questioning of assumptions, had already made significant contributions in the study of alcohol dehydrogenase (ADH), a zinc metalloenzyme [87]. In the 1950s, he encountered translated papers published in *Doklady Akademii Nauk SSSR*, the official journal of the USSR Academy of Science from 1941 and 1943, reporting the presence of cadmium in various biological systems, including Aspen trees, algae, marine species, amphibians, reptiles, and mammals [88]. Initial skepticism surrounded these findings, not least from Vallee himself. The issue lay with the fact that cadmium had yet to be demonstrated as an inherent component of a natural product [89]. Furthermore, the author, A.O. Vinar, lacked citations and relied on self-developed techniques to quantify cadmium in biological systems, a factor which cast doubt on the methodological rigor of the results and conclusions.

Despite these doubts and the inability to reproduce some of Vinar's findings (*e.g.*, inducing hypoglycemia in mammals following cadmium chloride (CdCl₂) injections), Vallee's curiosity was ignited [88]. He had been investigating the role of zinc in biological entities for several years, and given the chemical similarities between zinc and cadmium, he decided to embark on a similar exploration for potential cadmium proteins and enzymes and their metabolic roles [90].

Together with Marvin Margoshes (1926—2018), Vallee embarked on a study of kidney tissues from humans, horses, cows, hogs, and sheep. In 1957, they published findings

demonstrating the presence of cadmium in these species [89]. Further exploration of equine kidney cortex, which appeared to contain higher cadmium concentrations, led to the identification of a “[...] low molecular weight protein containing a small number of cadmium atoms” (1957, p. 4813) [89]. Despite the obscurity of its biological function and significance, this marked the advent of the discovery of metallothioneins (MTs).

The term “metallothionein” was first introduced in 1960, a descriptive label indicating the bond between a metal ion and thionine, a cysteine-rich apoprotein [91]. Unlike the functionally descriptive names, such as ADH discovered earlier, the term MT does not hint at the protein’s function rather points towards its chemical constitution [92]. While the function of MT remained elusive, this protein, nevertheless, became a focal point of an intensive and often contentious body of research since the 1960s [93–98].

Biochemically, MTs possess unique characteristics and are ubiquitous across taxonomic groups. Genetic data has identified 15 families of MTs in both mammalian and non-mammalian animal species, and four additional families in plant species [99,100]. These biochemical traits and their wide prevalence hint at their crucial roles in biology. Yet, even after more than six decades of discovery and extensive research into their structure, biochemical properties, and tissue distribution, MTs’ biological functions remain elusive [101,102].

2.6.2. Philosophical Lens on Metallothionein Research

In the forthcoming discourse, the underpinning methodologies within biochemistry are subjected to a critical evaluation, employing Vallee’s seminal research on metallothioneins (MTs) as the cornerstone. The methodological investigation orchestrates around three pivotal dichotomies: the distinction between an upward-looking research trajectory *versus* the reverse progression of downward-looking, intervention characterized by deliberate manipulations *versus* those involving mere interaction, and exploratory research as opposed to hypothesis-testing. Apparently, though typical biochemical research tends to prioritize hypothesis-testing, intervention-based and downward-looking strategies, the initial exploration into MTs, largely characterized by an upward-looking, exploratory, and interaction-based approach, offers an intriguing counter-narrative.

2.6.2.1. Upward-looking vs. Downward-looking

In many instances, scientific exploration proceeds *via* a ‘downward-looking’ approach. It must be noted, however, that such an approach is not the exclusive method of scientific

inquiry. Recent developments in the field of philosophy of discovery and pursuit have underlined that identifying the mechanism behind a particular phenomenon often requires the integration of ‘upward-looking’ research methodologies alongside the traditional ‘downward-looking’ ones [45,60,103], Figure 12. Simply put, the comprehensive understanding of a system does not solely arise from disassembling it and studying its individual parts in isolation. The contributions of individual components within the larger systemic context are also often examined.

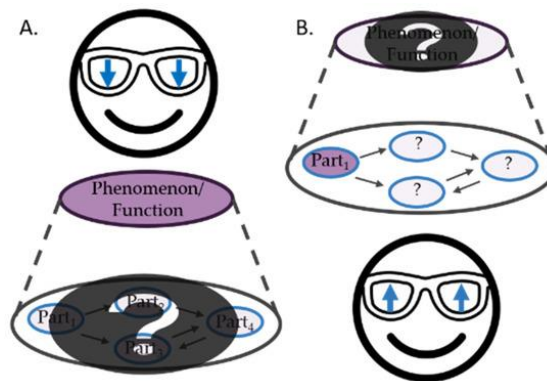


Figure 12. Illustrating the differences between upward looking and downward looking approaches to research. Tier A represents the downward looking approach, e.g., decomposition. Tier B represents the upward looking approach, e.g., composition or “re-composition”. Again, please note that the arrows represent causal relationships while interlevel constitutive relationships are conveyed with dotted lines.

Take hippocampal long-term potentiation (LTP) as an example. It is of interest not only to know that *N*-methyl-D-aspartate (NMDA) receptors play a role in LTP but also to discern *how* NMDA receptors contribute to LTP, their operational mechanisms, their triggers, and the impact on LTP in the absence of NMDA receptors. Consequently, even when starting with an explanandum, such as LTP, there may come a point where an upward-looking research focus on the component (NMDA receptor, in this case) becomes necessary.

To further illustrate, one may consider the case of penicillinase, which stemmed from a downward-looking research approach. About a decade after Alexander Fleming’s discovery of penicillin, the focus shifted towards deciphering antibiotic resistance observed in certain bacteria [104]. Researchers observed that penicillin would show a lower antimicrobial effect than usual when it was incubated with purified extracts from crushed penicillin-resistant *Escherichia coli* and then introduced to penicillin-sensitive bacterial cultures [105]. No such effect was observed when a similar extract was prepared and incubated with penicillin-sensitive *Staphylococcus aureus*. Subsequently in 1940, this led to the identification of an enzyme, penicillinase, deemed responsible for inactivating penicillin [106]. Further investigations were carried out to confirm different penicillin sensitivities due to the presence or absence of

penicillinase [107]. In essence, researchers initiated a downward-looking approach to identify *the cause* of penicillin resistance in bacteria, examining bacterial extracts and their molecular composition. Once they recognized penicillinase as a potential culprit, they evaluated the relevance of this specific enzyme employing an upward-looking experiment.

So, how does this relate to the case of MTs? The early research on MTs by Vallee, along with recent MT research to be discussed below, can be classified as upward-looking, since it begins with a molecule rather than a function to be elucidated¹⁴. This fact is of interest not because upward-looking research is seldom observed in biochemistry and related fields, but due to its predominance in MTs research. Interestingly, not all MTs identified to date have been discovered through an upward-looking research strategy. MT3 has been discovered following the observation that extracts from the brain cells of Alzheimer's disease patients supported the survival of rat neuronal cell cultures and has been initially dubbed as a growth inhibitory factor (GIF). Before delving into the nature and prospects of upward-looking research, it is useful to explore the two other distinctions which can offer insights into what differentiates Vallee's discovery of MTs from much biochemical research.

2.6.2.2. Interventions vs. Mere Interactions

Biochemical research carried out in the experimental realm is frequently defined by the concept of interventions. While this term is broadly employed in empirical sciences to denote any form of experimental manipulation, philosophers of science distinguish between various types of tactics. Specifically, the term 'intervention' is used to describe manipulations which systematically alter a certain factor x to induce changes in another y [108,109]. Such interventions could involve inhibiting or triggering the activity of a part of a system X , to observe how these changes impact the overall system behavior Y , or the reverse, a concept known as mutual manipulability [110]. Examples include investigating the impact of penicillinase on penicillin resistance, or the interference of damaged NMDA receptors with LTP. Such intervention-based experimentation manipulates certain variables to study the presence or absence of subsequent effects.

¹⁴ At first sight, it might seem that Vallee was adopting a downward-looking approach since he purposively tested for the presence of cadmium in the biology of different organisms. This might indeed be true. But then the question arises about which phenomenon was Vallee trying to dissect with this pursuit? He could have been looking for a protein which functions as a storage for cadmium such as ferritin for iron or ceruloplasmin for copper. Reading the initial literature published by Vallee on the topic it seems that he was conducting upward-looking, exploratory research and came across MTs with no initial expectations. Additionally, this initial publication does not refer to the idea of a storage protein.

Contrastingly, intervention-based research can be compared to experimental work involving mere interactions [59], Figure 13. Mere interactions represent an alternative form of experimental manipulation aimed at revealing structures and organization and disclosing features of a system without altering such features. Typical examples include the employment of staining techniques, fluid centrifugation, optogenetics, or spectroscopy. While these methods do indeed affect the system and change some aspects (*e.g.*, through staining or centrifuging), their application radically differs from interventions. Unlike interventions aimed at exploring the effects of specific manipulations on the system or its parts, mere interactions are utilized precisely due to their well-known effects, like attaching marker molecules to certain particles. Mere interactions do not aim to disrupt what a system or any of its parts is doing, but rather serve as advanced observation tools, aiding scientists uncover otherwise inaccessible features of a system or organism.

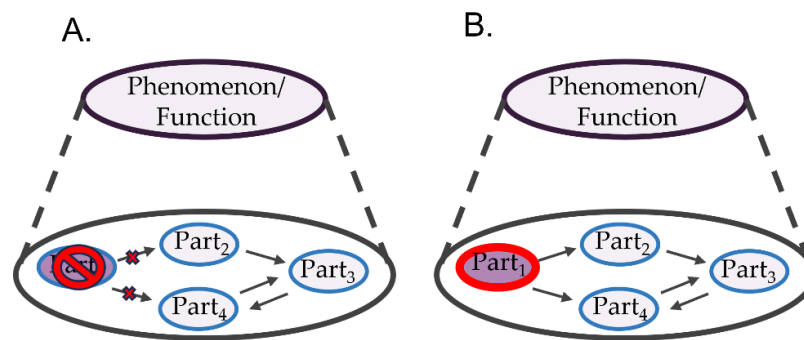


Figure 13. illustration of the differences between intervention and mere interaction approaches to research. Tier A represents the interventionist approach, *e.g.*, eliminating or knocking out a component and observing the changes in the system. Tier B, represents the mere interaction approach, *e.g.*, tagging the component of interest with a fluorescent dye.

Applying this distinction, it can be discerned that Vallee’s initial research on the kidneys of various species represented a case of mere interactions. There was no intention to alter the cadmium content of the tissues under study to understand what would occur if the cadmium content was increased or decreased. Instead, it was measured with the technology available. Furthermore, there was no alteration to the type of protein to which cadmium was bound. Its biochemical properties were analyzed through mere interactive experimentation. While Vallee’s initial mere interactions could be seen as a type of decomposition, they are not considered ‘downward-looking’ as there was no search for a component relevant to a specific *function* which demanded explanation.

2.2.3.3. Hypothesis-testing vs. Exploratory Research

Interventions, as previously outlined, are frequently employed to validate specific research hypotheses. If it is hypothesized that penicillinase holds a significant role in penicillin resistance, however, this hypothesis can be examined through an intervention. That is, by altering the presence of penicillinase and monitoring the resultant impact on penicillin resistance. Such an approach can be contrasted with exploratory research, that is, research not bound by testing hypotheses or theories. This form of exploration is commonly utilized to map a system's functional architecture without a preconceived theory, or to demarcate phenomena from their surrounding context [111–115]. Often, before a scientific theory or research tradition is established and specific hypotheses can be proposed, exploratory experimentation is the method chosen. Exploratory research could be considered prototypical in emerging research traditions.

While it may be tempting to associate exploratory research with mere interactions and juxtapose it with hypothesis-testing interventions, such a dichotomy would be too simplistic. Indeed, exploratory research can also incorporate interventions. Consider Hubel and Wiesel's systematic research on cat V1, for instance, or Charles Dufay's¹⁵ discovery of the “two electricities” (positive and negative) [116,117]. In parallel, hypothesis-testing research can employ mere interactions, for example, when hypothesizing about the presence of a chemical substance or a biomolecule in a sample, such as intracellular diagnostics which is a cell-based analytical technique utilizing simple systems for prescreening with dyes and/or antibodies [118,119].

To recap the terminology introduced: experiments can be either exploratory or devised to test particular hypotheses, they can employ interventions (to study the impacts of a manipulation) or mere interactions (manipulations to reveal certain structural features), and they can be downward-looking, *i.e.*, starting from a phenomenon and seeking what constitutes or produce it, or upward-looking, *i.e.*, examining the contribution of a component to a phenomenon or to the overall behavior of a system. It is essential to clarify that categorizations pertaining to these three aspects are independent. It is also noteworthy that exploratory research and experiments based on mere interactions are typically more prevalent at the initial stage of a research tradition, while intervention-based, hypothesis-testing research becomes more common as the research tradition matures and more results are available [118]. Thus, it is not

¹⁵ Charles François de Cisternay du Fay (1698-1739) is documented to be the first to identify the presence of two distinct electrical forms, termed as “vitreous” and “resinous” which were later recognized as positive and negative charges. He also differentiated between materials that could transfer electric charge upon touch and those that couldn't, labeling them 'electrics' and 'non-electrics' respectively.

surprising that the prevailing perception of biochemical research is that it concentrates on a downward-looking approach, employing interventions and hypothesis testing, since most of the scientific toil is rendered conspicuous and findings are shared and published once the research tradition has indeed matured.

In light of this, what do these insights reveal about MT research? Firstly, it has been noted that MT research is primarily an upward-looking investigation into the function of a biochemical component. While this approach may not align with the standard methods employed by scientists to determine the functions of molecules, it has proven to be a fruitful research strategy. Secondly, it can now be understood that Vallee's research was of an exploratory nature - he did not operate with any pre-established theories nor was he attempting to test any hypotheses. His methodology relied on mere interactions, such as spectroscopy. While these characteristics might seem peculiar in comparison to the wealth of published research in biochemistry, it is not surprising to find exploratory and mere interaction-based research at the commencement of a molecule's discovery, marking the start of a research tradition - in this case, the pursuit for the elusive function of MTs. The fact that Vallee later injected CdCl_2 into animals to examine its effects does not contradict this assertion; his initial research on MTs was undoubtedly exploratory and reliant on mere interactions. As will be discussed in the following section, MT research has evolved into a more hypothesis-testing and intervention-based research tradition since the 1960s. It has remained, however, to be heavily focused on upward-looking research.

2.6.3. A Function for Vertebrate MTs?

Even though MTs have been detected in a wide variety of organisms - encompassing numerous prokaryotes and nearly every eukaryote possessing genetic codes which encode MTs - it is mammalian MTs that have garnered the most scrutiny. The probable reason is that MTs were initially identified in mammalian tissues. Since the initial discovery of MTs, biochemistry has advanced significantly in terms of characterizing and categorizing vertebrate MTs. At present, we acknowledge MTs as metalloproteins with an unusually high sulfur content, specifically concentrated in 20 cysteine residues, thus enabling them to bind up to seven Zn^{2+} or Cd^{2+} ions, or 12 Cu^+ ions. The high negative charge of the distinctive metal-sulfur clusters, like the $\text{Zn}_4\text{Cys}_{11}$ - α -clusters and Zn_3Cys_9 - β -clusters in MT-1 and MT-2, is offset by seven lysine residues. This results in the unique dumbbell shape of MT proteins, differentiating them from a myriad of other biomolecules found in nature [120,121]. Documented are other primary

structures of MTs with varying Cys content and coordination, resulting in differences in metal load and affinities [122–124].

Within human cells, three distinct subfamilies have been identified, namely MT1/2, which are expressed and induced in nearly all cells, MT3 in the nervous system, and MT4 in squamous epithelia [125,126]. Further categorization through phylogenetic analysis identifies subgroups, for instance, m1P1 and m2P2 as subgroups of MT1 and MT2 respectively, in humans. These subgroups specify several human isoforms, such as MT1A and MT1B. On a genetic level, human MT1 and MT2 are less distinct than MT3 and MT4. Indeed, MT2 is a branch member of MT1, as depicted in Figure 14 [127]. Without delving too deep into particularities, it is notable that similar details about the biochemical properties and phylogenetic relations of MTs in other organisms have been firmly established (*e.g.*, [124]). Despite such comprehensive information, the phylogenetic tree of the MT family remains unrooted and our understanding of the function of MTs is still scant to date [100,126,128].

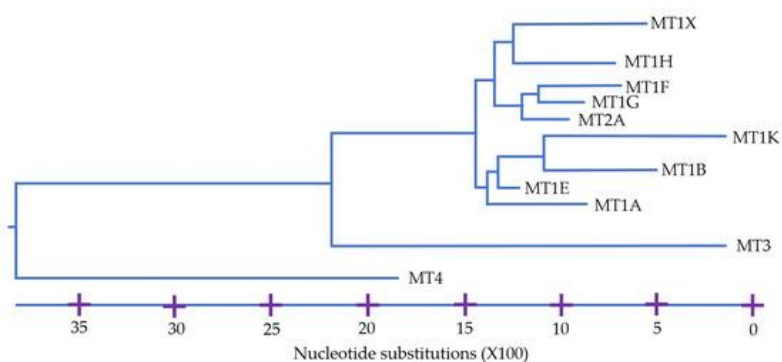


Figure 14. Phylogenetic tree of protein sequences of MT proteins found in humans. (Adapted from [127] p. 304).

Nevertheless, the broad prevalence of MTs across organisms and their unique biochemical characteristics imply that MTs fulfill, or have fulfilled, a crucial biological role(s). Recent studies indicate a divergence in the function(s) of MTs based on the type of cysteine motifs in invertebrates and vertebrates [122,129]. The newly identified γ domain in *Patellogastropoda*, for instance, exhibits preference for cadmium over zinc and demonstrates greater resilience against demetallation. Thus, the γ domain might hint at a specialized metal detoxification function in this natural group. It should also be recognized that a role for noncoordinating amino acids is emerging, as in the case of *Nerita peloronta* MT1 and MT2 (NpeMT1 and NpeMT2) [122,130]. While the evolutionary forces and progressions may be better understood in evolutionarily older and less complex organisms, the verdict is still pending concerning the precise function(s) of MTs and their evolutionary history (*e.g.*, [123,131]). This will be revisited in the following section. For now, we shall concentrate on the

function of MTs in mammals as this has been the primary focus of MT research since their unveiling in 1957.

Towards the end of the 20th century, research emphasized the reactivity and sensitivity of the cysteine ligands towards metalation, oxidation, and reduction, along with the associated physiological pathology in mammals [132–137]. Over the past six decades, three primary functions have been proposed for vertebrate MTs: (i) detoxification or metabolism of heavy metals, (ii) homeostasis or metabolism of essential metals, and (iii) oxidants scavengers or antioxidant protectants. The following sections shall briefly review these hypotheses and the principal research associated with them.

2.6.3.1. Detoxification or Metabolism of Heavy Metals

Historically, the earliest MTs have been extracted from horses which had been subjected to Cd²⁺ toxicity, subsequently laying the grounds for the hypothesis that MTs serve as detoxification agents for heavy metals. Mice lacking MTs have been reported to exhibit heightened sensitivity to tissue damage following cadmium administration, complementing other *in vivo* studies which have observed an upregulation of MTs in response to such exposure [138–140]. When a free Cd²⁺ ion intrudes into the cell, it dislodges zinc from the MTs, thereby elevating the intracellular concentration of free Zn²⁺. This released Zn²⁺ ion is then intercepted by a zinc-sensitive protein, specifically, the Metal Response Transcription Factor 1 (MTF-1), which subsequently translocates to the cell's nucleus.

Following this, the synthesis of thionine is initiated by a transcription promoter known as the Metal Response Element (MRE). The affinity exhibited by MTs towards various metal ions adheres to the binding constant of thiolates, which follows the order of Hg²⁺ > Cu⁺ > Cd²⁺ > Zn²⁺. In the scenario outlined, the surplus zinc that was liberated from the MT is then sequestered by the additionally induced thionine. Nevertheless, within the cell, MTs are predominantly coordinated with either zinc or copper, which are both essential and beneficial metals. As such, it is inferred that the association of MTs with cadmium and other heavy metals is likely a consequence of exposure to environmental factors¹⁶ [141].

Building on these foundations, it is important to consider how these interactions might impact various biological processes. The displacement of zinc by cadmium and the subsequent

¹⁶ It can be noted here that environmental could be considered as an indirect intervention. Interventions usually require an agent which intervenes. Human practices pollute the environment and, therefore, indirectly poison themselves with heavy metals.

rise in free intracellular zinc, for instance, may have broader implications for cellular homeostasis and signal transduction, given zinc's role as a signaling molecule. Moreover, the ability of MTs to sequester heavy metals such as cadmium, which are often toxic, can be seen as a form of cellular defense mechanism against environmental toxins. This is especially relevant in organisms that live in environments high in these heavy metals, and thus the role of MTs in these contexts would be a critical area for future research.

2.6.3.2. Homeostasis or Metabolism of Essential Metals

Predominantly, MTs examined in mammalian cells are found to be associated with zinc and copper ions. Both metals are pivotal for metabolic functions and despite their total intracellular concentration being in the micromolar range, their free ion intracellular concentrations are maintained in the picomolar range. Zinc plays multifaceted roles in biology, serving as a catalytic agent, a structural component, and a regulatory element. Notably, it acts as a cofactor for approximately 3000 human proteins [142,143].

Contrary to prior conceptions, which suggested that the metalation mechanism of MTs operated in a cooperative manner – the notion that the binding of a single zinc ion would subsequently facilitate the binding of another, and so forth, resulting in a dearth or instability of partially metalated MTs within the cell – accumulating evidence points towards a non-cooperative binding of metal ions by MTs [144]. This developing understanding of MTs and their uncooperative binding significantly shifts our perspective on the role of MTs in the metabolism of essential trace metals.

MTs are no longer seen merely as zinc reservoirs or thermodynamic sinks. Instead, they are increasingly viewed as active players in the regulation and cellular signaling pathways of zinc, thereby meticulously controlling its transient concentration as a protein buffer.

Expanding on this point, the role of MTs in homeostasis goes beyond buffering the transient concentration of zinc. In managing essential trace metals, MTs contribute to overall cell function and health. The copper ions associated with MTs, for instance, play significant roles in processes such as mitochondrial respiration and neurotransmitter synthesis, implying that MTs indirectly participate in these critical cellular processes. Furthermore, by ensuring the steady availability of these essential metals, MTs may aid in countering potential metal deficiencies or overload, thereby preventing metabolic disruptions which could otherwise lead to cell damage or death. As such, the role of MTs in essential metal metabolism underscores their significance in maintaining cellular balance and function.

2.6.3.3. Oxidants Scavengers or Antioxidant Protectants

The proposed antioxidant function of MTs emerges from their exceptional cysteine composition (30%), along with observations that oxidative stress (OS) also induces the upregulation of these proteins [127]. Studies conducted both *in-vitro* and *in-vivo* have evidenced that when subjected to hydrogen peroxide (H₂O₂) treatment, zinc associated MTs (ZnMTs) act as scavengers of free radicals, instigating the release of Zn²⁺ ions. These ions subsequently trigger the induction of highly reactive thionines and MTs *via* the Metal Response Element-binding Transcription Factor 1 (MTF-1) and Metal Response Element (MRE) respectively.

MTs are easily oxidized by reactive oxygen species (ROS), leading to their upregulation within the cell, an activity regulated by an antioxidant response element (ARE) and facilitated by an ARE-binding transcription factor [145]. The heightened expression of these proteins serves to alleviate reperfusion injury in myocardial tissues, highlighting their potential role in tissue recovery following stress or damage [146]. It has also been noted that MTs can inhibit the production of the copper induced hydroxyl radical (HO•), via the so-called Fenton-like reaction.

Extrapolating on this, the antioxidant function of MTs is of notable importance to cellular health and integrity. The rich cysteine content of MTs confers upon them the ability to neutralize harmful free radicals and mitigate oxidative stress, thereby protecting cells from potential damage and maintaining their functional state. Furthermore, the upregulation of MTs in response to oxidative stress underlines their essential role in the cellular defense system.

By inhibiting the production of HO•, MTs prevent these highly reactive entities from causing molecular damage which could disrupt cellular functions. This mechanism also points to the potential role of MTs in modulating the biological effects of copper, given that HO• is a byproduct of copper metabolism. The antioxidant properties of MTs, therefore, extend beyond mere scavenging activities directed towards free radicals or oxidants to include a role in metal metabolism and the modulation of metal-induced oxidative stress, further underscoring their multifaceted biological roles.

2.6.3.4. The Enigma Persists: *Quo Vadis?*

Despite the wealth of knowledge garnered from thousands of studies exploring the structural, biochemical features and tissue distributions of MTs, and even various hypotheses

around their potential functions in vertebrate and other organisms, the definitive role of the MT family remains a subject of intrigue and elusiveness [101,102].

Such a riddle naturally invites a query. Is there a systemic issue hindering progress in MT research? Several scholars have underlined the non-trivial experimental challenges that besiege MT research [93,144]. The application of X-ray diffraction, which has offered substantial insights into the dumbbell-shaped crystalline structure of MTs, for instance, is reported to encounter considerable obstacles. Hence, a substantial amount of structural data is gathered *via* Nuclear Magnetic Resonance (NMR) analyses, which shed light on the coordination of metal-thiolate ligands in the two functional domains, albeit without clarifying their interconnection and interaction [147–149].

Further complexity arises from the inherent characteristic of d^{10} metals, which are chromophorically silent in spectroscopic assays. This necessitates the substitution of zinc with cobalt as a spectroscopic probe when examining metal ion transfer [150]. Moreover, the *in vitro* analyses of MTs fail to consider the *in-vivo* heterogeneity of these proteins, especially their varying content and amount of metal ions. Furthermore, the structural models derived are typically based on a single isoform, namely, Zn_4Cys_{11} - α -clusters and Zn_3Cys_9 - β -clusters. It should be noted that MTs do not appear in an unbound, free form within the cell. They are either bond to a metal ion as discussed previously or to a cofactor to another molecule or molecules.

This landscape of experimental constraints might render it tempting to attribute the difficulty in “definitively” identifying the function of MTs to these limitations. It is important, however, to recognize that such constraints are hardly exclusive to MT research. Many empirical sciences grapples with the limitations of their experimental methodologies and tools yet continue to make substantial progress. Neuroscientists, for instance, routinely study the brain using a range of tools that have their own epistemic limitations, yet they still have a reasonably comprehensive understanding of the functions of various brain structures and molecules.

It could, therefore, be argued that while methodological limitations may impose certain challenges, they are unlikely to be the sole reason for our inability to definitively establish the functions of MTs. If the problem does not solely lie in the experimental methods, one might consider whether the issue is rooted in the nature of the experiments undertaken to identify MT functions. It seems that a focus on exploratory research and interactions is neither unusual nor

problematic for a phase of scientific inquiry that sets the stage for a new research tradition. And as depicted by recent MT research—as has been just outlined—progress has been made well beyond this initial phase, with the development of theories, proposal and testing of hypotheses, and implementation of interventions.

A critical examination of the trajectory of MT research may suggest a possible systemic issue arising from its predominant ‘bottom-up’ approach, that is, starting with a molecule and searching for its function rather than beginning with a function and identifying the relevant molecule(s) responsible for or underlying it. As we shall elaborate in the next section, however, this potential systemic problem is not as straightforward as it may initially appear.

2.6.4. Transcending One-to-one Mappings

Viewing this riddle through the lens of philosophy of science, the pursuit for a singular, definitive function of a biochemical molecule can seem overly simplified or idealized. The success of the upward-looking research strategy in associating particular molecules with specific functions does not necessarily guarantee similar results for the MT family. Each potential function proposed for MTs has seemed, at various times, a promising avenue of exploration [151].

Considering the lack of substantial progress, however, stemming from the assumption that MTs fulfill some form of uniform, evolved biological function, it appears that a change in research direction might be necessary. In the ensuing discourse, two alternative perspectives are proposed, both of which may facilitate fresh research agendas. It should be noted that although these proposals are predominantly drawn from research focusing on a phylogenetically recent branch of the MT family, specifically vertebrate MTs, and of course backed with philosophical considerations, recent investigations into invertebrate MTs seem to provide corroborative evidence for these proposed changes in perspective.

2.6.4.1. A Plethora of Functions?

As a starting position one may argue that MTs have no function at all or simply no specific function given the current evolutionary timepoint especially in vertebrate MTs. There might be organisms which can code for MTs but to serve no specific function rather MTs are evolutionary residues or vestiges from a common ancestor. Though this might not be necessarily true for all organisms, the evolutionary discussion below delves deeper into this matter. Subsequently, one might assume that MTs could be part of a mechanism which

constitutes a shared or a similar function. This would mean that the same or very similar function can be achieved with or without MTs. A third scenario might assume that MTs could serve a variety or multiple functions and, hence, be implicated in different mechanisms. Having no function or one singular function lacks scientific and philosophical consensus. In certain instances, MTs could indeed perform an essential biological function, but this function may not be unique to them. The same biological phenomenon could potentially be enacted by other biochemical entities. See Figure 15 for a summary of the different scenarios.

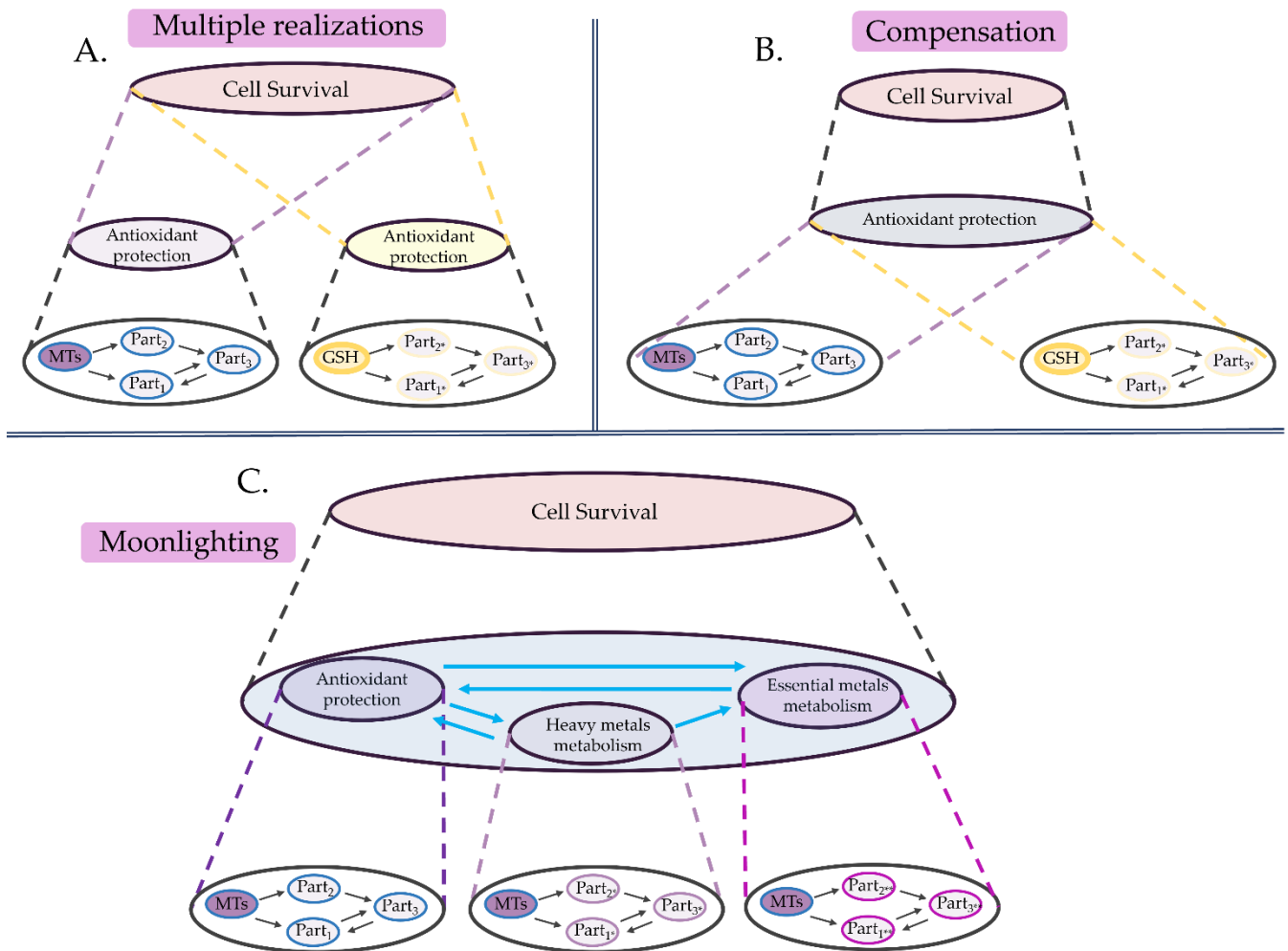


Figure 15. Different scenarios regarding the function of MTs in terms of their implications in mechanisms underlying cell survival. Tier A represents the scenario of *multiple realization* of a phenomenon. The same or similar phenomenon, e.g. antioxidant protection, underlined by a mechanism entailing MTs as a part, may be realized through multiple mechanisms such as the one entailing GSH. Tier B represents the scenario of *compensation* or *compensatory mechanisms*. Here, the same phenomenon, e.g. antioxidant protection, underlined by a mechanism entailing MTs may be compensated for by a different mechanism entailing GSH as a part. Tier C represents the scenario of *moonlighting*. MTs may moonlight different functions, e.g. antioxidant protection, heavy metals metabolism and essential metals metabolism, through different mechanisms or, in other word, be responsible for several phenomena constituting cell survival. Notice that each constituting mechanisms in which MTs are a part is indeed different as discussed in Section 2.6.3. In the antioxidant protection a part which is causally interacting with MTs is a radical, while a heavy or an essential metal in the others. The arrows and the dotted lines are intended to distinguish such causal and constitutive relationships.

As a case in point, consider the complexity of hemophilia. This debilitating condition is characterized by an abnormal blood clotting mechanism, leading to potentially fatal extended

bleeding. Notably, three distinct types of hemophilia have been identified, namely Hemophilia A, B, and C, each attributed to deficiencies in different clotting factors due to genetics, pregnancy, autoimmune diseases, or cancer. For a considerable period of time, the differentiation between these three types remained unrecognized [152]. In 1952, what is now known as Hemophilia B or Christmas disease, has been proposed [153]. The intriguing aspect of hemophilia is that not one, but three distinct biochemical factors may be a culprit, *i.e.*, responsible for inducing the delayed clotting resulting in extended bleeding which is characteristic to Hemophilia. This situation exemplifies a mapping from one phenomenon (a biological function) to multiple molecules which manifest that function, *i.e.* accounting to a case of *multiple realization*. In multiple realization very similar phenomena may be realized through different mechanisms, Figure 15, Tier A. If this concept is extended to MTs, it can be hypothesized that MTs might also be one of several realizers for one or more functions. This understanding could elucidate why the upward-looking research paradigm may have reached its limits in determining the role of MTs in biological organisms. It may, for instance, be possible that high(er) intracellular concentrations of Glutathione (GSH) override the impact of any other antioxidant activity within the cell, thereby rendering MTs irrelevant as an antioxidant protectant. Identification of different biochemical components associated with a single phenomenon necessitates understanding of the phenomenon in question, thereby requiring a shift towards a downward-looking research approach. It can be argued that while upward-looking research on MTs will continue to yield valuable insights, it may not lead to conclusive understanding of its function(s).

Another facet to consider is the possibility of *compensatory* mechanisms. If MTs are absent, their functions could be readily compensated for by other biochemical molecules or mechanisms. Here, compensation by a different mechanism would be responsible for the phenomenon in question, Figure 15, Tier B. Alternatively, MTs might themselves serve as a compensatory mechanism should other crucial structures or processes malfunction. Consider again the antioxidant function of MTs, GSH may compensate for the downregulation of MTs and through a different mechanism constitute the same phenomenon. The presence of such compensatory mechanisms is indeed plausible, considering the importance of redundancy and plasticity for the robustness of phenotypic traits which enable organism survival [154].

Moreover, a third possibility is that MTs, while appearing to be a unified family of proteins sharing a lot of biochemical traits, may *moonlight* various functions in different biological organisms, Figure 15, Tier C. As an analogy, Glyceraldehyde 3-phosphate

dehydrogenase (GAPDH) serves not only an enzymatic role in glycolysis but is also implicated in various non-metabolic functions [155,155–157]. The multifunctionality of MTs could indeed be a result of protein moonlighting, a phenomenon where biochemical entities acquire diverse functions through evolutionary processes [158,159]. Protein multifunctionality can depend on various factors, including intracellular or extracellular localization, cell type, substrate availability, quaternary structure, or interactions with other proteins to form more complex structures and multiplicity of binding sites [160]. If this holds true for MTs, then seeking a singular function is simply not a constructive research strategy. Instead, exploring the origins and evolutionary development of the MT family could be a more fruitful pursuit.

2.6.4.2. Rewinding the Evolutionary Track?

The second suite of suggestions to be presented draws its premise from this inquiry: Could the ubiquity of MTs be traced back not to their current biological function but rather to their evolutionary history? This brings into focus some evolutionary contemplations, Figure 16.

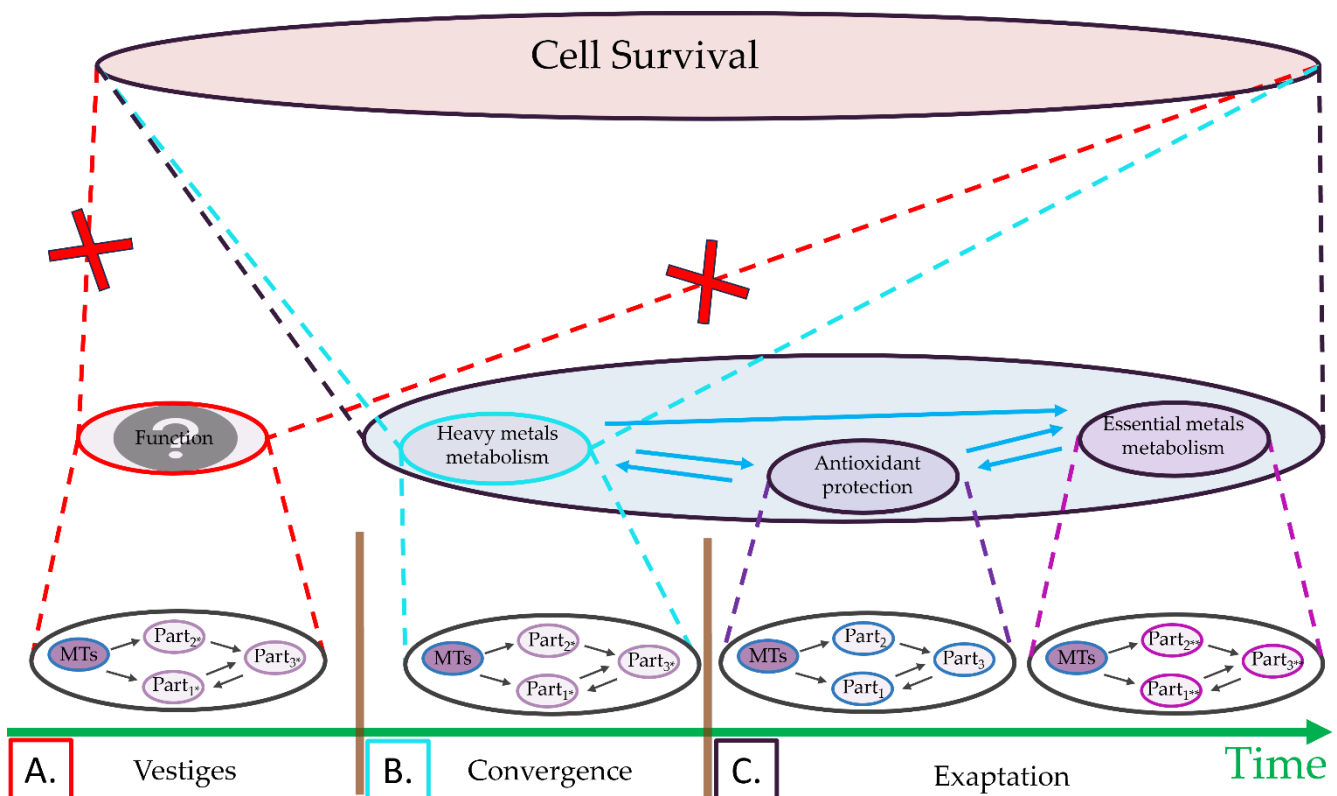


Figure 16. The different evolutionary scenarios given the function(s) of MTs with regard to cell survival. Tier A demonstrates the *vestiges* scenario. It assumes a common evolutionary root for the widespread of MTs and a function which is no longer required or needed for the survival of the organism. Tier B demonstrates the scenario of *convergence evolution*. MTs evolved individually in different organisms, with no common phylogenetic root, to serve different functions, e.g. heavy metals metabolism or detoxification. Tier C demonstrates the scenario of *exaptation*. MTs might have evolved to serve a specific function in an organism, e.g. heavy metals metabolism, which is no longer required. Therefore, species of the MT family managed to develop other role(s) in a mechanism(s) which constitute other function(s).

Initially, one might ponder if MTs could be *residues* or *vestiges* from the evolutionary past, no longer serving any discernible biological function. Given their widespread distribution across both animal and plant kingdoms, this would require an ancient common root in the phylogenetic tree of MTs, which currently remains vague, Figure 16, Tier A. An example of such vestigial molecular structures in humans can be seen in the cyritestin genes CYRN1 and CYRN2. These genes play a crucial role in fertility in other mammals, such as mice, but seem to be non-functional in humans [161–163]. Other more apparent vestigial structures in humans include the appendix and the tailbone, or coccyx. Alternatively, another theory which could be contemplated is that of *convergent evolution* for the MT family. This proposes that the same category of biochemical molecule could have evolved individually across diverse species to execute distinct yet possibly related functions. These functions might have a common feature related to metal metabolism, thus making these sulfur-rich metalloproteins suitable candidates for the tasks at hand. This scenario assumes no common phylogenetic root resulting in the wide spread of MTs but at least one past or current function, Figure 16, Tier B. Current studies on invertebrate MTs appear to corroborate this convergent evolutionary considerations [122,124,128].

Genetic and biochemical data derived from mollusks indicate that MTs may have had a pivotal role in metal detoxification during early evolutionary stages. In later stages, as organisms adapted to increasingly variable environments, MTs might have evolved to play a role in maintaining homeostasis of essential metals [164–167]. The capacity of MTs to alter in response to environmental factors and the resultant various forms could have been instrumental for organisms adapting to fluctuating levels of metal bioavailability.

These insights, however, are still insufficient to understand the evolution of MTs completely. The relevance and applicability of such findings about invertebrate MTs to vertebrate research is unclear. The evidence gathered thus far does not conclusively favor either of the hypotheses of vertebrate MTs being vestiges of an invertebrate evolutionary past or a product of convergent evolution prompted by adaptation needs. The construction of a comprehensive phylogenetic tree for the MT family might aid in disentangling these scenarios, but again, it is not currently available [101,129,168].

Exaptation is a concept which suggests that a function of a molecule may change during evolution. Consequently, a biochemically united family of MTs could now be performing varied functions across different species or organisms through different mechanisms, Figure

16, Tier C. This notion is echoed in rigorous research conducted on mollusk MTs as being initially utilized for detoxification before becoming vital for essential metals homeostasis [122]. This proposition is arguably the most encouraging among the evolutionary approaches discussed here. It does not necessarily require a common phylogenetic root and aligns well with the multiple functionalities attributed to MTs and the concept of moonlighting. This scenario also offers an evolutionary explanation for the common biochemistry amid the diverse functionality within the MT family without assuming a common evolutionary root.

It should be noted that these proposed scenarios may not be mutually exclusive. It is plausible that MTs first emerged independently, underwent convergent evolution to serve a common or similar function, and subsequently exapted to different functions across species or organisms under varying evolutionary pressures. This theoretical scenario is supported by the most recent data on mollusk MTs, indicating that exploring lineage-specific and evolutionarily old functions of MTs could shed light on their ancient roles, as well as, their current prevalence and function across animal phyla, including evolutionarily younger and more complex organisms such as vertebrates. Hence, shifting the focus of MTs research towards investigating their evolutionary history promises a potentially fruitful perspective.

2.6.5. Concluding Remarks

The pervasiveness of MTs across numerous species instigated research into their biological role. Yet, prevalence need not solely signify current function; evolutionary origins might elucidate ubiquity. Shifting focus to MTs' evolutionary trajectory may yield significant insights and embody a promising research strategy (*e.g.*, [14,169]). While the hypotheses articulated previously lack comprehensive theories of vertebrate MT function, they offer fertile ground for investigation. Vallee's initial upward-looking approach is neither inherently ineffective nor flawed. Progress in MT research, however, is less than anticipated, warranting reorientation. In line with recent mollusk MT studies, the hypotheses proposed reinforce the value of systematic philosophical analysis of empirical research and of evolutionary MT research. Such an approach may elucidate MTs' prevalence, functions, and origins across phyla.

Furthermore, the tripartite research strategy distinctions introduced here, *i.e.*, between upward-looking *versus* downward-looking research, intervention *versus* mere interaction, and exploratory research *versus* hypothesis-testing, enriches the comprehension of scientific practice and pursuit. This framework delineates the research focus either towards functions or mechanisms, the approach to empirical engagement whether manipulative or observational,

and the mode of inquiry if open-ended or confirmatory. These distinctions are complementary, rather than mutually exclusive, diversifying the biochemical research process according to the specific question and context. By promoting flexibility and adaptability in scientific inquiry, these distinctions can navigate the multifaceted landscape of scientific pursuit, creating opportunities for innovative theoretical and empirical advancements. The subsequent section represents yet another avenue in which combining philosophical considerations with actual scientific practice in pharmacy may yield tremendous benefit and aid in solving persistent problems related to causal inference.

2.7. Bridging Philosophy and Pharmacovigilance: Deciphering Rare Drug Reactions

Unraveling the causal fabric of the world is crucial in addressing various complex questions, prominently within the realm of healthcare. Decision-making processes tied to therapeutic strategies hinge significantly on understanding the associated with risks and benefits of specific treatments. While statistical approaches are proficient in data amalgamation and integration, their efficiency wanes when faced with basic scientific results or mechanistic evidence which does not conform to neatly constructed datasets detailing patient health outcomes.

This section delves into a deep investigation of so-called “E-Synthesis”, an emerging methodology with its foundations in Bayesian principles [170,171]. E-Synthesis is a computational tool, implementing a Bayesian framework, to efficiently consolidates various forms of evidence (including epidemiological research, molecular biology insights, and individual case studies). This tool is employed in the critical evaluation of medical causal hypotheses, with particular emphasis on the integration of mechanistic evidence [172]. This aggregated evidence then reaches the essential threshold necessary to determine whether a specific drug should be introduced or removed from the market. E-Synthesis has been specifically devised to assess hypotheses pertaining to drug-induced harm.

The discourse exploits a recent issue in drug licensing as an illustrative example. The focal point is the hypothesis that the widely prescribed antibiotic amoxicillin (AMX) may trigger a potentially severe condition known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). The goal is to underscore the methodological advancements and associated challenges in incorporating mechanistic evidence to guide decisions in real-world situations, thus contributing to the ongoing conversation among scientists and methodologists.

Accepted standards for drug benefit evaluation are largely based on statistical analyses of population-level clinical studies, particularly randomized controlled trials (RCTs). The protocols for post-marketing evaluation of drug-induced harm, also known as pharmacovigilance, are, however, less well-defined [173–176]. Additionally, certain Adverse Drug Reactions (ADRs) might escape detection via statistical analysis of RCTs due to their belated manifestation, extreme rarity, and grave consequences [177,178]. Therefore, the significance of considering non-interventional studies in drug safety assessments, despite their susceptibility to biases and confounding factors, and the integration of mechanistic evidence,

notwithstanding potential translational obstacles from the laboratory to real-world human applications, cannot be overstated [179].

Thus, this section seeks to highlight the potential role of philosophical tools in offering a unique and valuable lens through which to view pharmacovigilance and post-market surveillance of ADRs, especially those rare and inaccessible to randomized evidence. The overarching objective is to offer insights into how philosophical perspectives can assist in navigating the complex domain of drug safety assessment in real-world contexts.

2.7.1. E-Synthesis: A Methodology for Causal Inference

The lifecycle of a drug, starting from its discovery, through its clinical development phase, and well into its post-marketing stage, necessitates constant reassessment and recalibration of the risk-benefit profile. Any potential harm, in the form of adverse drug reactions, or an increase in the monetary cost associated with the drug, must be weighed against the expected benefits which it offers. If the balance leans towards the benefits, then continued research, market circulation, and development are indeed warranted. Conversely, if the harm and costs surpass the benefits, it may signal the need to reduce research efforts or consider (partial) market withdrawal. This approach is indeed very utilitarian as it focuses on maximizing the benefit and ceasing further action harms increase.

As drugs proceed through their lifecycle, the causal relationship between the drugs and potential harm becomes increasingly solidified through gathering and examining diverse post-market entry evidence. Detecting and anticipating such harmful *causal* relationships early on may help mitigate risk to exposed individuals, thereby underscoring the importance of basing decisions concerning drugs - including approval, suspension, and withdrawal - on the entirety of evidence available at any given time. Occasionally, decisions must be made based on what may currently be perceived as weak evidence, such as basic science studies or mechanistic evidence.

At present, the European Medicines Agency (EMA) relies primarily on narrative reviews for their assessments, which unfortunately do not formally incorporate basic science studies. Fundamental scientific investigations, often characterized as basic science studies or preclinical research, serve the function of illuminating the inherent principles of the natural world. Within a medical framework, such studies often employ laboratory experimentation, cellular or molecular level research, and animal testing in an effort to explicate biological and physiological operations. These primary scientific studies, while pivotal in spearheading

medical knowledge, exhibit innate limitations when it comes to clinical applicability, attributable to their specific design and focus. Firstly, they circumvent the direct involvement of human subjects, consequently circumscribing the generalizability of their findings to human health and pathology. The disparities in genetic, biological, and environmental factors result in the physiological responses and pathological processes in model organisms not being an exact representation of those in humans.

Furthermore, existing formal statistical tools also struggle to incorporate heterogeneous data from various sources, qualities, and differing degrees of external validity. While effective tools for systematic reviews and meta-analyses have been developed to assess the intended effects of interventions, their adaptation for evaluating the safety of health technologies, *e.g.* drugs, often runs into problems due to the scarcity, heterogeneity, and fragility of data concerning unintended effects or side effects of medical treatments.

E-Synthesis has been conceived out of the need for an effective tool to synthesize or aggregate diverse sources of evidence for the assessment of causal associations between drugs and harm at any given time. Its theoretical framework provides the basis for probabilistic confirmation of causal hypotheses, based on all available evidence. Using a Bayesian epistemic network¹⁷ which incorporates the Bradford Hill guidelines as indicators of causality, E-Synthesis quantifies the degree of support provided by the evidence available to the causal hypothesis in question [180,181]. While it is predominantly used during the post-marketing phase, it is versatile enough to provide constant monitoring and updating of a drug's benefit-harm profile.

Bradford Hill guidelines, also known as the Bradford Hill criteria or Hill's criteria for causation, are a group of minimal conditions or indicators necessary to establish a causal relationship between two items. They have been first outlined by the English epidemiologist Sir Austin Bradford Hill (1897—1991) in 1965. The guidelines include nine criteria: strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy. Despite criticisms, the Bradford Hill guidelines remain a rich source of inspiration for causal assessments of harm. E-Synthesis incorporates these guidelines because they allow to track the increased plausibility of causation as different types of evidence

¹⁷ Bayesian networks provide a convenient tool to graphically display and reason with probability functions which allow to specify and read-off conditional independencies from a graph. Formally, a Bayesian network is built up on several pairwise different propositional variables which form the nodes of a graph.

accumulate. Not all criteria are treated equally within E-Synthesis; for example, Bradford Hill's criterion *experiment* is accorded the most inferential weight [182–186].

The Bayesian epistemological foundation of E-Synthesis is based on a philosophical approach to rational beliefs in hypotheses which represent uncertainties in the form of probability functions [39,187,188]. Bayes' Theorem is applied to determine the conditional posterior probability of the hypothesis being true - in our case, this hypothesis is that AMX causes DRESS. The theorem exploits prior probabilities and likelihoods to calculate the posterior probability of the hypothesis given the evidence as follows:

$$P(\textcircled{C}|\varepsilon) = \frac{P(\textcircled{C}) * P(\varepsilon|\textcircled{C})}{P(\textcircled{C}) * P(\varepsilon|\textcircled{C}) + \sum_{i=2}^N P(H_i) * P(\varepsilon|H_i)}$$

Where \textcircled{C} represents the hypothesis of interest, ε is all the available evidence supporting the hypothesis and H_i any hypothesis other than \textcircled{C} or simply not \textcircled{C} . $P(\textcircled{C}|\varepsilon)$ represents the probability of \textcircled{C} holding given the available evidence ε and $P(\varepsilon|H_i)$ being the probability of the available evidence holding given any other hypothesis which also denotes the likelihood¹⁸ of \textcircled{C} .

This holistic approach offers an effective solution for managing the complexities and uncertainties which arise in the evaluation of causal associations between drugs and harm, providing a necessary tool for continuous assessment and management of a drug's risk-benefit profile. Here, it should be noted that the conception of mechanisms discussed earlier is indeed essential in the ensuing discussion. Scientific practice in pharmacy is nested within a mechanistic paradigm. Yet, the causality discussed above strictly relates to single level causation, *i.e.* producing mechanisms. The interlevel relationships as has been discussed in the Baumkuchen Model are strictly interlevel constitution, *i.e.* underlying mechanisms. In the case of E-Synthesis, the causal inference between a drug and an adverse drug reaction is probabilistic and can be quantified based on augmenting and synthesizing different types of scientific evidence, one of which is mechanistic evidence. Here, if \textcircled{C} is corroborated with enough evidence, then it would be assigned the highest probability and subsequently represent the candidate with the highest problem-solving adequacy. The likelihood of \textcircled{C} holding can also be calculated and this would allow the researcher to discern whether \textcircled{C} is beneficial or not.

¹⁸ Probability is used to make predictions about future events, whereas likelihood is used to estimate unknown parameters based on seen evidence.

2.7.2. Amoxicillin and DRESS: The Case Study

The association between Amoxicillin (AMX) and the Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome (DRESS) is not straightforward. AMX, being recognized as a vital and indispensable medication by the World Health Organization, plays a crucial role in combating a multitude of infections [189]. Conversely, DRESS represents a severe, potentially fatal, adverse drug reaction (ADR). The intricacy lies in evaluating the conjectural causal connection linking the administration of AMX and the emergence of DRESS. This analysis, inherently complicated, demands careful and rigorous examination.

2.7.2.1. AMX

Amoxicillin (AMX) is a semi-synthetic, broad-spectrum β -lactam antibiotic, classified under the Penicillin antibiotic group [190]. Characterized by its small molecular size (< 900 Daltons), it demonstrates high bioavailability upon oral administration. Its side chain, the β -lactam ring, is known for its susceptibility to nucleophilic opening, thus heightening its tendency for serum protein binding and drug-protein conjugate (hapten) formation [191,192]. Human Serum Albumin (HSA) is its primary documented binding protein in the bloodstream [193].

Discovered in 1958, AMX's advantageous properties were first widely recognized following its initial distribution by Beecham in the UK in 1972, and its replacement of the increasingly resistance-prone ampicillin in the early 1980s [194]. By 2014, data showed that approximately 13.0 million prescriptions were written for AMX in England, with the United States recording a significantly higher figure of 54.8 million prescriptions the following year [195,196].

Valued for its safety, efficacy, and cost-effectiveness, AMX has consistently been listed among the World Health Organization's essential medicines since 1990. It is viewed as a vital resource, integral to public health and community wellbeing. The American Academy of Pediatrics recommends AMX as the first line of treatment for acute bacterial sinusitis in children aged 1-18 years, with the American Academy of Family Physicians also endorsing its use for Otitis Media [197]. AMX is also indicated for a variety of conditions such as streptococcal pharyngitis, pneumonia, bronchitis, endocarditis, listerial meningitis, urinary tract infections and gonorrhoea [198].

2.7.2.2. DRESS

Drug Reaction with Eosinophilia and Systematic Symptoms (DRESS), also known as Drug-induced Hypersensitivity Syndrome (DiHS) or Hypersensitivity Syndrome (HHS), is a Type IVb Severe Cutaneous Adverse Reaction (SCAR) that can potentially be life-threatening, with a mortality rate of approximately 10% [199]. DRESS is differentiated from other SCARs due to the unique immunological components involved and the resulting signs and symptoms.

DRESS is a nonimmediate (2-6 weeks), T-cell mediated allergic reaction that provokes a Th2 (IL-4 and IL-5) response, resulting in eosinophilic inflammation [200]. This mechanism helps explain the severe symptoms associated with DRESS, including a general maculopapular rash, lymphadenopathy, fever, blood abnormalities such as atypical lymphocytosis and eosinophilia, and the pathological involvement of internal organs, for instance, the liver, kidney, or lungs, which are usually inflamed [201,202].

Two diagnostic guidelines for DRESS exist, both emphasizing the administration of a potentially offending drug and the delayed hypersensitivity reaction which follows. The list of drugs implicated in DRESS is continually revised due to the complex nature of the cause/effect relationship. A study, RegiSCAR, carried out over six years (2003-2009) across a network of hospitals in eight countries (Austria, England, France, Germany, Israel, Italy, Taiwan, and the Netherlands), involving over 120 million people, was successful in definitively diagnosing only 59 DRESS cases, with another 59 deemed probable [202].

DRESS is, therefore, a serious, yet relatively infrequent condition, with most of the current knowledge base assembled from retrospective analysis of case studies. A closer look at its pathology in terms of mechanistic evidence, however, might disclose a link between DRESS and AMX.

2.7.2.3. Laying out the Mechanistic Hypotheses

The current body of knowledge does not conclusively support or refute the hypothesized causal link between AMX and DRESS. The RegiSCAR study, for instance, identified only a single case where AMX was deemed a “probable cause” of DRESS [202]. Thus, only a minuscule fraction, if any, of the population exhibit DRESS post-AMX administration. This makes sufficiently powered randomized controlled trials indeed unfeasible. Some studies have proposed that AMX could act as a significant exacerbating factor

of DRESS, rather than being a direct cause. This calls for a deeper examination of mechanistic evidence to affirm or dismiss this supposed cause-effect relationship.

There exist three primary hypotheses concerning the mechanism linking AMX to DRESS. The first hypothesis posits that aberrant pharmacokinetics, specifically at the metabolism stage, could lead to elevated blood levels of the drugs or their metabolites and/or a prolonged half-life due to altered activity of liver metabolizing enzymes [203]. This unexpected spike in concentration and/or persistence in the body could facilitate interaction with immunological components, ultimately leading to DRESS. This hypothesis overlooks the role of immunological predispositions, viewing DRESS as a direct consequence of inefficient drug absorption, distribution, metabolism, or excretion (ADME). Given the delayed onset and rarity of DRESS, both genetic predisposition and the T-cell mediated pathway should be integral to any hypothesis. Thus, this abnormal pharmacokinetics hypothesis is somewhat limited and speculative and will not evaluate it further.

The second and third hypotheses tackle DRESS development by considering the inherent characteristics of drug/metabolite molecules, whilst also emphasizing the role of hereditary immunological predispositions. The hapten hypothesis suggests that small drug/metabolite molecules are not recognizable by the immune system independently. Thus, to induce stimulation, they must form irreversible conjugates with larger proteins. This hapten (drug + protein) is then processed by an accessory cell (such as a dendritic cell or macrophages), which presents the resulting antigen to an appropriate T-cell receptor [204]. Alternatively, the Pharmacological Interaction Hypothesis (p-i hypothesis) proposes that drug/metabolite molecules can directly bind to a Human Leukocyte Antigen (HLA) and/or a T-cell receptor, triggering an immune response. Unlike the hapten hypothesis, here, it is hypothesized that a drug/metabolite can bind to a pharmacological receptor, regardless of the presence of a carrier [191,204,205]. As both these hypotheses consider the genetic and immunological factors essential for causation of DRESS, they have been selected for further evaluation in the following section.

Before going into the specifics of each hypothesis, it is vital to acknowledge that both are derived and reached through analogical reasoning from known mechanisms for SCARs (Severe Cutaneous Adverse Reactions) induced by other drugs. This reasoning can be outlined as follows: Drug X is established to cause SCAR *via* causative mechanism(s) or pathway(s), *P_i*. DRESS is a type of SCAR. AMX is established to induce DRESS-like symptoms and shares

certain chemical characteristics with Drug X. Therefore, AMX induces DRESS via one or more pathways. Analogy is utilized at several stages in this inferential process, particularly in the chemical similarity between AMX and Drug X and in AMX inducing DRESS via certain pathways. This highlights similarity of symptom and structural/functional resemblances between AMX and other SCAR-inducing drugs. Moreover, grouping DRESS with SCARs is a form of analogical reasoning since the overarching class of SCARs may not exhibit identical biological features to DRESS.

An instance of such reasoning is the association of flucloxacillin, a β -lactam penicillin like AMX, with hypersensitivity reactions. Research into the pathological pathways underlying delayed allergic reactions induced by flucloxacillin revealed intriguing results: in genetically predisposed individuals, flucloxacillin caused drug hypersensitivity-induced liver injury (hepatitis). To determine whether this hypersensitivity arises in alignment with the hapten hypothesis or the P-i concept, researchers acquired flucloxacillin-sensitized T-cells and HLA-B57:01 molecules from healthy donors. They observed a dual T-cell activation, consistent with both the hapten hypothesis (irreversible binding of flucloxacillin to human leukocyte antigen molecules) and the p-i hypothesis (direct binding to HLA-B57:01) [206,207].

Interestingly, the same human leukocyte antigen (HLA) haplotype has been linked to the development of another drug hypersensitivity reaction associated with the antiviral drug abacavir, which is listed as a DRESS-inducing drug [35, 36]. Also, the molecular characteristics of other β -lactams have been associated with other SCARs, such as the association of the same HLA with flucloxacillin and abacavir-induced DRESS. These examples demonstrate that drugs can provoke hypersensitivity reactions via either pathway. The hypothesis that AMX causes DRESS could be strengthened if either of the pathways is established, and even more so if both

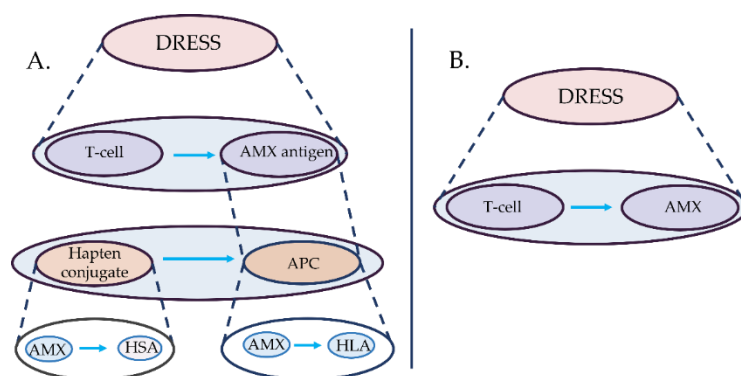


Figure 17. The two mechanisms proposed in which AMX may be responsible for instigating DRESS. Tier A demonstrates the Hapten hypothesis, while Tier B the Pi-hypothesis. AMX is amoxicillin, HSA is human serum albumin, APC is antigen presenting cell and DRESS is drug reaction with eosinophilia and systemic symptoms. (Please note that this is a simplified representation of the mechanism in which AMX would be responsible for eliciting DRESS).

are confirmed (they represent alternative non-exclusive mechanisms by which AMX could induce DRESS).

Hence, the salient features of the two proposed mechanisms which relate them to the available evidence can be detailed as follows: Firstly, the Hapten Hypothesis. AMX/metabolite forms an irreversible bond with a bloodstream carrier protein (primarily HSA), forming a “hapten conjugate” [208–210]. An Antigen Presenting Cell (APC) internalizes the hapten conjugate, which is then processed by a specific HLA haplotype [211]. The hapten conjugate’s processing by the specific HLA results in the creation of a respective “antigen” [211,212]. A T-cell recognizes the antigen presented on the APC’s cell membrane and binds to its receptor, stimulating an immune response eventually manifesting as DRESS, Figure 17, Tier A. Secondly, the P-i Hypothesis. AMX/metabolite binds directly and reversibly to a T-cell receptor. The activated T-cell stimulates an immune response (DRESS) Figure 17, Tier B.

2.7.3. AMX Causing DRESS?

To determine the ‘likelihood’ of AMX inducing DRESS the Bayes’ theorem is applied. To make this task manageable, the application of abstract indicators of causality based on Bradford Hill’s criteria is proposed. A philosophical dissection of the prevalent theories of causation, in conjunction with the Bradford Hill Guidelines, results in the isolation of six relevant causal indicators: strength of association, consistency, biological gradient, coherence, temporality, and plausibility [180]. In essence, these indicators function as testable (probabilistic) outcomes of the hypothesis under consideration. Consequently, they can be evaluated through experiments and observations which in turn validate or discredit these indicators, thereby further validating or discrediting the hypothesis at scrutiny. These indicators are indicative of causation in the sense that their probability of being true is higher if our hypothesis is accurate than if it is not.

Each piece of evidence gathered, be it from an experimental study, observational study, case series, case report, or basic science finding, is then linked to or classified within a group of the causal indicators selected. This procedure facilitates the extrapolation from medical data to theoretical constructs (causation) *via* abstract intermediary phenomena (causal indicators), a process which is analogous to Bogen & Woodward’s differentiation between data and phenomena [213].

The degree to which evidence confirms or disconfirms indicators of causation varies. To partially explicate this degree of (dis-)confirmation, evidential modulators are introduced. These modulators determine how much information a piece of evidence may offer. Population-

level studies are modulated, for example, by the quality of the study's control over random and systematic errors or biases. Generally, approaches to controlling bias in experiments and data analysis may include blinding, randomization and adjustment and stratification. This approach ensures a more precise and methodical evaluation of the evidence supporting or refuting the AMX-DRESS causal hypothesis.

2.7.4. Mechanistic Evidence Synthesis

At the core of the current investigation lies a binary propositional variable, termed as “ M ”. The M variable signifies the presence of a physiological pathway through which an adverse drug reaction might occur. When a scenario where a drug induces a negative reaction is considered, such a pathway or a mechanism must certainly exist, which implies that the probability of M under the premise of © holding is equal to one. Establishing a pathway through which an ADR may occur, however, does not necessarily mean that this ADR may manifest. Various factors, including potential inhibitors, compensatory mechanisms, feedback loops, and more, could obstruct the manifestation of the effect. In addition, the effect could potentially be so subtle that it escapes detection. Consequently, the probability of M occurring, assuming © not holding, ranges between 0 and 1. Subsequently, this does not make M an ideal indicator of causation because the existence of a mechanism does not ensure causation. It is suggested to adopt an indifference value of 0.5 for the probability of M , given that © not holding, *i.e.* the probability of a mechanism, whether the hapten or P-i hypothesis, existing yet not causing DRESS is 0.5.

The first step in this intricate process involves gathering all available evidence, ϵ , and identifying potential physiological pathways through which the AMX might trigger DRESS and assigning each a unique binary variable, *i.e.*, M_1 : hapten hypothesis and M_2 : P-i hypothesis. Next is to create a binary variable for every link in M_1 or M_2 which is not assumed to be definite, meaning, its existence probability is not taken as equal to 1. Subsequently, variables are assigned to the steps in the hapten hypothesis and the P-i hypothesis: HH_3 : the processing of HLA of to create AMX antigens, HH_4 : APC presented the resulting antigen which is recognized by a T-cell, HH_5 : T-cell recognizing the antigen and instigating DRESS and $P-i_1$: AMX or metabolites binding directly to a T-cell and $P-i_2$: activated T-cell induces DRESS.

A “report” variable for every piece of evidence which provides direct information about at least one link in the pathways is formulated. As new evidence is received, the beliefs are

subsequently updated. In this case, the variable “*Hautekeete*¹⁹” is created (representative of the findings in [211]), and information about *HH*₃ is provided. No direct evidence for the *P-i* variables implies that in the current discourse they do not contribute to (dis)confirming the hypothesis of interest and are thus removed from the model to simplify it without losing any (dis-)confirmatory power.

With the variables created, the network topology is established by inserting directed edges or arrows between the variables. *M* is a parent of *M*₁ and *M*₂. The variables symbolizing the links of *M*₁ form a clique (*M*₁ is a parent of every *HH* variable), with *HH*₃ being a parent of *HH*₄ and *HH*₅ and *HH*₄ being a parent of *HH*₅.

Next, the process of analogical inference is incorporated. Most of the basic science findings in this case provide indirect evidence. They are not evidence for AMX but for other drugs which induce SCAR via pathway *M*₁ and/or *M*₂. This analogical reasoning leads to the formulation of the two hypothesized physiological pathways. Since certain drugs are known to cause DRESS through *M*₁ and *M*₂, it seems plausible that AMX might cause DRESS through the same pathways. These drugs include abacavir (*ABC*, antiviral drug (HIV), *M*₁), Allopurinol (*Allo*, anti-gout, *M*₁), flucloxacillin (*Flux*, antibiotic, *M*₁ and *M*₂), and carbamazepine (*CZB*, anti-convulsant, *M*₂).

Interestingly, abacavir and flucloxacillin have been documented in literature to cause a T-cell mediated delayed drug hypersensitivity, as well as interacting with the same HLA haplotype (HLA-B:57:01). These two medications, however, manifest SCAR differently. Flucloxacillin leads to drug-induced hepatitis, while abacavir leads to DRESS. This distinction is important to note, as flucloxacillin is prone to interaction with biological components due to the β -lactam ring it shares with penicillins, such as AMX. For allopurinol and carbamazepine, a causal association with DRESS has already been established.

Subsequently, a variable to signify the analogy hypothesis is put forward, *ANA*. When the analogy holds true, it is highly probable that similar drugs would cause the same adverse drug reaction along the same pathway (*M*₁ and/or *M*₂). If the analogy fails, it becomes less likely that any drug of this type would cause DRESS. Hence, variables *ANA*₁ and *ANA*₂ are created.

¹⁹ Dr. Marc Leopold Hautekeete provides a seminal manuscript in the current discussion. His research offers compelling evidence suggesting that AMX elicits DRESS-like symptoms, aligning with the hapten hypothesis and provides support to the variable *HH*₃. Regrettably, Dr. Hautekeete passed in 2019, and in homage to his invaluable contributions, I have designated the variable in his name. Despite attempts, further biographical insights on Dr. Hautekeete remain limited in public records.

Additionally, a variable for each of these other drugs is introduced. For Flucloxacillin, two such variables account for it causing SCAR through the two different pathways are needed, $Flux_1$ and $Flux_2$.

To set up the network topology, the following arrows are added from ANA_1 to ABC , $Allo$, and $Flux_1$, from ANA_2 to $Flux_2$ and CBZ , one from ANA_1 to M_1 , and one from ANA_2 to M_2 . To ensure that the probabilities of M and consequently © increase when analogical information is received, an arrow from M to ANA_1 and from M to ANA_2 are added. The inclusion of these two arrows is necessary because the probability of M increases if an analogy holds true. The overall architecture of the model is presented in Figure 18.

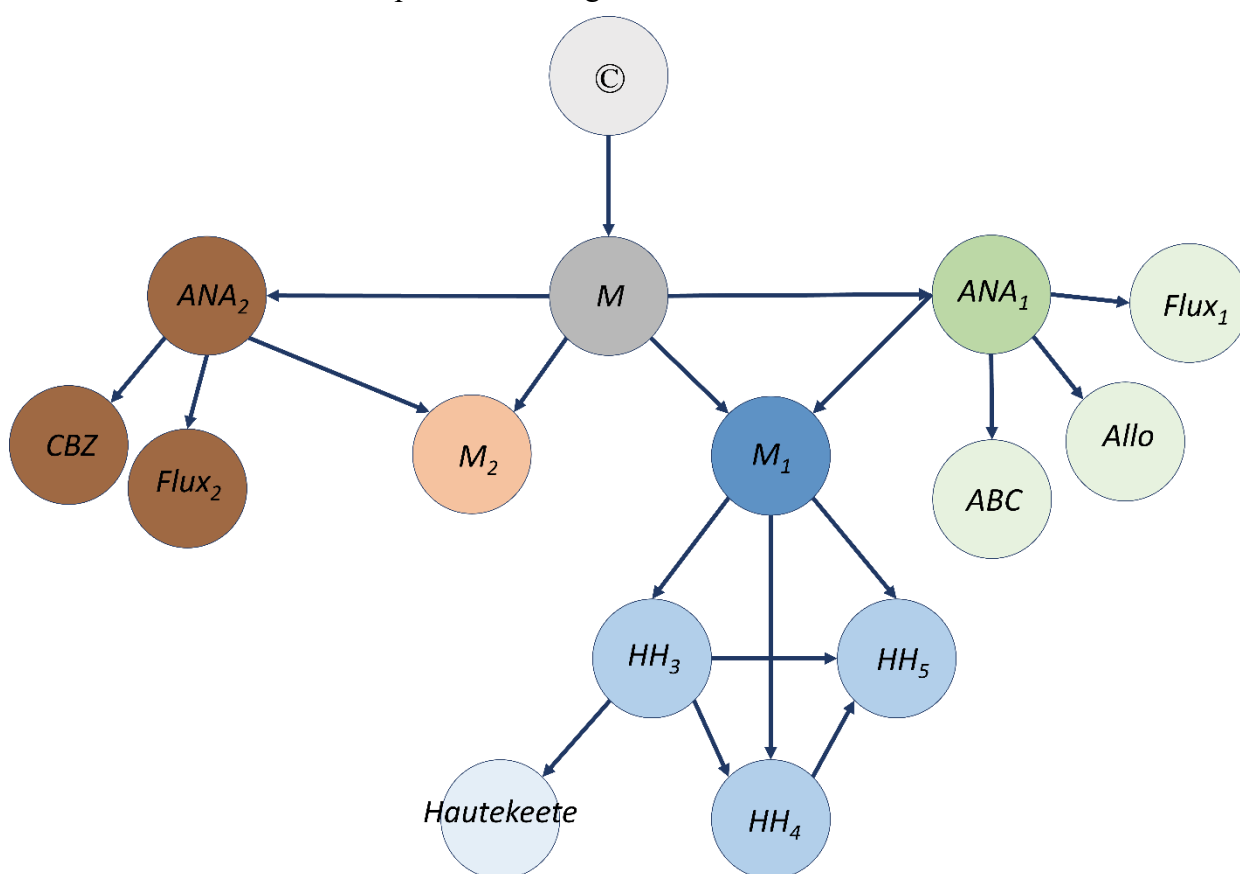


Figure 18. Architecture of the Bayesian network. The causal hypothesis variable at the top is the only variable without parent variable(s). The mechanistic indicator variable, M , may be confirmed by the hapten and/or P-i hypotheses as well as by analogies. The analogy variables are confirmed by evidence supporting hypotheses about other drugs causing DRESS according to the hapten and/or P-i Hypotheses. The study by *Hautekeete et al.* supports HH_3 . It should also be noted that while this model is indeed based on mechanisms and mechanistic components it is not a mechanistic model per se. It is a mathematical model representing the structure of the Bayesian network employed to calculate the probability of AMX causing DRESS.

In the next step the conditional probabilities of variables given their parents can be established. It is assumed that analogical hypotheses are quite probable if M holds, and rather improbable otherwise. The first pathway, M_1 , is considered more likely because AMX is a small drug molecule with high bioavailability, meaning most of the drug molecules in the bloodstream are bound to a carrier protein (HSA). On the other hand, the second pathway, M_2 ,

requires the drug to be unbound. Based on these premises, the probability of ANA_1 given M would be 0.9 and the probability of ANA_1 given \bar{M} is 0.1. Similarly, the probability of ANA_2 given M is set to 0.7, and the probability of ANA_2 given \bar{M} is 0.3.

If there is no mechanism along which AMX could cause DRESS, \bar{M} , then AMX cannot cause DRESS along either M_1 or M_2 , resulting in zero conditional probability for M_{1and2} given \bar{M} . If M holds true, however, then, once again, the hapten hypothesis is deemed more likely as the P-i hypothesis requires the drug molecule to be small and freely existent in the blood-suitable T-cell receptor, ultimately initiating an immune response. Given the high bioavailability of AMX, most of the drug molecules conjugate with HSA (hapten formation), which reduces the likelihood of the P-i hypothesis, M_2 , being the primary mechanism of action.

Accordingly, the probability of M_1 given M and ANA_1 both hold is 0.95, and the probability of M_1 given M and $\overline{ANA_1}$ would be 0.05. Furthermore, the probability of M_1 given \bar{M} and ANA_1 or $\overline{ANA_1}$ is 0. The probability of M_2 given M and ANA_2 is 0.6, and the probability of M_2 given M and $\overline{ANA_2}$ is 0.4. The probability of M_2 given \bar{M} and $\overline{ANA_2}$ or $\overline{ANA_1}$ is 0.

To simplify the model, the same conditional probabilities “X” is assigned to all instances of the analogy, $Flux_1$, $Flux_2$, ABC , $Allo$ and CBZ . Thus, the probability of X given ANA hold would be 0.9, and the probability of X given \overline{ANA} is 0.1.

The study referred to as “*Hautekeete*,” provides direct evidence about HH_3 . Here, the probability of M_1 is dependent on HH_3 because if the HLA fails to process the hapten no antigen will be available to be recognized by the T-cell which initiates the immune response. Hence:

$$P(Hautekeete|HH3) = 0.995 \text{ and } P(Hautekeete|\overline{HH3}) = 0.005$$

Accordingly, the posterior probabilities increase if the mechanistic evidence reported in *Hautekeete* holds:

$$P(\odot) = 0.001 \text{ while } P(\odot|Hautekeete) = 0.0011$$

$$P(M) = 0.5 \text{ while } P(M|Hautekeete) = 0.548$$

$$P(M_1) = 0.45 \text{ while } P(M_1|Hautekeete) = 0.5$$

With all these inputs in place, the model is now able to compute the updated probabilities of all variables, given the evidence, ϵ . This complex interplay of variables, hypotheses, and the evidence leads to the following posterior probabilities:

$$P(\textcircled{C}|\varepsilon) = 0.0019$$

$$P(M|\varepsilon) = 0.96$$

$$P(M_1|\varepsilon) = 0.92$$

$$P(M_2|\varepsilon) = 0.57$$

The values reflect the high uncertainty about the AMX causing DRESS, but they also indicate that if such a mechanism, M , exists, it is very likely to be M_1 (the hapten hypothesis) rather than M_2 [214].

2.7.5. Concluding remarks

In exploring the relationship between amoxicillin and drug reaction with eosinophilia and systemic symptoms, E-Synthesis provides a potent illustration of how philosophy of science complements scientific methodologies in establishing causality. This approach unravels a plausible, popablistic, causal link between AMX and DRESS, albeit without determining AMX as a universal causative agent for DRESS across a large patient population.

The rarity of severe side effects such as DRESS and the proven therapeutic benefits of AMX suggest that the philosophical approach aligns well with the real-world clinical decision to continue prescribing AMX for bacterial infections. This congruity of philosophical inference and practical decision-making testifies to the power of non-empirical methodologies in contributing to meaningful healthcare outcomes. The need for individualized patient care and monitoring underlines the fact that while population-level risk is minimal, individual susceptibilities to DRESS and similar Severe Cutaneous Adverse Reactions (SCARs) persist. This implies that the E-Synthesis approach, grounded in the philosophy of science, can help navigate situations where the scientific method may falter due to individual complexities.

This is also in line with the proceeding discussion about the nature of knowledge and truth with scientific practice in pharmacy. The example discussed here highlights the relativity or probability of knowledge representing truth. Despite its limitations, this mathematical approach nested in philosophical thought is pragmatic and adaptable and has indeed been able to establish a probabilistic causal link between a drug and an adverse side effect.

2.8. Chapter Conclusions

Concluding this chapter, a synthesis of the different sections is constructed, connecting the pursuit of truth in pharmaceutical research and development to the utilization of the philosophy of science. As discussed earlier, knowledge in pharmacy is communal, pragmatic and contingent and, therefore, fallible, relative and constantly changing, while truth is idealized, static and perhaps never attainable. Scientists active in pharmaceutical research constantly and rigorously pursue truth through the generation of knowledge which is dependable on the technologies and prevailing theoretical frameworks available. This has profound implication especially because the general approach to knowledge generation is rather reductionist. Scientists seem to reduce pharmaceutical phenomena to mechanisms and mechanistic components and interactions. The reductionist approach is indeed effective and has been very successful in providing a wealth of medication to maintain the health and wellbeing of society. Furthermore, this reductionist approach allows scientists to disentangle complex biochemical and/or biomedical phenomena rendering its control and prediction possible through a defined number of components and interactions. Yet given that knowledge is relative and truth is non-attainable such approach might risk oversimplification, potentially sidelining crucial insights. This skepticism also has serious implications in establishing cause-and-effect relationships in pharmacy as well as in compromising the certainty expected from medications in answering to societal health and wellbeing.

The three examples discussed, however, demonstrate how turning into philosophy might provide a complementary holistic account to augment the reductionist approach common in pharmaceutical scientific practice. The Baumkuchen model, which emerged from the mechanist philosophy of science may find promising applications. As discussions of mechanisms in pharmaceutical research are ubiquitous, this model distinguishes between different types of mechanisms as well as multilevel and interlevel relations and elucidates complex phenomena traditionally reduced to 'box and arrow' diagrams. The Baumkuchen model also has conceptual benefits in discerning to the scientist the different levels of complexity involved in explaining, controlling or predicting the phenomenon in question. This is indeed evident when the pursuit of one-molecule-one-function account has been critically criticized.

The systematic philosophical analysis of the enigmatic function(s) of Metallothionein represents yet another application of the Baumkuchen model. It highlighted that, generally,

scientists start with a phenomenon and subsequently break it down to its parts and their interactions, *i.e.* downward looking research. Interestingly, the case of MTs is rather unique because it is upward looking, *i.e.* scientists start from MTs which are considered parts of a mechanism(s) and aim upwards to try and link it to a function. This might be hinting toward MTs necessarily having a purpose, a goal or a telos. Such teleological explanations focusing on the function of proteins within the broader physiological setting might initially appear outdated. They are, however, increasingly perceived as useful tools for straightforward scientific explanations and guiding research directions. Indeed, most studies on MT proteins operate under the belief that each protein has a distinct, though sometimes unclear, purpose.

Examining the link between Amoxicillin (AMX) and the Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) highlighted the benefits of the E-Synthesis approach, a blend of philosophy of science and scientific methods, in positing a credible causal connection. The task of identifying a clear cause-effect relationship between AMX and DRESS is daunting due to DRESS's infrequency, delayed onset, and potentially life-threatening outcomes. This type of causality starkly contrasts with the straightforward cause-effect one expects when billiard balls collide or a knife slice through bread. E-Synthesis, grounded in the Bayes theorem and expressed *via* mathematical models and probabilities, embodies the relative and problem-solving nature of knowledge in pharmacy. This underlines the critical role of the philosophy of science in guiding individualized patient care, especially when conventional scientific methodologies might fall short.

Collectively, these investigations corroborate the indispensability of the philosophy of science in not only advancing the understanding of complex phenomena in pharmaceutical research and development but also enhancing the pragmatic, problem-solving effectiveness of healthcare outcomes. The convergence of philosophy and science, as demonstrated in this chapter, provides a compelling platform for further explorations, opening up innovative avenues for future research. Here, may wish to visit and dwell on the perspective of systems and systems science as this theoretical framework has been gaining increasing traction in recent years.

Chapter Three

3. Science Communication in the 21st Century

Building on the discussion of the previous chapter, it is vital to recognize the inherent limitations in scientific practice. Like any other human endeavour, science is shaped by the perceptual, cognitive, and experiential constraints of its practitioners. Drawing parallels to activities such as cooking or painting, science is, at its core, an anthropocentric pursuit.

Despite such limitations, science remains an effective tool for generating knowledge and problem-solving. Yet, the pursuit of truth becomes a complex endeavour. The very methods and approaches employed to capture truth are themselves limited and susceptible to biases and errors. These constraints are not limited to the process of discovery or justification, but they also pervade the act of *dissemination* or *publishing*, especially through mechanisms such as peer review. While discussions of science communication and dissemination are rife within different scientific disciplines and philosophical doctrines, a fully-fledged “*context of dissemination*” as yet another distinction in the scientific activity has not been proposed before²⁰. Such a conceptual distinction would serve as an umbrella under which discussions about how knowledge is conveyed in science, similar to scrutinizing how discoveries are reached, justified and pursued. Dissemination is indeed a pillar in the scientific activity.

Within the context of dissemination and directly related to the generation of knowledge and pursuit of truth is *peer review*. Despite its indispensable role in science, peer review is not immune to these anthropocentric limitations. In fact, it amplifies this human aspect of scientific pursuit, bringing forth a host of subjective factors into the judgment of scientific work. When attempting to predict the significance or impact of a study, peer reviewers are faced with the difficult task of making future-oriented assessments based on their subjective judgment, individual experiences, and personal expertise. Such predictions about impact and significance are inherently fraught with uncertainty and the potential for error, further underscoring the imperfect and human-centric nature of scientific practice.

²⁰ The discussion in this chapter is supported and based on four manuscripts published in international peer reviewed journals: Jacob, C.; Rittman, M.; Vazquez, F.; **Abdin, A.Y.** Evolution of Sci's Community-Driven Post-Publication Peer-Review. *Sci* 2019, 1, 16. <https://doi.org/10.3390/sci1010016.v1>, **Abdin, A.Y.**; Nasim, M.J.; Ney, Y.; Jacob, C. The Pioneering Role of *Sci* in Post Publication Public Peer Review (P4R). *Publications* 2021, 9, 13. <https://doi.org/10.3390/publications9010013>, **Abdin, A.Y.**; Jacob, C. *Sci*: An Inclusive, Multidisciplinary Scientific Journal. *Sci* 2022, 4, 10. <https://doi.org/10.3390/sci4010010>, and **Abdin, A.Y.**; Jacob, C. Make a Stand(ard) for *Science*. *Sci* 2023, 5, 7. <https://doi.org/10.3390/sci5010007>.

This inherent subjectivity and potential for bias within the peer review process is not a weakness but a characteristic which indeed warrants careful attention. To circumvent subjective opinion and protect the objectivity of scientific exchange, and hence knowledge, respectful journals may blind different aspects of the peer-review process or solicit the expert opinion of a large number of reviewers. Yet, the quality of the outcome would be intersubjective at best, *i.e.* a majority of reviewers share a subjective agreement on the quality a manuscript. Closer inspection further details the intricacies of the peer review process, its strengths, limitations, and how, despite these challenges, it continues to play a crucial role in the advancement of science.

This discussion also serves as a critical reminder that no individual, institution, or process is infallible. Recognizing this fact underscores the importance of transparency, openness, and critical, collective reflection within all stages of scientific practice, including the peer review process. This acknowledgement is crucial in our ongoing endeavour to align scientific practices with the noble goal of advancing knowledge and serving society and the environment.

3.1. The Context of Dissemination: The Role of Peer Review in the Scientific Activity

The pursuit of truth within the realm of pharmaceutical research might be rendered futile if the findings or output are not appropriately disseminated and shared within the scientific community. This might seem evident if not intuitive at first. An observation, a discovery, a pursuit, or a justification might be profound in their implications, yet, if they remain unpublished, they go unnoticed –much like Berkeley’s tree²¹ falling in the forest and no one around to hear it– and subsequently bear no significant impact on science. Such realization underlines the importance of science communication and set the ground for suggesting and subsequently developing and adding yet another distinction to the philosophical discussion of the scientific activity, the context of dissemination.

Such context would indeed be warranted as it allows to capture not only an essential part of scientific practice but also to account for the influence of practicing science as an activity grounded in communal exchanges. Scientists are members of scientific communities and disciplines and hence, to a large extent, they are expected to follow certain guidelines and standards and perhaps sometimes yield to the prevailing research traditions of their era. The context of dissemination may also reflect the existential pressure within the current academic atmosphere which emphasizes growth and expansion through heightened bibliometrics to secure essential grants and funding. This drive is perhaps one of the consequences of the phrase “publish or perish” and directly contributes to the devastating “replication crisis” in the various sciences [216,217]. Such pressure often pushes scientists towards focusing on the quantity of their publications, detrimentally impacting the overall quality of scientific output.

In considering this predicament, however, it is necessary to acknowledge that the fault may not solely reside with the scientists themselves. They often fall prey to a flawed publishing and reward systems, comprising desperate institutions, profit-oriented publishers, disinterested editors and reviewers, and rigid scientific communities. This systemic inadequacy naturally extends to the way we approach safeguarding high-quality, reproducible science.

Interestingly, there seem to be an important mismatch between the work done at the bench and what scientist eventually publish [218,219]. On one side, some philosophers of

²¹ George Berkeley (1685–1753) suggested a philosophical thought experiment in his book, *A Treatise Concerning the Principles of Human Knowledge*, from 1734 where he wrote passages which could be summarized in the following question: If a tree falls in the forest and no one is around to hear it, does it make a sound? His goal has been to emphasize the importance of observation and perception of phenomena in relation to their existence. He writes: “*The objects of sense exist only when they are perceived; the trees therefore are in the garden[...] no longer than while there is somebody by to perceive them*” [215].

science accept this mismatch on the basis that discovery and justifications are distinct and temporally independent, and that validity can only be examined in the presentation of a discovery, *e.g.* scientific publication or manuscript, not in the discovery-forging process²² [220]. Such philosophers proceed to claim that the mismatch is a consequence of scientists holding the logical, mostly inductivist, nature of scientific practice. These philosophers prioritize their logical models over the scientist's presentation and the actual practice at the bench. On the other side, some philosophers affirm the mismatch but reject such strict distinction between discovery and justification and adapt a more lenient perspectivist account of the distinction [221]. In their view, discovery and justification are concurrent processes. They suggest that the focus should be on the activities scientists engage in at the bench, rather than the logical reconstruction of their findings in the published form. They propose identifying the guiding principles or heuristics behind paradigm-shifting discoveries at the bench level and updating logical models based on these.

The philosophers from the two camps argue under the assumption that the logical models they build and demolish are of immense importance to the scientist, *i.e.* the pro distinction camp assumes that the scientist deliberately present their findings following a logical structure which is then judged for validity by the philosopher, whilst the anti-distinction camp of philosophers wants to analyze what leads to a discovery and establish new models. Attempts by other philosophers of science to analyze arguments presented in publications against several logical models *e.g.* Hypothetico-deductive and Bisayan inductive model, however, failed to account for more than a debatable 30%, hinting that scientists are lenient towards following logical structures in their publications on the micro level, *i.e.* individual arguments, and macro level, *i.e.* the entire scientific piece [222–224]. This is indeed reminiscent of the Exeter Method which serves the biochemical community to systematically locate logical inconsistencies arising from more theoretical aspects of the scientific activity [17].

Empirically, laboratory anthropologists have found a different explanation for the mismatch between what goes on at the bench and what is presented in the publication. They highlighted the scientific process at the bench as messy, back and forth, utilizing whatever resources around as opposed to the clear, inductive, and to the point presentation in a publication [225]. Such practices are so deeply rooted in the current publishing landscape that

²² Such views are closely related to the movement of logical positivism.

they have become the norm of most, if not all journal templates. The author is guided to provide a background on the subject matter, briefly record their experimental materials and methods, describe their results, discuss them and spend half a page to conclude. Yet to the surprise of philosophers, laboratory anthropologists found that scientists reconstruct their findings in such a manner, not with attention to logical models, but to satisfy and persuade their peers. The main concern of the scientists is that their publication withstands peer-review [5,226].

Contrary to the common perception of scientific activity on being a stepwise process, the borders between discovery, justification, and publishing are indeed blurry in actual practice. The potency of a discovery often hinges on its justification and subsequent publication, with each step shaping the other's evolution and integrity. This intricate interplay forms a backdrop for the central premise of this chapter: the role of peer review within the scientific process.

Referred to as the 'gold standard' of scientific dissemination, the peer review process bears substantial influence on what is eventually published. The feedback received in the form of a peer review report and the eventual incorporation of this input directly shape the discovery presented in the work published. Peer review not only helps to ensure the quality of scientific articles but also actively contributes to the advancement of the respective scientific field. The reality, however, is not devoid of its drawbacks. Overly restrictive or biased approaches can suppress and potentially damage good science, depriving it of the necessary nourishment to flourish [227–234]. Yet in the era of open science, the practice of peer review also calls for revisiting. This chapter will discuss these premises, exploring the role of peer review in the broader context of scientific practice, and examining the potential alternatives and innovations that may help in shaping its future. This exploration is guided by the understanding that the dissemination of scientific knowledge is not a mere auxiliary to scientific practice but an integral part of it.

In this chapter, the insights as authors, editors, and reviewers with post-publication public peer review (P4R) as applied in the international, open-access journal *Sci* is reported [235,236]. Section 3.2. provides a brief recollection of the history of modern scientific practices with a special focus on open science and peer review. Section 3.3. compares various publishing models on their openness and transparency. Section 3.4 introduces the self-publishing (SP) model and recounts the journey from SP to PurplePublishing.org and eventually *Sci*. Section 3.5. presents the P4R workflow, outlining its strengths and shortcomings and also introduces the P4R Hybrid, the cornerstone of *Sci*'s dissemination strategy since November 2020. Section 3.6 concludes the chapter.

3.2. History of Modern Science Communication

While it might appear that peer review is a recent development, introduced by scientific communities as a quality control procedure, it actually dates to the emergence of modern scientific publishing in the mid-17th century [237]. Scientific communication has an even more protracted history, influenced considerably by technological advances since ancient times [238].

The introduction of the printing press by Johannes Gutenberg (1400–1468) in the 15th century has indeed marked a significant shift, simplifying the tedious process of manually copying manuscripts. Initially, the focus during the 15th and 16th centuries has been invested in collecting, reprinting and circulating already available literature. Subsequently, this led to a period of letter correspondence and personal visits between “scientists”. It was only with the advent of the first scientific societies in the 17th century that journal-based scientific communication took hold.

Accordingly, the first scientific society has been founded in Paris (France) as the Académie Française. In 1652 and 1660 the Deutsche Akademie der Naturforscher Leopoldina has been established in Germany and the Royal Society of London in England, respectively [239]. Some of these societies began printing the contributions of their members in the form of journals. Among the first such journals were the *Journal de Sçavans* (the *Journal of the Wise*) and *Philosophical Transactions*, both established in 1665 [240,241]. The guardianship of these societies ensured the quality of their respective journals through an elementary form of peer review, implemented voluntarily by Henry Oldenburg (1619–1677), the inaugural editor-in-chief of *Philosophical Transactions* [237].

In the 18th and 19th centuries, the publishing landscape diversified and expanded, witnessing an influx in periodicity and establishment of more specialized journals, including the esteemed journals, *Nature* and *Science* [242,243]. Large publishing houses of today also have their roots in the 19th century. The history of Springer, now known as Springer Nature, dates to 1842 where it was established in Berlin, Germany [244]. Elsevier has been established in 1880 in Amsterdam, Netherlands as a bookseller and publisher. It took until 1945 for Elsevier to expand its activities into scientific publishing and in 1947 the company released its first English journal, *Biochimica et Biophysica Acta* [245]. Furthermore, the concept of “University Press” received tremendous attention during this period. Though the roots of

Oxford University Press and Cambridge University Press can be found in 1480 and 1534, respectively, their effort began to crystalize in the 19th century [246,247]. This institution based self-publishing model is nested in the premise that having a non-for-profit publishing house, represents an integral component of any respectable academic research university. Subsequently, several other universities followed suit such as the establishment of Cornell University Press in 1869, The Johns Hopkins University Press in 1878, The University of Pennsylvania Press in 1890, University of Chicago Press in 1891 and many others [248]. The second half of the 20th century welcomed technological developments which catalyzed a revolution in scientific communication, setting the stage for the debut of online journals such as *Psychology* and the *Journal of Medical Internet Research (JMIR)* in the 1990s, Figure 19 [249,250].

The early 2000s inaugurated the advent of open access publishing and marked significant milestones such as the Budapest Open Access Initiative in February 2002, the Bethesda Statement on Open Access Publishing in June 2003, and the Berlin Declaration on Open Access to Knowledge in the Sciences and Humanities in October 2003 [251–253].

Despite these invitations for a good, “open” practice, today, many parties –for a variety of reasons and purposes– constantly abuse the interpretation of this concept. Open science should not be blind and only limited to demolishing paywalls or allowing for easy availability, accessibility and reusability of the diverse types of scientific output and findings. Open science ought to further encompass full transparency, freedom and democracy, especially in the realm of scientific publishing. With this transition, the number of scientific publications surged, reaching an estimated total of 3 million peer-reviewed articles in science, technology, and mathematics (STM) in 2018 alone [254].

Concurrently, as a result of the speed and turnover facilitated by online and digital tools, the demands and strains placed on the peer review system are constantly escalating, with an estimated annual investment of 70 million hours by researchers in peer reviewing tasks alone [220]. Despite their developments, the traditional peer review system has persisted, largely unchanged, even as publishing has shifted from subscriber-paid printed journals to author-financed open access online platforms.

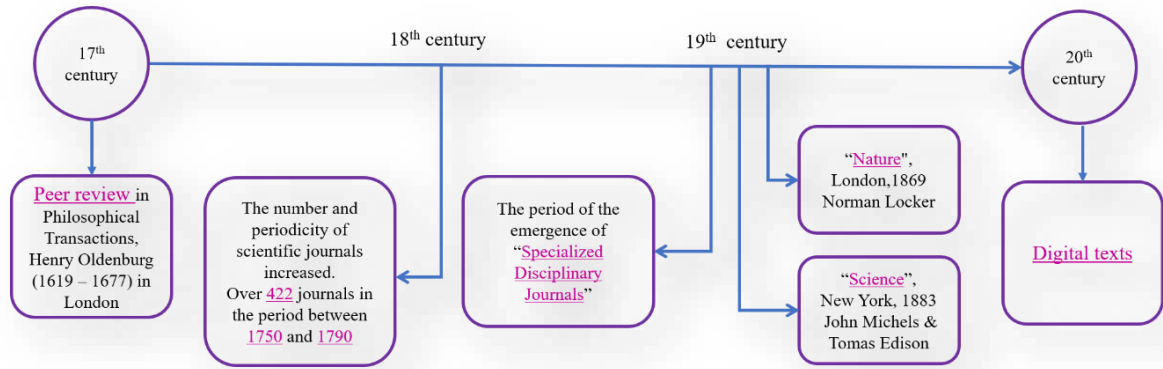


Figure 19. The main events which took place between the 17th and 20th century in terms of the development of science communication.

Maintaining the continuity of scientific discourse demands a critical reassessment and potential transformation of existing publishing and peer review systems. A system rooted in historical tradition now requires adaptation to meet the evolving challenges and needs of 21st-century science.

3.3. Mainstream Publishing Practices

Indeed, the practice of evaluating manuscripts pre-publication has not dramatically transformed since Henry Oldenburg’s time, notwithstanding its expanded international reach and increased speed. Blind forms of peer-review usually practiced behind closed doors by a limited number of reviewers are indeed questionable. These traditional systems, while steeped in history, have shown cracks under the weight of modern publishing speed and volume, signaling an impending system failure [230–234].

Table 1 illustrates the dichotomies between open access scientific publishing models in terms of their degree of transparency and scientific community involvement, revealing numerous problems inherent in today’s peer review process [255]. Notably, the enormous demand for swift, quality assessments by unpaid expert scientists is unsustainable, leading to rushed reviews often performed by less engaged or inexperienced colleagues. Recent surveys reveal a diminishing motivation among senior scientists to partake in traditional peer review, resulting in a shift of this responsibility onto their subordinates. An unethical yet pervasive issue of ghostwriting peer reviews has also emerged, highlighting a significant flaw in the system today [256].

Table 1: Distinctive schemes of open access academic publishing in relation to their transparency and openness are outlined [32]. In the sphere of online publishing, the term ‘open’ carries multiple meanings, encompassing open access for readers, public availability of reviews, open disclosure of reviewers’ identities, and within P4R, the potential for public open commentary on a specific manuscript. It is worth noting that various combinations of these open aspects are not only plausible but also desirable.

	Traditional Single Blind	Traditional Double Blind	Hybrid Single Blind	Hybrid Double Blind	P4R	P4R Hybrid
Open accepted version of publication	Yes	Yes	Yes	Yes	Yes	Yes
Open identities of authors	Yes	No	Yes	No	Yes	Yes
Open identities of reviewers	No	No	No	No	Yes	Optional ⁽¹⁾
Interaction with unreviewed publication	No	No	Depends ⁽²⁾	Depends ⁽²⁾	Yes ⁽³⁾	Yes ⁽³⁾
Open interaction with accepted publication	No	No	No	No	Yes	Yes
Open review reports	No	No	Optional ⁽⁴⁾	Optional ⁽⁴⁾	Yes	Optional ⁽⁴⁾
Post-publication peer review	No	No	Optional ⁽⁵⁾	Optional ⁽⁵⁾	Yes ⁽⁶⁾	Yes ⁽⁷⁾

⁽¹⁾ Reviewers can choose whether to sign their review reports. ⁽²⁾ Depends on whether the authors choose to submit to preprint platform or not. ⁽³⁾ Interested parties from the scientific community can interact with the submission in the form of commenting, endorsing, and re-using. ⁽⁴⁾ Authors can choose to render the review reports and their responses public and accessible alongside their publication. ⁽⁵⁾ Authors are offered the possibility to share their submission on a preprint platform. ⁽⁶⁾ Submission is immediately available on the journal platform prior to peer review. ⁽⁷⁾ Submission is immediately available on a preprint platform.

Unfortunately, this traditional practice often excludes genuinely interested parties, including early-career researchers and colleagues from less affluent countries. Here, the “best

practice” assumed to objectively evaluate the science and quality of a given manuscript is to solicit the expert opinions of reviewers who possess a high Hirsch Index or H-index. Indeed, the more the better. But it cannot be too many because this will enormously prolong the manuscript processing time and, therefore, in many cases the acceptable number of reviewers is between two and six reviewers per manuscript. Nevertheless, the reviewing process exhibits discrimination, privileged access to a select few while maintaining a closed-door policy. Such secretive and restricted reviews conflict with the ideals of a global society pursuing openness and transparency in their scientific practice. In scrutinizing a manuscript’s impact, the secretive nature of traditional review amplifies the subjectivity of the process [257,258].

In essence, the traditional single- and double-blind peer review systems, although widely lauded, are increasingly recognized as a hindrance to open and fair scientific discourse. Its restrictive and subjective nature contradicts modern societal values. Even open peer review models, while seemingly more transparent, maintain the *a priori* assessment by a select few reviewers, potentially leading to the acceptance of mediocre work and rejection of superior manuscripts. It is important to note that a manuscript’s true impact cannot be predetermined but is only discernible *a posteriori*, perhaps years its after publication [259,260]. Evaluating a manuscript’s impact *a priori* intrudes into a domain outside the reviewers’ purview. This critique is equally applicable to triple and quadruple blind review practices²³.

Furthermore, peer reviewers often impose major alterations on manuscripts, potentially infringing on the authors’ originality [262]. Authors frequently perceive these demanded changes as unwarranted interventions into their work. The issue of preserving the author’s voice, seldom addressed, is of importance as a manuscript is not only a scientific contribution but also a reflection of personal expression. Just as literary or artistic works by William Shakespeare or Beethoven were not subject to external revisions before public presentation, scientific work should be accorded similar respect. Thus, the traditional review process has come under criticism for being ineffective, discriminatory, cumbersome, biased, and undemocratic. Efforts are needed to reassess and reform these practices, incorporating more democratic, transparent, and inclusive mechanisms to maintain the integrity of scientific discourse while respecting the originality and voice of the authors [263].

²³ Triple-blind: author identities are hidden from reviewers, reviewers from authors, and the editor from the authors. Quadruple-blind: further extends anonymity, masking author and reviewer identities from each other and the editor, with reviewer selection based on keyword relevance. [261].

3.4. Alternative Publishing practices

Understandably, the challenges and limitations of the traditional publishing paradigm have incited authors to explore alternative means for disseminating their scientific findings [255,264–269]. One such option includes self-publishing (SP), wherein authors directly post their work on personal, institutional or university websites. This practice, although seemingly unconventional, is reminiscent of the publishing method prevalent for centuries, as indicated by institutes such as Oxford University Press (OUP) discussed before. With the current state of technology, self-publishing is technically straightforward as long as archiving and proper indexing are possible and has been adopted by platforms such as ArXiv, BioRxiv, ChemRxiv, and F1000 [270,271].

Despite its appeal, self-publishing is not without its drawbacks. Protection of copyrights and against plagiarism necessitates cumbersome registration and archiving processes involving platforms such Crossref to generate digital object identifiers (DOIs). Moreover, self-published work lacks independent validation, which affects its perceived credibility and reach. An attempt to adopt the SP model on the website of the Institute for Bioorganic Chemistry, www.academics.eu in 2017, illuminated these shortcomings, emphasizing that this approach does not equate to casually disseminating scientific findings like social media posts.

To balance scientific rigor and independence, a more particular and considerate approach ought to incorporate self-publishing with components of external endorsement. This could be technically achieved by including public commenting and rating options, much like consumer feedback on online marketplaces such as Amazon or eBay. Therefore, the ‘Purple Publishing’²⁴ project was established in 2018 to overcome the initial challenges encountered in the first attempt with applying SP via Academics.eu. Purple Publishing sought to combine self-publishing with an open forum for public commentary. Rather than resisting the inherent communal and societal aspects of the scientific activity and knowledge generation within the context of dissemination, this purple initiative offered tools to harness and amplify these exchanges with utmost transparency and openness.

²⁴ Purple has been chosen arbitrarily to mimic the common terminology in open access publishing such as green, gold, diamond and black. The idea was that “purple” would convey that the publishing model implemented is post publication public peer review, though usually the other colors mentioned pertain to the accessibility to the scientific piece itself.

PurplePublishing.org served as a platform offering social-media and online market style features ranging from easy submission of manuscript, post-publication open commentary and also rating and messaging functions. Similar attempts to foster post-publication public peer reviews, such PubMed Commons, have been launched in the past, though with limited engagement leading to their discontinuation [272,273]. Nevertheless, platforms like Pubpeer continue to offer opportunities for public and anonymous commenting on manuscripts after their publications, albeit not without controversy [274–276]. This purple model of post-publication public endorsement amalgamates the contemporary aspects of scientific communication and the interactive nature of online marketplaces. The practice is transparent, open, democratic, and allows global exchange and rating of scientific manuscripts. However, ‘purple style’ self-publishing also faces issues of registering and archiving manuscripts, coupled with dilemmas about how revisions should be managed.

Another significant challenge is the lack of standing and popularity within the scientific community. Such platforms often do not register with major search engines like SciFinder or Medline and do not possess an impact factor. In the case of PurplePublishing.org, visitor numbers were scant, leading to the project’s suspension in 2021. Despite these hurdles, the exploration of alternative models is crucial today in redefining and enriching scientific publishing practices.

3.5. *Sci*: An Inclusive Multidisciplinary Journal

Recognizing the potential pitfalls associated with self-publishing, an innovative and more effective approach can be conceptualized: blending the virtues of a professional publishing house with the benefits of post-publication public peer review [277]. Under such an arrangement, manuscripts would be processed by the editorial staff of a recognized publishing house and subsequently disseminated in a well-established online journal.

Post-publication, the manuscript is rendered accessible for scrutiny by the entire academic community. This open dialogue between authors and reviewers is not only publicly documented but also useful for potential revisions of the manuscript. It helps uphold the author's originality while ensuring the review process remains transparent and engaging for genuinely interested reviewers. The acknowledgement of the reviewers' contributions is an additional advantage of this model, as their efforts no longer remain inconspicuous.

In the context of this alternative approach to publishing, the journal "*Sci*" (ISSN 2413-4155) is introduced [278]. *Sci* is an international, open-access journal launched by MDPI in March 2018. It spans numerous areas of scientific research. Striving to demystify the so-called black box of peer review associated with single- and double-blind models, *Sci* adopted the post-publication public peer review model (P4R) in March 2019, embodying the inclusive and democratic ethos of scientific publishing [279].

3.5.1. P4R

Stripped from technical terms and advanced technological and editorial support, the P4R scheme is similar to a simple self-publishing model [277]. The original submission from the author is rendered available online for interested members of the scientific community to volunteer and openly provide expert review reports and comments which subsequently the author can incorporate with rectifying and enhancing their manuscript.

Upon submission, manuscripts undergo a brief and limited editorial check to ensure a level of scientific professionalism and avoid posting plagiarized or inappropriate material in the online journal. The manuscript submitted receives a Digital Object Identifier (DOI) and becomes publicly available awaiting interested experts to voluntarily review or comment on it. Subsequently, the author amends their manuscript accordingly, resubmit and the final decision

whether to accept or reject the manuscript is left to the editor. Here, each version of the manuscript receives an individual DOI and an appropriate label is assigned to clearly distinguish whether it is peer-reviewed or still undergoing the process. Interactions between the authors and reviewers are openly available alongside each manuscript together with their identities and affiliations. As a future step in this project, the implementation of a star-like rating, similar to popular online markets, has been envisaged, Figure 20 [236].

The P4R scheme protects the originality of the author's initial submission and maintains transparency in the interactions between authors and reviewers. This approach to peer-review specifies no fixed number of reviewers and allows for the evaluation of scientific quality to transpire after the manuscript has already been online. Hence, it neutralizes depending on the *a priori* and subjective opinions of a few reviewers. It seeks to foster a more transparent and democratic crowd reviewing *a posteriori*.

It should be noted that during the period of implementing the P4R scheme in 2019 and 2020, the journal *Sci* required no article processing fees (APCs), has been promoted at international conferences and several special issues have been organized. Yet despite the considerate and auspicious approach to open science offered by the P4R scheme, submissions have been sparse. Furthermore, several technical issues have limited continuing with the P4R as it stood. Firstly, waiting for "interested" reviewers proved somewhat unrealistic and led to a lengthy and time-consuming peer-review process. The editorial office has been forced in some cases to invite relevant reviewers. Secondly, allowing the manuscript to appear directly on the journal's website left some authors under the wrong impression that their manuscripts were, *de facto*, fully accepted in line with traditional publishing models. So, when the editorial office informed such authors that review reports of their manuscripts were ready, unpleasant replies were sent; they simply resisted conducting any corrections. This indeed prolonged the manuscript processing time (MPT) even more.

Thirdly, despite being informed about the process, some authors were against publishing the review reports of their manuscripts and some reviewers opposed sharing their identities. Some review reports were simply inadequate and, in a few cases, even nasty, and therefore authors were perhaps too ashamed to attach them to their manuscripts and reviewers were probably worried about future retaliation. Whilst these experiences have hugely complicated publishing using the P4R model, they also say a lot about the current state of science and what may otherwise go on beyond "closed doors", *i.e.* blind publishing models.

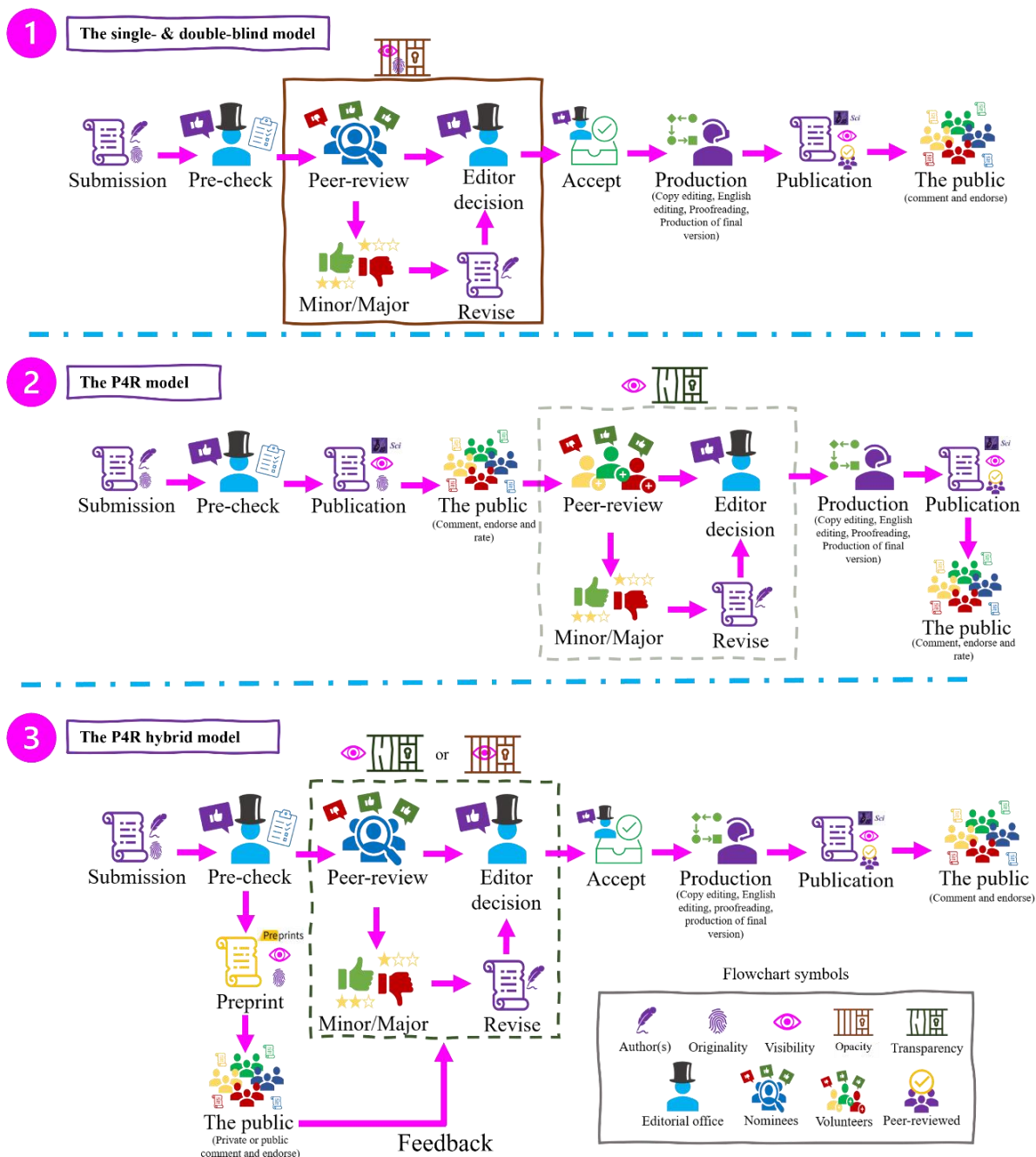


Figure 20. The conventional approach to peer review typically depends on a few, often selected reviewers who provide professional critique of a submitted manuscript within a limited timeframe (Panel 1). Based on these selected reviewers' reports, the manuscript is either declined, amended, or published. Conversely, the public post-publication review (P4R) model implements a pre-evaluation to screen for unsatisfactory form and content (Panel 2). Upon passing, the manuscript is rapidly published as an original contribution to scientific knowledge and art and is open to public comments. Given the complications associated with implementing revisions leading to multiple DOIs, a hybrid model involving two online platforms and journals has been suggested. In this model, both volunteer and professional reviewers collaboratively engage after the manuscript is published on *Preprints*, and before it is revised and published in *Sci* (Panel 3). The decision to publish is based on a collective appraisal, and once the manuscript is published in *Sci*, additional public commentary for extended periods is encouraged, the feedback arrow, although no further refereeing or revisions are possible.

Fourthly, manuscripts of lower scientific quality -and which received negative review reports- leading the editor to eventually decide to reject them had, at that point, already been published on the journal's website. Rejecting manuscripts has not been an obvious and

posed a serious flaw in the P4R. This issue also blocked authors from attempting to try and submit their work to other journals.

Fifthly, many open access journals use several indexing services, yet generally the system is designed to accommodate the final, peer-reviewed version having a unique DOI. In the case of the P4R scheme several versions of the same manuscript each having their own unique DOI got indexed in several databases and started circulating the internet, sending notifications left and right on Google Scholar, ResearchGate and other platforms. (The situation in practice was even much messier than how the previous sentence reads). This further affected the possibility of benefiting from services providing article-level metrics such as Altmetrics.

3.5.2. P4R Hybrid

Against this backdrop, a modified form of the P4R has been adopted in *Sci* since November 2020 [280]. The P4R Hybrid aims to resolve most of the hurdles mentioned above. Firstly, interested reviewers can still volunteer to provide their expert opinion yet not for individual manuscripts, rather for the journal as a whole and the assignment of the task is left to the editorial office and is based upon relevance and demand. Hence, the manuscript processing time has been significantly reduced. Secondly, manuscripts remain to be readily available publicly upon submission in their original form after the brief editorial check. To this end an intermediate platform specialized in hosting such type of non-peer-reviewed scientific literature, *Preprints.org*, is utilized [281]. This approach resolves the issues related to the author's confusion about the peer-review process as well as the issues with rejecting low-quality submissions. Having this intermediate repository allows also for the journal to acquire article-level metrics and eventually an impact factor. Thirdly, sharing of the review reports and reviewers' identities became optional. Authors who are interested in attaching the review reports alongside their manuscripts still have the possibility and reviewers willing to reveal their identities can do so as they wish. Notably, the decision to opt out of revealing their identities has indeed been unfortunate and regressive, but eventually it seems this is what the majority of scientists wants.

Since the P4R Hybrid scheme has been implemented, submissions have increased and the journal is gaining more attention from the scientific community. Apart from the pioneering approach to open science and peer-review, the fact that the journal is multidisciplinary renders

it an inclusive hotspot for scientists from different disciplines to exchange ideas and to cooperate. This aspect has been exploited early on through organizing annual multidisciplinary and interdisciplinary special issues aimed at addressing the most pressing challenges humanity and the environment are facing. Additionally, *Sci* is promoting further inclusion by incorporating a summary in simple language away from technical jargon to truly bypass scientific boundaries. This initiative would even allow the general public to be able to read, digest and comprehend research, usually funded by public means, directly from the author. Hence, the journal would become even more inclusive and promote some aspects of citizen science in the near future.

3.6. The Future of *Sci*

The advent of open access publishing, inaugurated at the dawn of this century, has indisputably precipitated a rapid expansion in scientific communication. Nonetheless, this progress has simultaneously pushed the boundaries of the conventional peer review system. This tension has catalyzed exploring alternative solutions such as P4R, although these, too, wrestle with their own array of challenges [235].

Notably, the scientific journal *Sci* has emerged as an innovator in committing to P4R. Having distilled invaluable lessons from its experiments in 2019 and 2020, it has subsequently established the P4R hybrid, which forfeits the transparency and openness of science communication and invites greater public engagement as much as the scientist can handle and the community is ready to provide. Highlighting *Sci*'s growing influence and reputation, it is noteworthy that as of early 2023, the journal has been indexed in Scopus and has recently been awarded a commendable CiteScore of 3.1. This recognition underscores the journal's position as a possible player in reshaping the landscape of scientific publishing.

It is essential, however, to acknowledge that the transition towards a more democratized scientific discourse necessitates a proactive involvement of the scientific community itself. This means more scientists volunteering their expertise for the review of manuscripts that are professionally intriguing, mirroring the active engagement observed in thriving marketplaces. Furthermore, the spirit of open access extends beyond the mere provision of unrestricted access to scientific literature. It embraces a holistic transparency – from revealing the identities of reviewers, to welcoming the wider scientific community's participation and input. For those discontented with the traditional review processes, it is time to embrace this viable alternative.

The coming years will undoubtedly shed light on the continued progression of online, open access publishing, and illustrate how both *Sci* and P4R can enhance their operations to maintain their pioneering status in contemporary scientific publishing. The fulfillment of this revolution, however, largely rests in the hands of the community that has demanded such modernity. Their proactive involvement will determine the successful realization of this transformation.

3.7. Chapter Conclusions

Drawing from the insights of this chapter, the critical role of sharing and communicating scientific findings is appreciated. The context of dissemination sits alongside discovery, pursuit and justification as a fundamental aspect in scientific practice and thus should also be examined with the same rigor by philosophy. Peer review, with its ability to shape, limit, or nurture scientific work, is a key part of this process. The lines between these steps are often blurred in actual scientific work, further highlighting the need to understand each aspect's unique role and challenges. Here, a wide range of other issues call for closer attention such as the proliferation of chemical syntactic pathways, patents restricting access to essential medication and the use of artificial intelligence in manuscript evaluation and possibly peer review.

Open science has yet a long way to go. Imperative questions remain on how to motivate the different stakeholders operating and interacting in the scientific publishing landscape to deepen their practice of serious open science. Science is the most effective and accurate method for constructing, explaining and understanding the world around us, yet it remains also vulnerable and amenable to the senses. It is, therefore, crucial to cooperate and exchange as freely as possible in a transparent and democratic manner. One program of action is to promote and initiate replication studies and grants. Perhaps, even popularize a “Replication Label” as a stamp and standard of higher scientific quality.

Inevitably, we circle back to the theme introduced at the beginning: the inherent fallibility of every person, institution, and process. Accepting this reality highlights the need for transparency, openness, and critical reflection throughout all steps and aspects of scientific work, including peer review. As we strive to align scientific practice with the broader goals of knowledge advancement and serving society and the environment, the discussions within this chapter underline the intricate dynamics which underpin the world of scientific publishing.

*To summarize lastly,
in a way which rhymes nicely.*

*Publishers, scientific communities, academic and funding institutions,
should work together and find solutions.*

*Cooperate and act.
Decisive action to be the pact.*

*Relieve the “publish or perish” pressure off the scientist’s neck.
It may seem simple, but it is turned into a wreck.*

*Put the pressure away,
so the transparency can stay.*

*Open science practiced democratically,
will counteract the replication crisis drastically.*

*A crisis managed so duly,
will turn into a revolution surely.*

*The word must spread,
a “Replication Revolution” looms ahead.*

Chapter Four

4. Controlling the Pharmaceutical Product: Decisions, Regulations and Consequences

As mentioned already on several occasions, pharmacy is a science, an art and a craft. It is also an industry with immediate relevance to the wellbeing and health of humans, animals and the environment. In this context, a pharmaceutical substance is not “just” a subject of research, it is also of substantial importance in society and elsewhere. The concept of control, therefore, plays an essential role in governing the internal relations within pharmacy and its external relation with politics, economy, society and the environment. This critical juncture exerts influence, in both directions through the employment of policies, regulations, standards, and guidelines, while simultaneously being shaped by the possibilities inherent in scientific evidence and technology available and the evolving necessities and expectations of society and the environment, Figure 21.

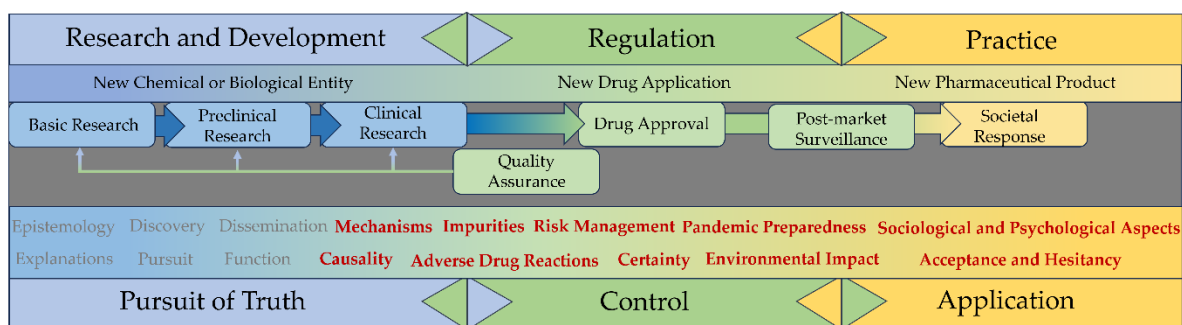


Figure 21. A schematic illustrating the phases of developing a new chemical or biological entity into a pharmaceutical drug product. The “Regulation” step is at the center imposing standards for assuring the quality of research and development, evaluating new drug application for approval and conducting post-market surveillance in terms of pharmacovigilance and environmental impact of pharmaceuticals. Relevant aspects to regulations and control are depicted in red.

This regulatory dynamic extends beyond just a directive framework; it spans a broad spectrum of actions ranging from “Good Laboratory Practice” in basic and preclinical research and “Good Clinical Practice” in the clinical phase to “Good Manufacturing Practice” in production. The regulatory apparatus is also responsible for evaluating new drug applications related to approval and market entry of pharmaceutical products as well as their aftermarket surveillance of potential adverse drug reactions and environmental impact. Its aim is to ensure that the products of pharmaceutical research, primarily drugs and medications, foster health and wellbeing of society while being administered safely and effectively. Importantly, control also serves to mitigate potential detrimental impacts; because of the intimate relationship between pharmaceutical products, human health, societal well-being, and environmental health, the potential risks can be considerable. Decisions directing control towards safely attending to societal needs are usually informed and based on scientific evidence.

Maintaining the safety and effectiveness of pharmaceutical products, therefore, embodies a dual purpose: it aims to ensure therapeutic benefits while minimizing potential harm. As will be discussed, this goal is reached through implementing risk management approaches and quality assurance standards. In both cases, decision and action is usually predicated on knowledge or evidence generated through scientific practice in pharmacy and dependent on the approaches and technologies available. These aspects form the bedrock of regulatory oversight, policy formulation, and informed or evidence-based decision-making in pharmacy.

The subsequent section further explains the concept of control in pharmacy²⁵. Section 4.2. is dedicated to the recent regulatory deliberations of the COVID-19 vaccines. This section addresses risk and risk attitudes in decision-making and methodological constraints imposed by global health emergencies and suggests possible solutions. Section 4.3. is dedicated to the issue of pharmaceutical impurities. This section exemplifies the strict regulation on pharmaceutical impurities and reflects upon them from a chemical, biological and environmental perspective. Section 4.4. is dedicated to reviewing the environmental and ecological impact of unused and expired medication from the perspectives of guidelines and regulations. Section 4.5. is the chapter's conclusion.

²⁵ The discussion in this chapter is supported and based on three manuscripts published in international, peer reviewed journal: **Abdin, A.Y.**; Yeboah, P.; Jacob, C. Chemical Impurities: An Epistemological Riddle with Serious Side Effects. *Int. J. Environ. Res. Public Health* 2020, 17, 1030. <https://doi.org/10.3390/ijerph17031030>, Alnahas, F.; Yeboah, P.; Fliedel, L.; **Abdin, A.Y.**; Alhareth, K. Expired Medication: Societal, Regulatory and Ethical Aspects of a Wasted Opportunity. *Int. J. Environ. Res. Public Health* 2020, 17, 787. <https://doi.org/10.3390/ijerph17030787> and **Abdin, A.Y.**; De Pretis, F.; Landes, J. Fast Methods for Drug Approval: Research Perspectives for Pandemic Preparedness. *Int. J. Environ. Res. Public Health* 2023, 20, 2404. <https://doi.org/10.3390/ijerph20032404>.

4.1. The Concept of Control in Pharmacy

The term “control” traces its origins back to the early 14th-century Old French “*contrarotulus*”, a register or roll used to cross-check other registers, or “*rolles*”. The root of this term can be broken down into two Latin parts: “*contra*” meaning “against” and “*rotulus*” meaning “roll, a small wheel”. Over time, the term evolved and came to be associated with the idea of exercising restraint or maintaining authority over something so to achieve a goal.

When juxtaposed with similar terms such as “standard”, “regulation”, and “guideline”, “control” carries unique nuances. A standard often refers to an established norm or requirement which has been widely accepted. It functions as a benchmark “roll” against which performance or quality can be measured and evaluated. Conversely, a regulation is a rule or directive enforced by an authority, while a guideline provides general advice or recommendations about how something should be done. The concept of control, while overlapping with these terms in some areas, primarily focuses on the authority or power to influence, direct or dictate the course of events.

In the context of scientific practice, particularly pharmaceutical sciences, control refers to implementing measures which ensure that experimental conditions are strictly maintained or that a particular variable is held constant. In clinical trials, for example, a control group may receive a placebo treatment, allowing researchers to compare the effects of a drug against a baseline. This type of control provides a means of verifying the reliability and validity of experimental results. From an industry perspective, control involves processes to manage operations, ensure quality, and optimize productivity. For pharmaceutical manufacturers, control mechanisms may include quality assurance procedures, process optimization, and regulatory compliance.

From a social perspective, control might refer to social norms, regulations, laws or traditions which shape behaviors and attitudes and subsequent action. In a pharmaceutical context, this could be observed in public campaigns promoting vaccination, banning the use of contraceptives or discouraging misuse of analgesics or painkillers. From an environmental standpoint, control represents the measures taken to mitigate adverse environmental impacts. Within pharmacy, this includes developing and implementing strategies for managing millions of tons of unused or expired medication and minimizing their disastrous impact on biodiversity.

In policy-making -perhaps most relevant to the ensuing discussion- control denotes the measures taken by governing bodies to regulate activities, often with the goal of protecting public interests. An example in pharmacy is the control exerted by agencies such as the European Medicine Agency (EMA) in the European Union and the Food and Drug Administration (FDA) in the United States and the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom, which sets strict regulations on the development, testing, market entry, distribution and post market monitoring of drugs to ensure their safety and effectiveness.

Within pharmacy, the role of control indeed stands out as pivotal, serving to align the diverse interests of its many stakeholders. Such interests may range from individual consumers and vast industries to vigilant regulatory bodies and environmental concerns. Central to all these interests is the pharmaceutical product, the culmination of rigorous research, development, and regulation. Each stakeholder brings a specific lens to the notion of control. An individual might focus on therapeutic outcomes, industries on profit and market performance, regulators on public safety, and environmentalists on responsible disposal. Despite these varied viewpoints, the hope is for a common thread: ensuring the product's safety and efficacy while meeting the broader needs of society.

4.2. Regulating under Pressure: Lesson for Future Pandemic Preparedness

Emergencies in public health, such as novel infectious disease outbreaks, present a difficult challenge for scientific communities, practitioners, and drug regulatory bodies. The pandemic of COVID-19 represents a case in point, which has thrown the spotlight onto the concept of pandemic preparedness and stimulated an impressive volume of academic literature [282–286]. Pandemic-related discourse has become so ubiquitous that it has permeated even traditionally less related fields such as philosophy [287–292]. Though the topic of pandemics attracted grand attention, little has been devoted to the process of decision-making regarding the approval and implementation of medical countermeasures, such as vaccines, in the event of future pandemics.

The approval and authorization of such pharmaceutical products serve as crucial regulatory mechanisms to guarantee their safety and efficacy. Under usual circumstances, the trajectory of drug development and approval is protracted and costly, with low success rates and sluggish clinical implementation [293,294]. In contrast, an effective response to pandemics necessitates swift decision making [295]. Meanwhile, the urgency of such situations inherently introduces uncertainty, as time pressures preclude comprehensive randomized clinical trials (RCTs) [296,297].

In the absence of randomized evidence, decisions must rely, at least in part, on non-randomized or Real-World Evidence (RWE). Characterized by observational data obtained outside of RCTs, RWE provides clinically pertinent evidence for decision-making.

A conceptual examination of decision-making in the context of pandemic-driven drug approval reveals three intertwined issues [298]. Firstly, which risk attitudes should be adopted? This relates to the management of risk in drug approval decisions amid substantial uncertainties. Secondly, which methodology should be employed for evidence production? When feasible RCTs are not an option, the emphasis shifts to study designs which can generate the best supporting evidence for drug safety and effectiveness. Thirdly, how should already available evidence be consolidated? This addresses methods for bias reduction and evidence aggregation to support decisions.

Advancements in the understanding of these complex questions concerning the methodology for drug approval during pandemics could enhance pandemic preparedness and, ultimately, yield better public health outcomes. It is worth noting that pandemic preparedness often refers exclusively to human and physical resources. In the context of this thesis, however,

a broader definition, encompassing methodologies for making uncertain inferences in public health decision making is adopted [299].

Hence, the ensuing discussion will explore these three aspects and possible means to address them. Providing definitive answers to these questions remains beyond the scope of this section, the aim is to conceptually (i) outline relevant questions, (ii) highlight challenges to answering such questions, and (iii) suggest potential methods for overcoming these challenges, with the end goal of enhancing pandemic preparedness. The conceptual analysis draws upon recent advancements in the philosophy of science, philosophy of medicine, and risk assessment theory.

The subsequent section initiates the discussion by addressing risk attitudes and concepts. It also suggests strategies for handling risk in public health emergencies and lists some lessons learnt from the COVID-19 pandemic. Section 4.2.2. contemplates the optimal study design amidst pandemic constraints. Section 4.2.3. highlights strategies and constraints of amalgamating and synthesizing the evidence available to render informed decision-making. Section 4.2.4. is a brief conclusion.

4.2.1. Risky decisions

Risk, with all its complexities, occupies a central position in decision-making, particularly during public health emergencies. Risk is conceptualized as the probability and severity of adverse health outcomes arising from pandemics, compounded by uncertainties in medical decision-making and response strategies. It encompasses both the direct health implications and the nuanced challenges presented by societal, ethical, and methodological considerations. The attitudes of decision-makers towards risk are shaped by the inherent uncertainty of potential choices or courses of action so to achieve specific outcomes. This significantly influences the approach to managing crises such as the COVID-19 pandemic.

Three primary risk attitudes highlighted by traditional decision theory play a vital role in crisis management. Risk-neutral individuals focus on maximizing expected benefit, irrespective of uncertainties. Those with a risk-averse stance prioritize being on the safe side, opting for less uncertainty even at the cost of potential benefits. Conversely, risk-seekers willingly trade some expected utility for the chance of larger benefit, emphasizing better-than-expected outcomes.

Underlying these risk attitudes is the concept of “uncertainty”, a condition marked by the absence of complete, definitive evidence, knowledge or data. Beyond scientific unknowns due to methodological or technological limitations, uncertainty permeates various aspects of a crisis, including societal responses, policy effectiveness, healthcare system capacity, and the broader impacts on socio-economic structures and even individual or group psychological factors.

In the context of a global health emergency, uncertainty is not inherently negative. Instead, it is a reality requiring recognition, quantification where possible, and effective management. The intertwining of uncertainty and risk attitudes underscores the complexity of decision-making during crises. Risk attitudes fluctuate with changing disease dynamics, cultural norms, and emerging scientific evidence, hence capturing and managing them together is paramount in navigating the terrain of uncertainty effectively, making it an essential component of crisis management. Therefore, an understanding of risk attitudes, their relationship with uncertainty, and their impact on decision-making processes is crucial in mitigating the challenges posed by public health emergencies.

4.2.1.1. A Set of Risk Attitudes and Concepts

Decision-making in the domain of public health emergencies holds intricate dynamics between risk and the consequent attitudes towards it. These dimensions have an extensive impact on the collective response to crises, evident in the global navigation of the COVID-19 pandemic. An exploration into these multifaceted risk attitudes and the broader paradigms of concepts for handling such risk in healthcare decision-making offers significant insight into how to comprehend, confront, and handle uncertainty.

When confronting novel diseases, how can regulatory bodies or public health practitioners navigate vast uncertainties surrounding the potential benefits or effectiveness of a medical intervention? The debate on prescribing hydroxychloroquine for treating COVID-19 exemplifies this challenge, with profound uncertainty surrounding its effectiveness and safety leading to hesitation in its endorsement [300,301]. Typically, benefit assessments employ a comprehensive array of statistical tools which quantify anticipated benefits. Such methods also allow for the statistical representation of uncertainties in terms of expected average benefits and variance. Such deliberations are fundamental in drug approval dialogues. During pandemic situations, however, the data available might not provide a steadfast quantification of expected

variance or average benefit. Hence, the question remains: how should we address and act upon these embedded uncertainties?

In terms of safety, how should regulators address the profound uncertainties concerning the magnitude of adverse reactions, both in severity and frequency, when evaluating a medical intervention for a novel disease? For instance, concerns about the Oxford–Astra Zeneca vaccine’s association with blood clotting led regulatory bodies to tread cautiously in its implementation [302]. Safety assessments differ from their benefit counterparts in that they emphasize tracking rare adverse events, potentially leading to severe outcomes. Given the infrequent nature of these events and the limited scope of many randomized clinical trials, safety evaluations often incorporate evidence from non-randomized studies [179,303–305]. Such assessments routinely feature narrative reviews which integrate Real-World Evidence (RWE). Though methodologies to assess safety based on non-randomized evidence exist, a pronounced lack of randomized data can amplify uncertainty about expected adverse reaction magnitudes, variances, and populations at increased risk. Navigating these uncertainties, already challenging in standard conditions, becomes even more critical during medical emergencies [306].

Similarly, how should one effectively balance the benefits of a medical intervention against potential risks (harm)? In other words, how can we trade the effectiveness of a medical intervention for its safety or *vice versa*? The case of the Oxford–Astra Zeneca vaccine’s suspension due to blood clot concerns offers insight, revealing that reactions varied across countries, possibly influenced by differing risk attitudes or decision-making speeds [297,302]. One should also not forget that the general public play a role as in most cases they have a right to accept or refuse not only vaccines but any medical intervention, more on this in Chapter Five. From a decision theory perspective, many experts assert that the normative approach should seek to maximize expected utility, *i.e.* effectiveness, by mitigating risks, *i.e.* adverse reactions [307–309]. This principle, which equates benefits and losses at a 1:1 rate, conflicts with the normative medical doctrine of “*primum non nocere*” – “first, do no harm”. In drug approval contexts, how should authorities, well-acquainted with such evaluations under regular circumstances, weigh expected benefits against anticipated adverse reactions, especially given the substantial uncertainties in adopting interventions directed to curb the spread of a novel infectious disease?

Regulatory bodies hold substantial responsibility in managing risks and benefits of medical interventions. Entities such as the EMA and the FDA oversee the market entry and distribution of medicines, ensuring that only those deemed effective and safe are accessible to the public [310]. These regulatory measures are, however, sometimes contested by patient groups and drug manufacturers, who argue for greater patient autonomy in medication choices, especially when the individuals are the ones directly affected by the drug outcomes [311–314]. Amidst time constraints and a scarcity of robust scientific evidence, the pivotal question arises: should regulators grant patients enhanced discretion in their medical choices?

Furthermore, mandating vaccination in specific subpopulations, such as health workers or the elderly, has been observed in numerous countries [315]. Given the exceptional potential of pandemics to adversely affect entire societies, the question arises: in light of the collective responsibility to combat widespread diseases, should health interventions be made mandatory, particularly for symptomatic patients who pose a greater risk contagion? Or, given the broad societal impact, should individuals have a greater voluntary role to undertake and participate in such interventions?

The issue of regulating during a public health crisis is further complicated once resource allocation is scrutinized. Distributing scarce medical resources during a pandemic brings about critical ethical considerations. While drugs vetted by the EMA and the FDA are usually abundant in non-pandemic scenarios, a pandemic's urgency demands swift resource allocation. The prioritization of vital workers and vulnerable, usually older or immune compromised individuals for COVID-19 vaccines has been a notable global strategy [316]. It should be noted that this has not been the case globally. China, for instance, prioritized its young population to receive the COVID-19 vaccine as they represented individuals who are most likely to contribute to society and help to minimize the impact of the pandemic [317]. Yet, scarcity, as exemplified by ventilator shortages [318], and the nascent understanding of drug risk-benefit profiles complicate this approach. Critical questions emerge: Should allocation favor those with higher life expectancy or quality of life, potentially prioritizing younger individuals over the elderly? How do the varying risk profiles and recovery prospects by age, as well as considerations of booster shots *versus* global aid to less fortunate countries with low vaccine coverage, play into these decisions [319–321]?

In the race to counter pandemic threats, prioritizing research funds is also rendered pivotal. Both public and private sectors have channeled resources towards researching therapies and

preventive strategies, especially vaccines [179]. Organizations such as the WHO have funded initiatives like the “Solidarity Trials” to evaluate the effectiveness of existing drugs against COVID-19 [301]. Given the inherent advantages of existing drugs, including lower costs, better-understood risk profiles, and immediate availability, they have garnered significant attention. This direction of funding aligns with the predominance of treatment-focused trials on platforms such as ClinicalTrials.gov, underscoring the broader strategic approach to resource allocation in research [179].

Yet availability of research funding is only part of the story. In the urgency of a pandemic, determining the most ethical means of generating reliable evidence about drug safety and effectiveness also presents significant challenges. During the COVID-19 pandemic, the prevalence of animal experimentation has been notable [322], while human challenge trials, which involve the intentional exposure of healthy volunteers to pathogens, have been sparse and eventually controversial [323]. Animal models offer means of conducting trials at the potential expense of their welfare [324]. Human challenge trials, however, promise even quicker and more reliable evidence yet poses substantial health risks to participants [325,326]. This raises an ethical dilemma: Should we prioritize human welfare by increasing potential harm to animals, or put humans at risk for faster and more reliable data collection? Advocates of animal rights and several ethicists champion the principles of “replacement, reduction, refinement” [327], emphasizing alternatives like *in vitro* and *in silico* research. The pivotal question remains: How should ethical bodies navigate the intricacies of human challenge trials and animal experimentation amidst a health crisis?

While each pandemic or health emergency presents unique challenges to regulatory authorities, health practitioners and the general public, an improved understanding of these risk attitudes and concepts may significantly enhance preparedness for future pandemics. Analyzing risk attitudes, as showcased during the COVID-19 pandemic, and the broader paradigms of risk management offers essential insights into how the global society can navigate such crises in the future.

4.2.1.2. Balancing Risky Decisions: Experience Meets Theoretical Frameworks

Drawing on past and previous events and experience offers a valuable approach in discerning rational risk attitudes for navigating future pandemics. Presently, pervasive diseases such as malaria, HIV/AIDS, and hepatitis in regions such as Ghana compel health professionals to handle difficult decisions [328,329]. An analysis of these decisions and courses of action

employed, whether through direct elicitation or observation, may offer critical perspectives to guide responses in upcoming crises. It has been observed, for instance, that during previous outbreaks, notably Ebola, quarantine measures often posed challenges, sometimes leading to adverse outcomes such as community or social resistance [330].

In complementing past experiences, theoretical frameworks may play an indispensable role. Ethical theories, despite their normative nature, guide actions towards morally sound decisions. Pertinent discussions in this realm revolve around the level of oversight by drug regulatory bodies, the delicate balance between risks and benefits, responses to unforeseen risks, concerns surrounding animal welfare, and the ethics of human challenge trials [324,325,331–333]. *Consequentialist theories*, such as *utilitarianism*, tend to advocate actions which would maximize societal wellbeing, such as the rapid approval of medications or vaccines. Conversely, *deontological* approaches might support adhering to the established regulatory guidelines irrespective of external pressures. *Virtue ethics* pose the question of how a virtuous and moral actor would handle such a situation. This could translate into finding a balance between the urgency of a situation and the safety of medical intervention. *Care ethics* might necessitate the distribution of medications or vaccines to individuals who are in critical conditions while still in the period of conducting safety and effectivity assessments. *Contractarianism* holds that moral actions are those resulting from unbiased, collective consensus. In this context, moral principles are derived from the idea of a social contract or general agreement among individuals towards mutual advantage. Similarly, *relativism* involves factoring cultural or societal norms. Notably, in real-world situations, these ethical frameworks might not necessarily be in conflict when considering the ethical or moral course of action and regulatory bodies tend to draw on insights from different ethical theories.

Drawing from the experiences of battling the COVID-19 pandemic, it becomes evident that effective risk communication plays a pivotal role in managing such crises [334,335]. This sentiment is reinforced by the EMA's assertions. Insightful exploration of the interplay between evidence and decision-making processes has been highlighted [336]. It is stressed that during emergencies, rapid evaluation models present innovative methodologies for the production of evidence. Intriguingly, in the throes of an emerging infectious disease crisis, evidence gathering, its synthesis, pivotal decisions, and public health responses unfold concurrently. It has been advocated for a fluid and reflective strategy which necessitates continuous dialogue between policymakers and the population impacted.

4.2.2. Generating Evidence during Emergencies: Frameworks for Reliable Study Designs

Certain attributes of study design are essential for drawing reliable conclusions. In situations where such designs are inaccessible such as the urgency of a pandemic, the reliance shifts to expert opinions, mechanistic evidence, and observational findings, *i.e.* RWE.

In light of the urgency for expedited decision-making and evidence gathering during a pandemic, conducting thoroughly powered randomized studies represents a serious challenge. At the initial stages of a pandemic, owing to the nascent understanding of the pathogen's biological and epidemiological properties, participants in vaccine trials may not encounter consistent exposure, thus hindering a robust assessment of therapeutic strategies [337]. Likewise, clinical trials may face hurdles in achieving the desired patient recruitment thresholds [338]. Faced with such complexities, the overarching aim remains to harness the most robust evidence possible. Thus, the pertinent question arises: How might we formulate study designs which offer the most robust and actionable evidence?

Establishing an optimal study design *a priori*, without considering the specific context, proves impractical. Directing the discourse, however, towards addressing aspects of study design associated with reaching reliable conclusions is indeed insightful. Duration of observational studies, for instance, is a modifiable element in study designs and plays a pivotal role. Specifically, the duration of observation is rendered indispensable when discerning potential drug-related side effects or adverse reactions [177,339,340]. While an extended observation period aids in recognizing a drug's harm, the urgency of pandemics or the outbreak of novel infectious diseases the overriding urgency intrinsic to pandemics significantly reduces the time available.

The challenge is compounded when considering patient enrollment count in trials, another manageable parameter. It is assumed that the larger the sample the more reliable the conclusion. Constraints, such as limited number of volunteers, drug supply shortages, time constraints for clinical trial preparations, and reduced chances of patient-pathogen interactions, represent considerable obstacles [337,338]. A comprehensive sample endows researchers with confidence against statistical anomalies *i.e.* promotes precision. Yet, it offers no assurances of the true representation of effect size: precision does not necessarily equate to accuracy [341]. Effect size is a quantitative measure which captures the magnitude of a difference or relationship between variables in a study. In COVID-19 vaccine trials, for instance, an effect size might represent the degree of difference in infection rates between vaccinated and

unvaccinated groups, highlighting the vaccine's practical efficacy beyond just statistical significance.

Conflicts of interest, an often-overlooked factor, may distort study designs and their subsequent interpretations [342,343]. Some public health experts even advocate for the nationalization of drug research and development, evaluation, and monitoring [331]. Given the financial interest at play in such decisions, one way to reduce inherent biases could be by excluding pharmaceutical developers from drug monitoring. Moreover, employing covariate adjustments²⁶ during both design and analytical phases may serve to reduce biases. It is worth noting that current practices in the academic community already advocate such techniques in randomized trials and observational studies, provided certain conditions are met [344]. Upholding these standards, even in the midst of pandemics, emerges as a reasonable step forward.

Surrogate models, including animals, *in vivo*, *in vitro*, and *in silico* studies, have consistently offered cost-effective, large-scale research avenues. To translate findings from such models to humans, external validity²⁷ is paramount [345]. In contrast, acquiring direct evidence necessitates its source to be from the target patient population, such as human challenge trials discussed earlier. Rendering inferences and subsequent medical intervention based on evidence or findings from the broader population to handle the needs of a specific patient introduces myriad challenges. The selection of an appropriate reference population presents a complex task: opting for a broad reference class may yield a diverse group of patients, not all of whom might mirror or account for the need of the patient in focus. Conversely, a narrower reference class might yield limited observations, making dependable frequency estimation problematic [346]. This delineates an intricate balance between the richness of data and its precision *i.e.* favoring quantity of evidence over its quality or *vice versa*.

Furthermore, hounding external validity frequently leans on analogical reasoning, where the parallels between the model and human subjects are construed based on specific resemblances [347–349]. Yet, these determinants of resemblance or similarities inherently validate the relevance of the analogy, leading to a futile circular argument known as the

²⁶ Covariate adjustment refers to the statistical process of controlling for potential confounding variables in an analysis. It aims to isolate the effect of a primary predictor on an outcome by accounting for other influencing factors.

²⁷ External validity pertains to the extent to which study results can be generalized to settings, people, times, and measures beyond those used in the experimental setup. It addresses the applicability of findings across varied conditions and populations.

extrapolation circle [350]. This recursive cycle poses significant challenges to the validity of evidence derived from surrogate model experiments. Notwithstanding, the quest to successfully adopt analogical reasoning persists in science, as seen in recent explorations [351,352].

4.2.2.1. Decisions from Imperfect Evidence

Several fields deal consistently with suboptimal data. Take astrophysics as an example, where direct interactions with black holes remain elusive. Instead, researchers rely on table-top experiments (dumb holes) which mimic certain properties of black holes [353]. Nutrition science, aim to delineate the effects of diet on health. Due to the subtle and protracted nature of such effects, however, randomized controlled trials are indeed, generally, impractical and inapplicable [354]. Regardless, a consensus on what delineates a healthy diet has been largely achieved [355]. Delving into their causal inference techniques could offer insights into better addressing pandemics. Such insights, however, should be handled and applied with caution. These disciplines discussed here do not and perhaps cannot intervene on the subject of their study, such as the blackhole, in a similar manner say in a controlled experimental setting employing a specific microorganism or a cell-line. These sciences are descriptive in nature and their causality is counterfactual discerned through theorizing retrospectively. Turning to the medical sphere, orphan drugs, by their very nature, target infrequent medical conditions [356]. The effectiveness and potential side effects of such drugs remain relatively obscured during their initial approval stages. This mirrors the urgency and ambiguity seen during drug approvals amidst public health crises. Therefore, methodologies employed in the evaluation of orphan drugs might offer valuable lessons when navigating drug evaluations during pandemics.

The incorporation of a control group is an integral component of RCT methodology. It enables assessing the effectiveness of medical interventions in RCTs by comparing their outcomes against the control group, which may exhibit the placebo effect. In contrast, the “nocebo effect” represents the perception of adverse effects after the administration of a medication. The nocebo effect is a psychological phenomenon arising when negative expectations of a treatment lead to detrimental outcomes or side effects in a patient. It is the counterpart to the placebo effect, where the belief in a treatment's efficacy can produce positive outcomes, even without therapeutic intervention. The magnitude and frequency of nocebo manifestations are influenced by risk communication and have been analyzed in the context of COVID-19 [357,358]. Such observed nocebo reactions offer a model to anticipate the intensity

and prevalence of nocebo responses in subsequent pandemics. Furthermore, one may increase the sample size by simply devising more inclusive criteria, actively engage in patient recruitment and avoid pre-setting a designated count.

From a broader perspective, one may also focus on including the social and contextual dimensions in evidence-based reasoning within data science. Adopting a “holistic, reflexive, socially conscious, and participatory research approach promises more resilient, trustworthy, and ethical results, albeit demanding greater investment in time and resources” [359]. Additionally, there is a growing call for heightened transparency in evidence evaluations, pertaining to data selection, measurement methodologies, model choices, and so on, and to conduct these discussions in public forums [360].

4.2.3. Crafting Evidence during Emergencies

The attention is now shifted to the task of consolidating or amalgamating existing evidence so to craft informed decisions and regulations. In pressing public health crises, regulatory entities such as the EMA and the FDA have formulated protocols to speed the drug approval procedure. These methods encompass rapid review and assessment of marketing submissions, along with sanctioning the emergency deployment of medical interventions [361,362]. The nature of these methodologies is overarching and somewhat general, for instance, stipulating a favorable benefit-risk ratio and an individualized examination. Several successful COVID-19 vaccines, however, received approval via these channels [363]. The point of departure is a pressing need to refine such evidence synthesis strategies to aptly tackle ensuing pandemics.

Building on the prior discussion, the framework of an informed decision would draw upon all evidence available which encompass RWE (real world evidence) manifested as population-centric observational research, animal trials, basic science findings or mechanistic evidence, and *in silico* clinical experiments. The conundrum then is to leverage this vast pool of knowledge optimally. What approach should be adopted to efficiently put together this plethora of evidence?

In an ideal scenario, one would possess a strategy to eliminate or rectify biases within available evidence to extract reliable insights to inform the best course of action. Regrettably, such an optimistic approach remains elusive. The aspiration to purge data of bias remains a distant mirage at this juncture. The most sophisticated concepts and structured techniques for evidence amalgamation revolve around meta-analyses rooted in statistical approaches. Yet,

meta-analyses grapple with assimilating data from diversely designed studies, such as randomized, case-controlled, longitudinal, and cross-sectional. To incorporate findings from tests on surrogate models, a broader albeit less regimented evidence amalgamation approach is adopted. Regulatory bodies responsible for drug approvals have already started employing such less structured amalgamation methodologies. They are indispensable, especially when considering individual case studies pivotal in pharmacovigilance [364,365].

Considering the urgency for evidence amalgamation methodologies in pharmacovigilance, which is equipped to handle a diverse array of potentially biased evidence, it is understandable that a plethora of techniques have emerged targeting either the quality/bias assessment or the overarching synthesis of data. The challenge is not rooted in a lack of techniques or methodologies [366]. Conversely, the conundrum lies in the overabundance of techniques available, with a blurred vision regarding which one to employ and in which scenarios.

4.2.3.1. Navigating Uncertainties in Evidence Synthesis

Philosophical interest deeply probes into the facets of evidence synthesis, yet the actual management of profound uncertainties remains unresolved [367,368]. As discussed above, mere statistical methodologies fall short when synthesizing evidence, particularly in pandemic-induced drug evaluations. Below are additional considerations to overcome uncertainty which might reinforce causal inference, supporting drug approval decisions during pandemics.

The dominant approach addressing scientific and medical uncertainties leans on *Bayesian epistemology* [369–371]. Similar to Bayesian statistics, the uncertainties in Bayesian epistemology are anchored in (i) prior probabilities which encapsulate the evidence available and (ii) update mechanisms to express evidence accumulation and posterior probabilities [372]. The main difference from Bayesian statistics is that this epistemology defines probabilities across all relevant variables. Its foundational premise is that evidence accumulation supersedes any initial beliefs, with developing posterior convictions gradually aligning with the actuality (the real world) [373]. This facilitates comprehensive evidence amalgamation, enabling the computation of probabilities concerning drug effectiveness and safety [170,171,214,374]. Yet, there is a stumbling block with Bayesian synthesis. It relies on a large number of probabilities which objectivity is sometimes questionable as this approach in many cases requires subjective, expert opinions [375]. The debates concerning this subjectivity are notable [376–379], and one

may argue that decisions impacting millions if not billions of people should transcend the subjective allocation of prior probabilities and instead seek objective means.

Another approach to navigate uncertainties is to deploy the *imprecise probabilities framework*. Here, instead of a definite percentage, a range is given to represent uncertainty. During the early phase of COVID-19, for instance, experts applied the imprecise probabilities framework, suggesting a 15% to 25% hospitalization rate for a specific demographic. This approach aptly captures the large uncertainties faced in decision-making given evidence available [380–382]. Another challenge, however, emerges: there are multiple ways to interpret and exploit these ranges of probability to derive decisions in terms of medical interventions [383]. While some interpretations may suggest inaction due to lack of clarity or evidential support, decisions and action often remain imperative. Currently, there is no universally accepted guideline on how to choose among these interpretations. Hence, such a broad range poses challenges for the planning and allocation of healthcare resources.

Several other methodologies warrant mention. *Qualitative decision theory* represents an aspiring approach [384]. Qualitative decision theory focuses on decision-making without relying on numerical quantification. Instead of using numbers, it emphasizes the nature or quality of choices available. In medical contexts, however, quantifying the magnitude or effect size of a treatment or medication is crucial, which poses challenges for solely relying on qualitative approaches. *Ranking functions* represent another qualitative approach. they provide a hierarchy of outcomes based on their importance, systematically ordering them without assigning explicit numerical values. Ranking functions encapsulate uncertainties by assigning distinct ranks to outcomes within the sequence $\{0,1,2,3,\dots,\infty\}$ [385]. Yet, reaching decisions while exploiting ranking functions remains obscure, and no strategy exists to translate medical evidence into such functions. *Severe testing* primarily focuses on appraising statistical hypotheses through rigorous evaluations [386]. This statistical approach mandates stringent statistical evaluations, ensuring that only hypotheses withstanding robust empirical scrutiny are endorsed. *Machine learning* and the broader scope of *artificial intelligence* are rapidly gaining traction in evidence synthesis [387–394]. Philosophical explorations on the potential of computer simulations in evidence management span foundational perspectives, theoretical constraints, and their inherent values [395–398].

Notably, advances in synthesizing and amalgamating real-world evidence stemming from the COVID-19 Literature have been scarce. A recent discourse on expected challenges has been

presented by the EMA. Some experts contend that the unique challenges posed by COVID-19 compel the scientific community not merely to hasten established evidence-based methodologies but to embrace a reformed perspective [336]. Such a perspective would not only address prevailing uncertainties but also adapt proactively to the dynamically evolving scenario of a public health emergency. Such progress, it is argued, demands a renewed receptiveness to varieties of evidence and specialized knowledge, which may often be overlooked in conventional evidence-based practices.

4.2.4. Concluding Remarks

The approval of medical or pharmaceutical interventions remains pivotal in addressing the intricate repercussions of pandemics and public health emergencies. This section delved into the facets of regulating and drug approval in the midst of a public health emergency, namely the COVID-19 pandemic. The overarching objective lies in formulating a robust methodology which seamlessly assimilates, refines, and applies evidence for health-related decision-making. This is possible by focusing on risk attitudes and management strategies, study designs to generate evidence and statistical techniques to synthesize and amalgamate all evidence available to reach an informed decision. Ethical considerations based on the frameworks discussed above remain imperative in navigating such tragic circumstances. Preemptively combating a pandemic, ensuring it does not escalate into a worldwide health catastrophe, remains the optimal strategy to mitigate potential tragedies. In this pursuit, interdisciplinary collaborations and pioneering research methodologies stand together as indispensable allies.

4.3. Pharmaceutical impurities: the “Dark Matter” of Pharmacy

Pharmacy and the pharmaceutical industry have witnessed an astonishing, swift evolution. This discipline has gone from small compounding dispensaries to global corporations and a science worth billions of Euros. While the research and development of new drugs, often referred to as R&D, continue to reach significant milestones in terms of effectiveness, the spotlight has increasingly moved towards ensuring safety and mitigating adverse reactions. The past few decades have seen several pharmaceutical crises emerge, ranging from unsafe ingredients and mislabeled dosage forms to deliberate falsification of medications and accidental contamination. Contemporary healthcare strategies predominantly aim at guaranteeing patient safety and comfort, which necessitates impeccable manufacturing regulations and high-quality medication and treatment protocols.

Regulatory bodies have indeed made visible strides in this regard. The transformation of the acronym GMP from Good Manufacturing Practices to cGMP, the “c” standing for “current”, underscores an unwavering commitment to uphold GMP [399]. In a parallel stride, the FDA proposed a shift from Quality by Testing (QbT) to Quality by Design (QbD) in 2004 [400]. This approach was effectively integrated by the International Council for Harmonisation (ICH), leading to the creation of numerous quality guidelines [401]. The primary goal of QbD is to formulate large-scale manufacturing procedures based on the principle of producing high-quality, consistent products.

Actual practice and application of these principles, however, proves more complex, particularly when we consider the unpredictability of chemistry and the subsequent biological activity. Side products and impurities must be factored into the equation. Such contaminants are typically perceived as risky²⁸ and present a significant challenge to the pharmaceutical industry and drug regulatory bodies today. Several historical and recent examples demonstrate the catastrophic consequences of such manufacturing variations. The infamous thalidomide scandal, for example, continues to serve as a reference point for scientific, philosophical, societal, and legal inquiry [402–404]. This event in the 1960s dramatically heightened awareness about the differing biological activities of racemic compounds and forever altered the ethical considerations surrounding chemical synthesis. The incident also influenced subsequent drug development processes and regulation. Another distressing incident from the same era is the case of “Agent Orange” [405,406]. Although not directly linked to pharmacy and pharmaceutical manufacture, the case involved a synthetic chemical which caused severe harm to millions of people and the environment due to a dioxin impurity.

In the years since, there has been a significant increase in the availability and sophistication of analytical tools applied to detect, identify, and eventually reduce or eliminate such impurities. Yet, instances of pharmaceutical scandals persist. The hypertension medication valsartan, for instance, made headlines worldwide in July 2018. The EMA and the FDA issued recalls for several batches of the drug due to a potential cross-contamination with the carcinogenic compound *N*-Nitrosodimethylamine (NDMA). Subsequently, the Chinese manufacturer *Zhejiang Huahai Pharmaceutical Co.* announced additional contamination with another carcinogenic impurity, *N*-Nitrosodiethylamine (NDEA) [407,408]. More recently, in

²⁸ Here too, risk and risk attitudes are essential in decision-making as pharmaceutical impurities are rife with ontological, epistemological and ethical issues. For an elaborate discussion on risk related issues, please refer to Section 4.2.1.

2019, tests indicated the presence of NDMA also in certain batches of the widely used H₂-inhibitor ranitidine, Figure 22 [409,410]

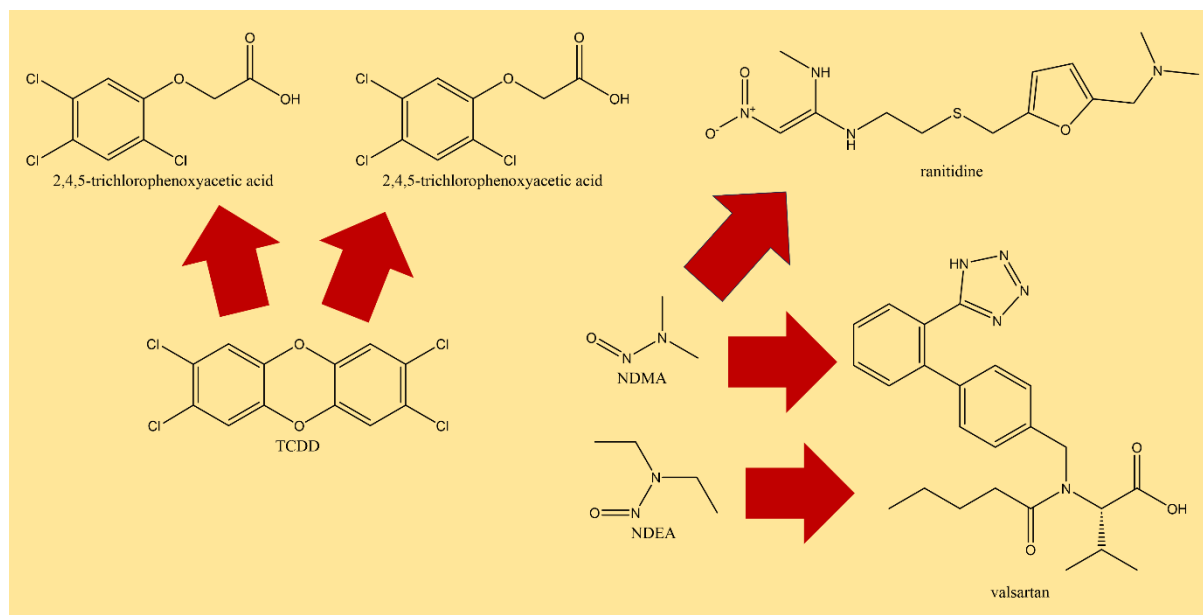


Figure 22. The left side shows Agent Orange which is an equal mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and the notorious dioxin impurity 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). The right side shows ranitidine which was contaminated with *N*-Nitrosodiethylamine and valsartan which was also tainted with *N*-Nitrosodimethylamine.

At this point, one may ask: What lies at the heart of this issue? Is it a lack of adequate analytical methods or is there a deeper underlying reason why such impurities arise and evade detection? This query paves the way for a deeper exploration of impurities, what they really are and how regulations can account for them all. Most compounds contain a certain degree of impurities which are typically established and quantified. In practice, this information about impurities is often indicated on the packaging of such chemicals. Such obvious or known impurities are expected and characterized. There exist, however, “hidden” impurities: substances which may only become evident and known due to a discrepancy in the mass balance or as unidentified signals in certain spectral analyses. These “substances” can be divided into two broad categories. On one hand, there are well-established and characterized chemicals such as NDMA and NDEA, which are sometimes not anticipated and thus not tested for. On the other hand, any synthetic process might yield entirely novel molecules which have not been chemically isolated or characterized before, such as the impurity in Agent Orange. As these “novel” impurities are structurally unidentified, that is, escape the scope of known chemical information and paradigm, their detection and identification are not straightforward, given their undetermined analytical properties at that point. Consequently, the presence of such novel, unintended substances in pharmaceutical products could lead to serious side effects.

This section applies the term ‘Xpurity’ to differentiate these unidentified impurities from those associated with an established analytics and chemistry. An Xpurity is an entity which exists yet not in an epistemological sense as information is absent about its chemical composition and structure; chemicals outside of chemistry. It is comparable to “dark matter” which is almost certain to exist, yet there is no information about it. Interestingly, it still does not fall outside the pharmaceutical product itself. Note that Xpurities are a subset of impurities, although the term “impurity” is broad and includes identified and unidentified entities as per the guidelines. The deliberate regulation of unidentified entities in drug products is a significant aspect, and thus the coinage of a new term like ‘Xpurity’ emphasizes this importance.

The next section addresses impurities in chemistry and pharmacy and reviews the different grades of purity and means of detection. Section 4.2.2. is dedicated to recounting the regulatory guidelines of impurities in pharmacy. Section 4.2.3. provides a detailed and updated classification of the types of impurities encountered in different contexts based on information available about their presence in a sample, chemical identity and biological activity. Section 4.2.4. consists of concluding remarks.

4.3.1. Impurities Everywhere!

In chemistry, the term “impurity” designates a chemical substance which is found within a specified chemical phase yet deviates from the phase’s chemical composition [411]. To label a chemical substance as “pure”, it must meet three key criteria [412]. The first of these criteria involves the presence of the chemical in at least one thermodynamic phase, as evidenced by a one-component-phase diagram. The second criterion is practical; the pure chemical must demonstrate homogeneity, meaning it exhibits consistent properties even after extensive consecutive analytical chemical procedures. Ideally, the pure chemical should resist all further separation and purification attempts. The third criterion refers to the classic chemical definition of purity, where the substance should contain no traces of any other chemical species. In actual scientific practice, however, absolutely pure chemical compounds hardly exist due to inevitable minor contaminations. Furthermore, as the detection capabilities of analytical chemistry improve, the number of identified impurities tends to grow [413].

While impurities are generally regarded as a drawback in chemical synthesis, they are typically of minor concern if their identity is known and their quantities are manageable. Chemists may accept substances with purity levels as low as 85% or even less, provided the reagents serve their intended purpose. The situation becomes significantly more complex,

however, from a pharmaceutical perspective. In this context, the result of the chemical synthesis is not merely a chemical substance, but a product specifically designed to address a particular medical condition in a safe manner. Consequently, impurities play a critical role, as they could inadvertently be administered to patients alongside the intended medication.

Given these considerations, it is understandable why the subject of impurities receives a special interest in pharmacy. According to the United States Pharmacopeia, impurities are “any component of a drug substance which is not the chemical entity defined as the drug substance; for a drug product, any component that is not a formulation ingredient” [414]. Similar definitions have been adopted by the International Council for Harmonization (ICH) and related agencies, which will be discussed in the following section [415].

Impurities are unavoidable and may emerge at any stage of drug product formulation, including from raw materials such as active pharmaceutical ingredients (APIs) and excipients. In most instances, the emergence of impurities during the manufacture of APIs can be anticipated and subsequently addressed, thanks to what is described as “conservative” regulatory guidelines and significant efforts by the pharmaceutical industry to abide by these regulations [416]. Due to the highly reactive reagents involved in the production of APIs, however, the likelihood of hazardous residues increases [417]. This imposes a substantial responsibility on regulators and the pharmaceutical industry to produce and supply safe and effective drug products [418].

Chemical and pharmaceutical manufacturing employs a classification system known as “grades of purity” to denote the level of impurities present within a substance. Each grade signifies specific standards which a substance must adhere to, to be recognized within that category. The variability in these standards caters to the unique needs of different sectors within the chemical and pharmaceutical industries.

At the lower end of the spectrum, the “Technical Grade” chemicals boast relatively low purity, rendering them ideal for industrial processes where impurity levels are not critical. This grade is often characterized by a high percentage of impurities, typically between 10% and 15%. Conversely, “Reagent Grade” chemicals are a step above in terms of purity, qualifying for application in most laboratory practices, usually $\geq 95\%$ pure. They are similar to the purity levels of the “Analytical Grade” chemicals standing strictly above 95%, and which are utilized in analytical procedures where any amount or number of impurities could potentially influence the outcome.

“Laboratory Grade” chemicals are identified by a broad classification, implying a minimum level of purity which is apt for teaching and educational purposes but unfit for quantitative chemical analysis or synthesis. On the other hand, ‘Pharmaceutical Grade’ chemicals represent the zenith of purity standards, rendering them appropriate for human administration. The purity of this grade of substances complies with strict testing criteria outlined by pharmacopeias such as the United States Pharmacopeia (USP), British Pharmacopoeia (BP), and European Pharmacopoeia (EP) to verify their identity, strength, quality, and purity.

Pharmaceutical grades are further divided into multiple categories, such as the ‘USP/NF Grade,’ ‘BP Grade,’ ‘EP Grade,’ and ‘JP Grade,’ adhering to the standards set by the respective pharmacopeias. ‘Food Grade’ and ‘Cosmetic Grade’ chemicals are designed for utilization within the food and drink manufacturing and cosmetics and personal care products sectors, respectively, mandating absence of *harmful* contaminants and impurities. The ‘ACS Grade’ signifies chemicals which meet or exceed the American Chemical Society (ACS) standards, essentially aligning with the analytical grade and suitable for high-precision laboratory tasks.

It is paramount to understand, however, that a purity grade does not determine its safety. Even substances of the highest purity can pose hazards contingent on their nature and application. This is the case, for instance, when the impurity despite present in small amounts has a disastrous biological activity manifested as witnessed in the dioxin impurity contaminating Agent Orange. Adherence to safety data sheets and necessary precautions during chemical handling is, therefore, a non-negotiable requirement.

The evolution of these different standards for chemical purity reflects the growth and advancements within scientific understanding and industrial needs over time., The ACS, established in 1876, for instance, has been relentlessly working on developing and standardizing purity grades. Similarly, the USP, founded in the US in 1820, provides standards for medicines, food ingredients, and dietary supplement products. These regulatory authorities adopt meticulous scientific testing and research to establish the purity levels required for each grade. This procedure entails the analysis of the chemical for impurities and other properties to ascertain its compliance with the standards of its designated grade.

The rationale behind different grades of purity lies in the impact which varying purity levels can have on the outcome of a specific application. Pharmaceutical manufacturing, for instance, necessitates extremely high purity levels, as impurities may induce undesirable side

effects or compromise a drug's effectiveness. Conversely, many industrial applications may accept a lower level of purity, as certain impurities might not significantly affect the process or the product. This variation in grades permits manufacturers to select a chemical grade which aligns with their specific needs, striking a balance between cost and intended outcome.

The identification and characterization of a specific impurity may be achieved through a range of methods. The method chosen largely depends on the quantity of the impurity and its sensitivity to the analytical technique selected [419]. Typically, multiple analyses are conducted to sufficiently characterize a sample and identify any signs of impurities, such as a spot on the thin layer chromatography (TLC) or a peak in the mass spectrum. Modern and automated characterization methods are often utilized due to their capacity to simultaneously separate and quantify impurities such as capillary electrophoresis, accelerated solvent extraction, supercritical fluid extraction, high-performance thin-layer column, flash chromatography and spectroscopic methods such as Raman spectroscopy, mass spectrometry and nuclear magnetic resonance spectroscopy. Traditional methods such as titration and colorimetry, however, continue to be of immense value [420].

4.3.2. Impurities in Regulatory Guidelines

Maintaining strict control of impurities in pharmaceuticals is a priority driven by ethical, financial, competitive, safety, and effectiveness considerations. This has catalyzed a global initiative to deepen the understanding of impurities in drug products [421]. This dedicated attention to such minute quantities of chemical contaminants underscores their significance.

The process of monitoring impurities in the pharmaceutical sector and research laboratories is influenced by numerous regulatory compliance stipulations. Primary guidance often comes from pharmacopeias or reference books which provide methods for impurity regulation and monitoring [422]. Historical mishaps within the pharmaceutical industry, however, necessitate a broader, potentially global, collaborative effort to establish governing principles within the field.

The first step toward this harmonization has been taken in the 1980s by the European Community, now the European Union (EU), which established the foundation for harmonizing pharmaceutical regulatory requirements. In 1989, the WHO's Conference of Drug Regulatory Authorities in Paris laid out plans for international harmonization. Soon after, in 1990, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was launched in a Brussels meeting hosted by the

European Federation of Pharmaceutical Industries and Associations [401]. Presently known as the International Council for Harmonization, this institution signifies a joint endeavor of regulatory bodies and representatives from the EU, Japan, and the United States. The ICH has spent decades formulating guidelines for new chemical entities to be considered for use in drug compounds and products for human consumption. These guidelines aim to ensure uniformity in requirements for new drug applications and have been ratified by both the EMA and the FDA [423,424].

Impurities have remained at the forefront of the ICH’s attention, generating a wealth of information and facilitating tighter impurity limits and more stringent control of drug substances and manufacture [425]. Alongside, the ICH has sought to unify industrial nomenclature and impurity categorization, with pivotal information provided in Figure 23 [415].

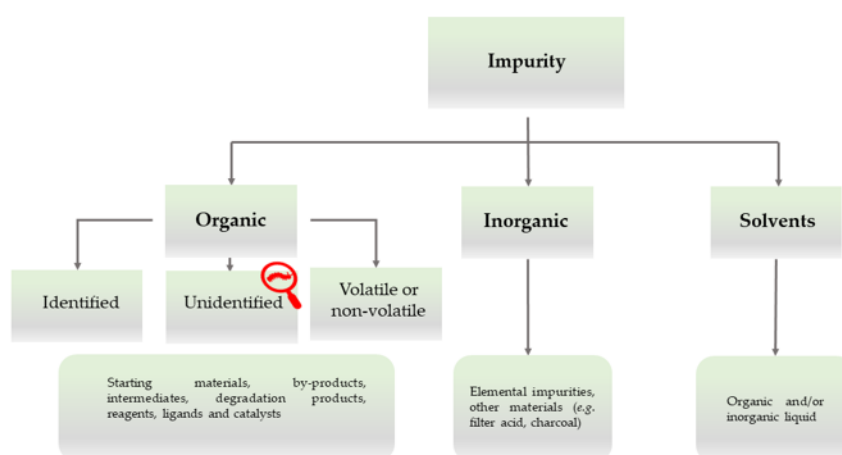


Figure 23. The classification of impurities by the ICH

ICH’s impurity classification covers a wide array of potential impurities which could contaminate specific drug products. These impurities should be detectable by an appropriate chemical analytical method, especially when the impurity profile of a chemical substance is questionable [413]. This substance includes impurities which remain undetected or undetectable using available methods, yet make their presence known through mass balance, spots on plates, signals in spectra, or in severe cases, through instigating toxic biological activity. These are designated as “unidentified impurities”.

These unidentified impurities present a unique philosophical quandary, as they differ from identified and structurally characterized impurities. As per the ICH glossary, these impurities lack chemical characterization and are defined solely by qualitative analytical properties [415].

Epistemologically speaking, these substances are outside the realm of current chemical knowledge and, strictly speaking, are non-identifiable *per se*.

The particularities of identified and unidentified impurities can be appreciated using a simple analogy involving common table salt. In this context, the naturally occurring potassium chloride, or sylvite, can be identified and quantified, albeit not removed. This sets it apart from trace impurities such as rubidium and cesium chloride, which, although present in small quantities, have not been analyzed and determined due to practical reasons. Xpurities, however, represent substances with entirely undefined chemical identity and biological activity. For instance, contaminants in sea salt derived from complex secondary metabolites of algae, or even recent findings of microplastics, may fit into this category [426].

The presence of unidentified impurities or Xpurities presents not just analytical, pharmaceutical, and epistemological challenges, but also ethical implications, as they potentially pose dormant threats. The presence of chemical substances in drug products with no available information about their chemistry or biology, necessitates revisiting the current classification of impurities.

4.3.3. A Philosophical Analysis of Impurities

Impurities in pharmacy bear an inherent ethical dimension, given their deviating biological activities in medicinal products intended for human use. Far from contributing to therapeutic effectiveness, these impurities typically introduce undesirable biological effects such as toxicity, carcinogenicity, and teratogenicity. Consequently, these minute substances attract interest not only from a pharmaceutical standpoint but also from an epistemological perspective. The key question here is how to discern the biological properties of an impurity, given that its chemical nature might be unknown, despite its confirmed presence within the drug product [427].

To unravel this complex situation, consider a delicious bowl of sausage soup tainted with a caterpillar or a hair. The fundamental query is whether the caterpillar truly exists in the soup, a question steeped in metaphysics, not epistemology. Then follows the epistemological question of our cognitive and experiential abilities of the caterpillar's existence in the soup. The subsequent stage involves the identification of the caterpillar, perhaps as a local German delicacy. Furthermore, in terms of biological effect, we need to decide if the caterpillar is a delicacy or a toxicant.

In this context, a complex network of epistemological associations among the categories which characterize and classify these impurities is recognized. These epistemic variables, *i.e.* presence, chemical identity, and biological activity, are best represented by a Cartesian coordinate system conceived by René Descartes (1596–1650), as illustrated in Figure 24.

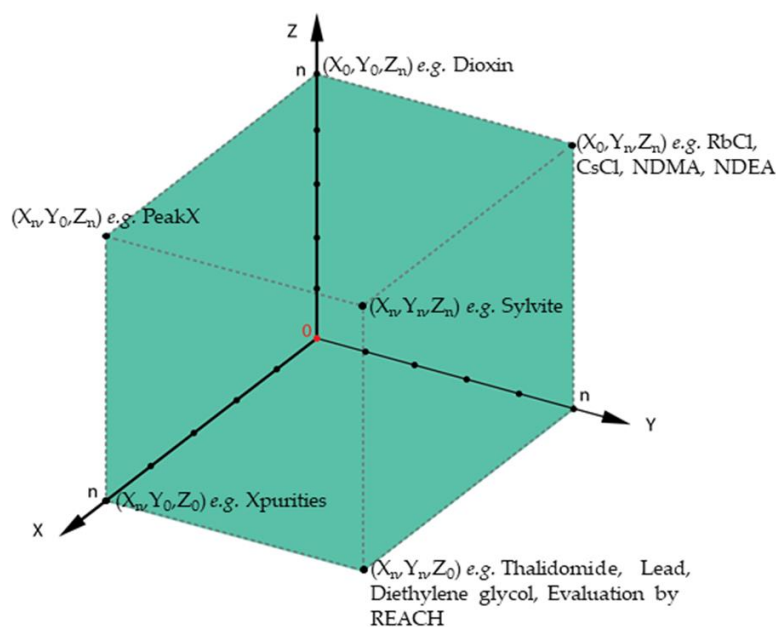


Figure 24. The Space of Information highlighting the different types of impurities in a drug product provides a temporal snapshot. The X-axis represents the presence of the impurity, while the Y-axis represents information about its chemical structure and the Z-axis represents information about its biological activity. The location of an impurity within this matrix helps determine necessary actions, whether it is a deeper examination of its presence, chemical properties, or biological effects, or perhaps no intervention. This framework also charts the evolving discourse of impurities as data accumulates. It is noteworthy that this matrix can be augmented to align with more rigorous regulatory standards and may include other aspects.

To preclude any unnecessary discussion about existence itself, it is held that all chemicals, no matter how pure, always contain some proportion of an impurity. Consequently, the metaphysical and ontological presence of an impurity is affirmed, even though details or information about such presence in terms of chemical characterization and biological implication could be unavailable due to the limitations of the analytical methods employed.

In this Cartesian Space, three different types of information along three different axes need to be distinguished. Firstly, to what extent are we informed about the presence of an impurity? Analytical chemistry can shed some light on this, through indications from mass balances and unusual signals in various spectra, such as MS and NMR. Information about an impurity’s presence along the X-axis increases with more “odd” or noise signals with further confirmation with other methods such as Atomic Absorption Spectroscopy (AAS) or TLC, thus suggesting the presence of impurities, or “The Ghosts” as they could be nicknamed due to their

elusive nature. Over time, the point representing the impurity thus moves higher along the X-axis.

Secondly, do we possess information about the impurity's chemical structure or identity? Here, we might have a mass peak, a spectrum, an elemental composition, an electronic structure, or even data about optical isomers. This information tends to increase as chemical analysis becomes more sophisticated and may examine additional aspects, such as crystal structure. As this information grows, the impurity in question, or "Xpurities" *i.e.* detected uncharacterized impurities, smoothly moves along the Y-axis.

The Z-axis, is critical for pharmacy as it corresponds to the information available concerning the biological activity of the impurity. Does the impurity inflict any harm or adverse effects on humans? Could it damage the environment when disposed, metabolized and/or excreted? The Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH²⁹) regulations have demonstrated that information along this dimension is often limited. However, information about an impurity may accumulate over time, allowing the pinpoint of the impurity to move along the Z-axis [428]. Impurities which are undetected with uncharacterized chemical identity yet manifest a biological activity (X_0, Y_0, Z_n), can be called "The Silent Scourge".

In an ideal scenario, an impurity, such as the sylvite impurity in the cooking salt or the hair floating on the sausage soup, would reside in the corner of maximum or sufficient information in all three directions, *i.e.*, about its presence, its chemical identity, and its biological activity (X_n, Y_n, Z_n). Impurities belonging to this category may be referred to as the "Usual Suspects" due to their well-characterized nature. The position could certainly expand as analytics and regulatory requirements progress. In fact, for cooking salt, considered in Figure 24 to be contaminated with the usual suspect, sylvite, its impurity profile might change given the growing concerns around contamination with microplastics.

Any impurity not located in this corner of maximum X_{max} , Y_{max} , and Z_{max} , however, presents a problem, each for individual reasons. This can be visualized in Table 2, which demonstrates the eight epistemologically and logically possible scenarios of an impurity in a drug sample or product.

²⁹ REACH is a European Union agency which came into force in 2007. It is dedicated to devise regulation designed to ensure better protection of human health and the environment from potential risks of chemicals. It places responsibility on industries to manage and provide information on the chemicals they produce and import.

Table 2: A truth table highlighting possible scenarios of an impurity in a drug sample or drug product with insufficient information about either existence, chemistry, or biology.

Impurity	Presence	Chemical identity	Biological activity
The Ghosts: unidentified impurities	X_0	Y_0	Z_0
Xpurities: detected yet uncharacterized chemically or biologically	X_n	Y_0	Z_0
The Missing Culprits: chemically identified yet undetectable and biologically elusive	X_0	Y_n	Z_0
The Silent Scourge: biologically impactful yet undetectable and chemically elusive	X_0	Y_0	Z_n
The Uncharted Territories: biologically uncharacterized yet identified impurities	X_n	Y_n	Z_0
The Hidden Villains: undetected yet well-characterized	X_0	Y_n	Z_n
The Enigmas: structurally uncharacterized yet detected and biologically impactful	X_n	Y_0	Z_n
The Usual Suspects: fully characterized	X_n	Y_n	Z_n

Impurities which reveal their presence in purity profiles and are responsible for devastating side effects despite their unknown chemistry, for instance, these “Enigmas”, are represented by (X_n, Y_0, Z_n) , exemplified by the notorious impurity Peak X in *L*-tryptophan [429–431]. Meanwhile, impurities with confirmed chemistry and biological profiles, such as RbCl and CsCl in the cooking salt, the hidden hair, and the NDMA and NDEA in valsartan and ranitidine, represent a case of “Hidden Villains”, designated as (X_0, Y_n, Z_n) . Added poison, such as arsenic, would also be found here.

The other scenarios highlighted in Table 2, ranging from the “Missing Culprits” to the “Uncharted Territories”, may be less common, yet practical examples probably exist for each of them. Moreover, the diagram depicted in Figure 24 not only differentiates between various impurity scenarios but also allows us to appropriately place the suspects of modern pharmaceutical scandals and determine the necessary actions which may indeed differ according to this classification. Notably, the epistemological approach represented in Figure 24 is not confined to a 3-dimensional Cartesian space. The model, starting with the Cartesian coordinates (X_n, Y_n, Z_n) , can evolve to accommodate additional pharmaceutical criteria such as the economic aspects of handling impurities. This adaptability could lead to a “Multidimensional Space of Information” model.

4.3.4. Concluding Remarks

Pharmaceutical impurities represent a complex phenomenon, spanning chemistry, analytics, biology, drug safety, epistemology, and ethics. Such impurities pose several types of

philosophical challenges, *ontological* related to the limitation of the analytical method, *epistemological* related to the knowledge of their chemical structure and biological activity and indeed *ethical* related to their possible dire consequences. Notably, the current regulations should accommodate and elaborate on the taxonomy of “unidentified impurities”. These entities exist beyond the current chemical language [75] and therefore, arguably reside outside the realm of chemistry, just like “dark matter” in astronomy and physics. Such substances necessitate in-depth chemical and epistemological scrutiny. Here, the Space of Information has been employed, representing a versatile conceptual tool designed to highlight the epistemic status of these impurities. Hence, a novel perspective on impurities, classifying them into eight distinct categories based on presence, chemical identity, and biological activity has been proposed. This fresh taxonomy presents an opportunity to improve conception, understanding and management of impurities, beyond the confines of chemical and biological analyses, and extends into the philosophical and epistemological realms.

This discourse elucidates the challenges of regulating and controlling practices within pharmaceutical manufacture. Here, risk management approaches are embedded in Quality Control and Assurance strategies and in the case of impurities represented in current Good Manufacturing Practices. Such regulations or standards are designed to handle the risk or uncertainty of substances down in the microgram levels. It is in the context of impurities that the significance of such regulation and control becomes apparent, reflecting the balance between drug safety and patient wellbeing. Herein lies the crux of the challenge: achieving control while simultaneously acknowledging the limitations of current knowledge and analytical techniques. Ultimately, there is a persistent necessity for improved regulatory measures, more potent analytical techniques, and continuous epistemological contemplation in ensuring drug safety and effectiveness.

4.4. Pharmacy in the Environment: Pharmaceutical Waste Management

The last century has witnessed significant medical advancements, leading to enhanced life expectancy and improved quality of life. Such developments have been paralleled, however, by a surge in pharmaceutical waste due to increased patient numbers, prescription rates, medication consumption, and overproduction. The repercussions of this growth manifest as ecological, economic, and ethical challenges which require comprehensive examination [432].

Data from the Consumer Healthcare Products Association indicates that over-the-counter medication (OTC) sales in the US surged from USD 16.8 bn in 2008 to USD 35.2 bn in 2018 [433]. Furthermore, Variant Market Research projects the global OTC market to expand from USD 125 bn in 2016 to USD 273 bn by 2024 [434]. The German Federal Ministry for the Environment highlighted that annually, pharmaceutical manufacturers across the globe are synthesizing approximately 100,000 tons of diverse synthetic chemicals [435]. Notably, only a small fraction of this output is actually utilized, with the remainder contributing to the pharmaceutical waste dilemma. Here, the matter is further complicated if one were to also take the metabolites excreted after administration and ingestion in bodily discharges such as urine and feces.

Economically, the implications of pharmaceutical waste are profound. Unused medications from the US senior population currently amount to over USD 1 bn annually [436]. Analogous findings have been reported in other developed nations, with Australia registering an average of USD 1280 wasted per patient each year [437].

Beyond economic implications, environmental concerns loom large. Improper disposal of unused drugs, replete with biologically active and potentially harmful compounds, jeopardizes ecosystems and poses as a detrimental threat to biodiversity. The U.S Geological Survey, for instance, identified estrogen-induced intersex fish in the Potomac River [438]. Canadian researchers also found traces of 25 antibiotics in drinking water, and numerous studies have underscored the ubiquity of pharmaceutical residues in terrestrial and aquatic environments [439]. Disturbingly, these residues can re-enter the food chain and circulate back to humans [440].

The paradoxical situation of pharmaceutical waste in developed nations juxtaposed against medication shortages in developing countries raises ethical questions. The World Health Organization (WHO) in 1977 curated a list of essential medicines, promoting their categorization as vital national resources [441]. While redistributing unused medication to

underserved regions seems a viable solution, WHO guidelines from 1999 discourage such practices [442]. Globally, the approach to managing expired or unused medication remains suboptimal. In many jurisdictions, discarding pharmaceuticals via general waste or sewage systems is prevalent, emphasizing the lack of proper disposal mechanisms [443]. Moreover, clear strategies for pharmaceutical waste management from regulatory and healthcare bodies are conspicuously absent.

This section aspires to elucidate the multifaceted challenges surrounding expired medications, encompassing societal, regulatory, and ethical dimensions. The exploration will encompass societal behaviors toward medication disposal, pertinent regulations, and waste management strategies. By tracing the lifecycle of expired medications, the aim is to foster a more comprehensive and realistic dialogue and to propose viable “disposal” solutions.

4.4.1. Disposing Medications: A worldwide perspective

Discarding unused medications *via* ecologically harmful methods, may include garbage disposal or flushing them into sewers. This has contributed to the accumulation of active pharmaceutical ingredients in ecosystems, posing substantial risks to both, human health and the broader environment [444,445].

Surveys addressing the practices related to handling such active pharmaceutical waste reported polarized outcomes. Western and Northern European nations indicate varying degrees of responsible drug disposal practices. In Germany, Sweden, and the Netherlands, 29%, 43%, 58% respectively, typically return unused medications to pharmacies [446–448]. Comparable practices have been observed in Australia, New Zealand, and England, 23%, 24% and 25% respectively [449–453].

A unique initiative in Türkiye by Turkcell Global Bilgi aimed to foster awareness about proper medicine disposal among its workforce. Following a symposium, distant learning sessions, and the dissemination of informative resources, a survey demonstrated a significant shift in employee practices. Notably, 66.1% of respondents either returned unused medicines to pharmacies or utilized the company’s designated drug-box [454].

Numerous studies have, however, reported a concerning trend where the disposal of expired medications in household trash remains the most common practice. Throwing unused medication in household trash is reported to be the most common practice in England, Lithuania, Serbia, Malta, Ireland, Romania, and spanning continents to include places like

Malaysia, Thailand, and the United States, among others [453,455–467]. Notably, disposing medication as part of municipal solid waste is not necessarily the wrong practice if such waste is subsequently gathered properly and incinerated. In Germany throwing unused medication in the household trash is actually encouraged. Yet, the environmental impact of incineration in terms of energy consumption and emissions is highly discouraged and other possibilities ought to be explored.

Perhaps more worrisome, flushing medications down toilets or sinks, particularly the medications in liquid forms, represents yet another widespread practice. Such behavior has been reported in countries like the United States, England, and Bangladesh, to name a few [451–453,464,465,467–469]. Yet, in places such as Sweden and Oman, sewer disposal seems less prevalent. Distinct practices emerge in regions such as Ethiopia and Sudan, where burning unused pharmaceuticals is the predominant method [447,470–472].

4.4.2. Pharmaceutical Waste in Regulations

The swift expansion of pharmaceutical industries accentuates the necessity for stringent regulations overseeing the disposal of unused drugs. Yet, a unified, global approach is still in its infancy. While global agencies offer overarching guidelines, the nuances of enforcement and adherence vary by country. This subsection delves into some of these pivotal regulations and their worldwide application.

The post-World War II era experienced a heightened global sensitivity to environmental issues, culminating in the 1972 United Nations conference. This historic event, attended by 113 nations, not only marked a pivotal focus on global environmental challenges but also saw the inception of the inaugural environmental law aimed at safeguarding the environment from both direct and indirect human-induced harm [473]. Fast-forward to 1999, the World Health Organization (WHO) set forth guidelines for the judicious disposal of unused drugs, advocating for their return to donors or manufacturers, high-temperature incineration, waste encapsulation, or chemical decomposition, contingent on available expertise and resources [442].

European Union (EU) regulations, in present times, mandate member countries to employ sound pharmaceutical disposal practices. Clarity, however, remains elusive in terms of their execution. Belgium, Italy, Greece, and Norway legally enforce the return of unused drugs to pharmacies. Yet, other countries such as Austria, Croatia, and France provide a choice between pharmacies and recycling facilities for medication disposal.

Local municipalities have also taken the initiative. Specialized collection points are established in cities such as Gręboszyce in Poland, and Luopioinen in Finland. Meanwhile, Germany categorizes unused medications as “municipal waste” and belong in the “black bin”, directing them through incineration, biological treatment, and subsequent landfilling, harmonizing their disposal with regular household waste. Noteworthy contributions also emerge from the private sector, with entities like “WasteServ Malta Ltd” in Malta championing the collection and recycling of pharmaceutical waste [474]. France stands out with its innovative approach. Collaborative efforts from organizations like LEEM, Adelphe, and Cyclamed have led to the introduction of instructive logos on drug packaging, fostering public awareness about responsible drug disposal [475].

In 2017, the FDA unveiled guidelines, emphasizing methods such as mixing medications with unpalatable substances and using sealed containers for disposal [476]. Similarly, the Therapeutic Goods Administration in Australia, in 2019, underscored the environmental repercussions of careless disposal, urging the public to utilize community pharmacies for safe disposal [477].

Globally, waste management strategies exhibit stark contrasts. Developed regions, like the EU and the US, embrace tightly regulated waste disposal methods, from landfills to incineration [478–484]. On the other side, many regions in Asia, Africa, and South America grapple with rudimentary landfill systems and open dumping, exacerbating environmental concerns. The pharmaceutical residues eventual leaching into water systems from these disposal methods can have severe ecological implications, as indicated by a study in Denmark [485].

The open burning of pharmaceuticals, common in numerous countries, also comes with its own set of hazardous impacts. Inadequate incineration may release toxic compounds into the atmosphere, especially given the halogen content in many drugs [486]. Even dietary supplements, laden with heavy metals, resist easy incineration. Hence, without meticulous oversight, residues from these incineration sites continue to jeopardize the ecosystem [487].

4.4.3. Tackling Pharmaceutical Waste: Practices and Recommendations

In addressing the escalating issue of pharmaceutical waste pollution, one finds a complex web of ecological concerns. Pharmaceuticals, once commercialized, infiltrate the environment through diverse channels, including but not limited to waste from medication production, metabolized excretions from humans and animals, and mismanagement of unused or expired

medication [80]. Mounting evidence reveals substantial quantities of these active substances in various ecosystems, notably topsoil and surface water [488]. Notwithstanding, assessing the direct health implications remains indeed challenging. Yet, common sense suggests that the introduction of any chemical into the ecosystem can exacerbate environmental deterioration and contribute to climate change.

There seems, however, to be a clear pattern: many individuals globally are simply uninformed about proper disposal practices of medication. Common practices, such as flushing medicines or discarding them as regular trash, are globally prevalent but environmentally disastrous. The environmental implications differ based on waste management systems, which may involve incineration, landfilling, or even open dumping. Here, one promising initiative, the drug take-back program (DTP), allows for secure disposal of medications. Its application, however, is inconsistent across nations. Experts affirm the urgent need for heightened public awareness about the impact of pharmaceutical waste on the environment and health [489].

Globally, current waste management strategies for pharmaceuticals are, without a doubt, not up to the standard. This calls for robust legislative measures to regulate the disposal of unused and expired medication. To put things into perspective, the WHO and the FDA have provided definitions of an “expiry date” for medications [490,491]. The utility and efficacy of many drugs, however, stretch beyond these dates [492]. Stability tests determine these expiry dates, but post-expiry, the drug’s stability, which hinges on handling and storage conditions, remains an open-ended. To visualize this, consider “Blue Medication” as one which is pre-expiry, “Red Medication” as one which is degraded post-expiry, and “Purple Medication” for those with uncertain stability post-expiry [493]. If testing demonstrates that such a medication remains intact after expiry, it simply moves back to be considered green and if not, then it constitutes a red medication which deserves disposal. Several studies have indicated that many medications, like Bayer Aspirin, maintain their efficacy well beyond their marked expiration [492]. Another example comes from a study published by the which found 90% of more than 100 drugs, both prescription and over-the-counter, have been perfectly suitable for administration even 15 years after the expiration date.

Moreover, the ethical implications of wasted pharmaceuticals are profound. In stark contrast to the tons of unused medicines discarded in developed nations, a significant portion of the African population succumbs to preventable diseases due to scarcity related to lack of availability and/or accessibility to medication [494]. Past attempts at drug donations have been

flawed, often resulting in irrelevant or unusable shipments [495]. Programs such the Shelf-Life Extension Program (SLEP) in the U.S., however, have found success in extending medication shelf-lives for military stockpiles [496].

Drug take-back programs, while environmentally conscious, often eventually incinerate the drugs collected, subsequently leading to environmental harm [497]. Innovative solutions such as mathematical modeling could provide more sustainable waste management strategies [498]. Additionally, recycling specific high-cost medications, *via* extracting their active ingredients, and repurposing them could offer both economic and environmental advantages [499].

4.4.4. Concluding Remarks

The escalating production and consumption of pharmaceuticals has yielded an alarming quantity of unused medications, posing profound environmental threats. Such medications symbolize a multifaceted dilemma, influenced by manufacturers, prescribers, and consumers alike. A primary contributing factor is the lack of robust regulation controlling and enforcing the proper disposal of unused medications. Here, the question is not simply about identifying whether garbage disposal and incineration represent a suitable approach or not. The issue is with the lack of a strategic approach to tackle this disastrous dilemma from every angle, *i.e.* industry, prescribers, patients, society and the environment.

The pharmaceutical industry plays a key role. There is an exigency for one of the richest industries to recalibrate the production-consumption balance. Prolonging expiration dates through advanced stability tests, for instance, could drastically reduce waste. Additionally, companies should be motivated to use eco-friendlier packaging, reducing plastic use in favor of biodegradable alternatives. Such packaging could also incorporate chemical or physical indicators revealing storage conditions. A patch which changes color under adverse storage conditions informs about the state of the medication. Furthermore, packaging should guide consumers on environmentally sound disposal based on country law, such as directing them to local drug take-back programs, thereby enhancing public awareness. In a similar breath, healthcare providers who are ascribed the task of prescribing can also contribute. As for quantities of medication, tailoring a prescription according to patient needs can prevent excesses which typically expire, degrade and end up polluting the environment. This would mitigate the waste from happening and would exert restraint on manufacturers.

A novel idea worth exploring is a “pharmaceutical thrift shop” for unused medications, primarily catering to stable dry dosage forms such as tablets and capsules. Firm regulations enforcing a drug take-back program and a storage condition patch on packaging, coupled with societal acceptance and individuals’ sense of responsibility towards the environment would create the context in which a pharmaceutical thrift shop is possible. The tasks of such a facility would probably include sorting, testing and labeling the different types of medications. Such upcycled, safe and effective medications would then either be sold or donated. Yet, it seems that the main obstacle here might not be the regulations, rather societal acceptance of “used medications”. It could also be that such a strategy might not be financially feasible or rather profitable, and therefore, the environment, again, pays the difference.

The path to addressing pharmaceutical waste requires the collective efforts of regulators, manufacturers, health practitioners and consumers. A synergistic approach which considers innovative solutions, from thrift shops to packaging modifications, may pave the way for a more sustainable pharmaceutical future.

4.5. Chapter Conclusions

The concept of control in pharmacy is multifaceted. It dynamically evolves in response to scientific advancements and also pre-emptively steers pharmacy towards ensuring safety, effectiveness, and even ethical robustness. The implications of policies and regulation explored in the context of public health emergencies, impurities and the environmental impact of pharmaceuticals indeed emphasizes this. Philosophical issues at this essential juncture linking research and development on one side and practice and societal needs on the other, are indeed vast. They call for careful epistemological and ethical analysis especially where scientific rigor meets its limits.

Philosophical analysis of the process of approving medical interventions in the context of public health emergencies may aid in increasing pandemic preparedness. Such challenges may be related to risk, its attitudes and management as well as to the adequate production of evidence and its amalgamation. While indeed this list is not exhaustive, examining and investigating these challenges may contribute to saving the lives of many in the future. Risk management and uncertainty translates in the context of pharmaceutical manufacture into standards and guidelines for quality assurance and good manufacturing practices. Scrutinizing pharmaceutical impurities based on their chemical structure, biological activity and presence in a drug sample provided a novel perspective. The Space of Information presented an innovative taxonomy classifying impurities into eight categories. This approach is seen to delve into the epistemological domain, emphasizing the need for a deeper understanding of ‘unidentified impurities’. It is suggested that while current regulatory measures, grounded in quality assurance and good manufacturing practices, aim to ensure drug safety, there remains an imperative for ongoing epistemological reflection and improved analytical methodologies. Furthermore, proper and comprehensive strategies and regulations ought to be devised for the disposal of pharmaceutical products. These active ingredients represent a serious hazard to the ecology, negatively affecting its biodiversity and stability. All stakeholders must act collectively to protect the environment.

Chapter Five

5. Application of Pharmaceutical Products: Beyond Pathology and Medicating

In this chapter³⁰, the aspects of practice and application pertaining to pharmacy will be discussed. As pharmaceutical products transition from research and development *via* the regulatory apparatus to enter the market, they encounter an important step: the response of the patient to the application of such products, Figure 25 This can manifest as acceptance, hesitancy, or outright refusal. While it may seem that healthcare professionals, such as pharmacists and physicians, heavily influence such outcomes, the actual scenario is multifaceted. Evidence of this complexity is apparent in the observed non-adherence to therapeutic protocols for chronic ailments such as hypertension, or varying stances on vaccines, including the ones against COVID-19.

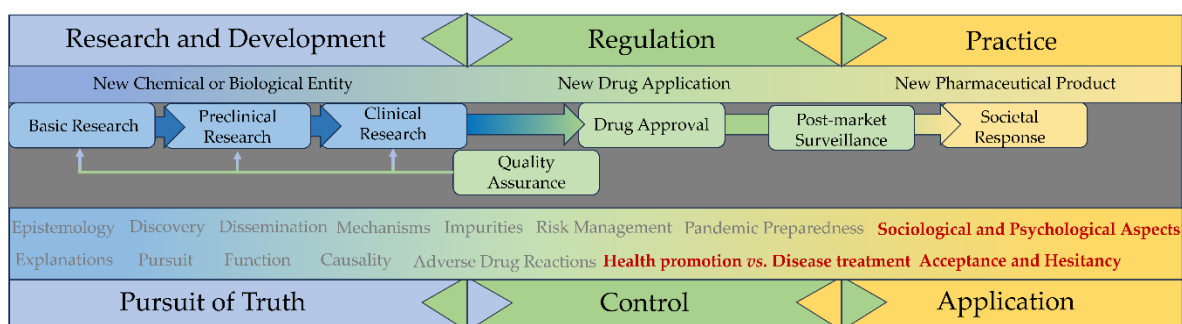


Figure 25. Several issues will be discussed within the context of application and practice in pharmacy. Meanwhile, the main focus is societal response to new pharmaceutical products. Relevant issues to this chapter are depicted in red.

Historically, the concept of ‘application’ in relation to remedies and treatments has been intrinsic to the wellbeing and survival of human societies. Recent advances, particularly the strides in personalized medicine and pharmacogenomics, highlight an existing paradigm predominantly centered around pathology and pathogenesis, often relegating patients themselves to a secondary role.

This chapter advocates for two foundational perceptual shifts or “*gestalt-switch*”³¹. Firstly, the necessity to transition from a purely disease-driven paradigm to one which

³⁰ The discussion in this chapter is supported and based on three manuscripts published in international, peer review journals: Yeboah, P.; Forkuo, A.D.; Amponsah, O.K.O.; Adomako, N.O.; **Abdin, A.Y.**; Nasim, M.J.; Werner, P.; Panyin, A.B.; Emrich, E.; Jacob, C. Antimalarial Drugs in Ghana: A Case Study on Personal Preferences. *Sci* 2020, 2, 49. <https://doi.org/10.3390/sci2030049>, Yeboah, P.; Daliri, D.B.; **Abdin, A.Y.**; Appiah-Brempong, E.; Pitsch, W.; Panyin, A.B.; Adusei, E.B.A.; Razouk, A.; Nasim, M.J.; Jacob, C. Knowledge into the Practice against COVID-19: A Cross-Sectional Study from Ghana. *Int. J. Environ. Res. Public Health* 2021, 18, 12902. <https://doi.org/10.3390/ijerph182412902> and Razouk, A.; **Abdin, A.Y.**; Yeboah, P.; Pitsch, W.; Nasim, M.J.; Maarouf, M.; Jacob, C. Corona in the Time of War: A cross-sectional study from Syria. UNESCO Books 2023, (accepted; forthcoming).

³¹ The term “*gestalt switch*” signifies a sudden change in perception or understanding. It originates from Gestalt psychology, a German movement in the early 20th century which emphasize perception of something as a whole rather than individual parts. This is exemplified by illusions such as the “Necker cube”. In addition, this concept mirrors Thomas Kuhn's “paradigm shifts” in “The Structure of Scientific Revolutions” (see Section 2.1. and 2.2).

emphasizes the patient as the central entity is stressed. This reorientation underscores that the application of pharmaceutical products should be more than just a biomedical procedure, *i.e.* diagnosing a biomedical condition and handling it by prescribing the appropriate medication. It advocates for a comprehensive approach, factoring in the sociocultural and psychological dimensions of patients and, therefore, fosters their active participation in therapeutic decisions. Secondly, there is a proposed broader transition from a paradigm which predominantly counteracts disease to one which promotes overall health and wellbeing. This perspective underscores the importance of health promotion and probes into the foundational aspects of health. By exploring these themes, this chapter seeks to contribute to the discourse on reshaping the modern application of pharmaceutical products to be more holistic, patient-centric, and geared towards overall wellbeing and health promotion.

The subsequent section aims to disambiguate the concept of application in pharmacy. Section 5.2. is a historical dive into the history of pharmaceutical application. Section 5.3. departs from the traditional conception of application in pharmacy and brings in an interdisciplinary approach. Section 5.4. and 5.5. represent case in point examples on how addressing issues beyond the biomedical aspect of application may aid in counteracting public health challenges. Section 5.6. is a tentative conclusion.

5.1. The Concept of Application in Pharmacy: *Gestalt-switch*

The term “application” traces its origins to the Latin word *applicare*, which means ‘to attach or to apply’. By dissecting its root, ‘*ap-*’ suggests ‘toward’, while ‘*plicare*’ implies ‘to fold’. In essence, the term historically encompasses the act of bringing two things into close proximity, much like folding layers together.

In the realm of pharmacy, the term contrasts yet complements terms such as ‘administration’, ‘dispensation’, and ‘utilization’. While ‘administration’ typically refers to the act of giving a drug to a patient, and ‘dispensation’ is associated with the delivery and distribution of a prescribed drug product from the pharmacist to the patient, ‘utilization’ broadly captures the use of drugs within a population. ‘Application’, in this context, becomes particularly nuanced. Cannabis, for instance, is legalized for medical use in a lot of countries such as Germany and the United States. At the hospital, a medical professional may administrate cannabis orally with food, while the pharmacist may dispense it in different dosage forms and, subsequently, patients utilize it to relieve their ailments.

In pharmaceutical research, the concept of drug application mostly pertains to pharmacokinetics and pharmacodynamics. Researchers aim to decipher how drugs interact at molecular levels with the physiological processes of the body. The application, in this context, extends to understanding the drug’s absorption, distribution, metabolism, and excretion (ADME). Healthcare professionals, particularly physicians, view ‘application’ as the act of prescribing or administering the drug. This involves an inquiry into the patient’s medical history, potential drug-drug interactions, and the specific pharmacological properties of the drug itself. For the pharmacist, the application of a pharmaceutical product is not merely about its dispensation. It concerns the process in which the drug is chosen based on its formulation, dosage, and intended therapeutic effect. The application of a topical cream containing an antibiotic, for instance, requires understanding not only of its medicinal properties but also of its excipients, which ensure the drug’s stability and enhance its absorption through the skin. From a regulatory perspective, the application of a drug extends beyond its therapeutic use. Regulatory bodies are concerned with how a drug is produced, stored, distributed, and even disposed of. In this setting, the application encompasses the entire life cycle of the pharmaceutical product.

For patients, the application involves not only the act of taking the drug but also possibly understanding its mechanism, potential side effects, and the expected therapeutic outcomes. The decision to apply a transdermal patch, for instance, could be influenced by factors such as convenience of washing the arm first, frequency of administration and a steady release of the drug, which might lead to enhanced therapeutic efficacy.

Historically, ‘application’ in the context of pharmacy has been viewed through a primarily biomedical lens, emphasizing the presence of a medical condition as well as the physiological impact and outcome of a treatment. This is especially true in the period known as the “therapeutic revolution” in the mid-20th century from which most of the prescribed and over-the-counter medications of today originate. This period witnessed tremendous technological breakthroughs allowing researchers to pinpoint pathogenesis and develop a firm understanding of pathology. This approach proved successful in manipulating the outcome of disease at the molecular level with the aid of empirically tested substances so to *restore* health. Yet, as the understanding of health keeps evolving it seems to increasingly incorporate a holistic viewpoint and so has been addressing what drives the application of these products. It has been recognized that a patient’s decision to apply a pharmaceutical product is not purely dictated by biomedical knowledge or expert recommendations or even orders. Indeed, in some English-speaking countries, “doctor’s orders” is a phrase which has become an idiom meaning that one must do something because their doctor has told them to do so. It highlights the sort of authority healthcare professionals are or have been ascribed to possess. Instead, a plethora of social, psychological, and traditional factors interplay in this decision-making process.

On one side, social factors often play an intrinsic role in the application of pharmaceutical products. Peer influence, traditional beliefs, societal norms, and even socio-economic conditions may sway a patient’s decision. In certain societies, for instance, a person might be inclined to use a particular medicine, not solely because of its proven effectiveness, but due to its prevalence and acceptance within their social circle. Similarly, socio-economic conditions can dictate accessibility and, subsequently, the application of certain pharmaceutical products and not others. Psychologically, on the other side, individual or collective beliefs, trust, fears, past experiences, and perceptions about a drug’s benefits or harms are equally relevant. A patient who has witnessed severe side effects in a family member might be hesitant, even resistant, to apply the same pharmaceutical product, irrespective of new formulations or evidence suggesting safety. In contrast, a strong belief in the therapeutic benefits of a drug,

stemming from anecdotal experiences or personal testimonials, might augment its application. Moreover, traditional beliefs and cultural practices shape health behaviors in profound ways. In many cultures, the use of herbal medicines, passed down through generations, takes precedence over contemporary pharmaceutical products. The inclination to apply a certain remedy could be deeply rooted in ancestral practices and beliefs, often prioritized over modern medical advice. Notably, such sociological and psychological aspects of application could also lead to the endangerment of wild animals such as rhinoceros which is hunted in some cultures to collect and consume its horn as it is believed to be nature's best Aphrodisiac.

As patients transition from being passive recipients to active participants as part of their therapeutic journey, it becomes paramount for healthcare professionals to recognize and factor in these intricate aspects. Knowledge about the drug's mechanism, its potential side effects and therapeutic outcomes are vital, but so is an understanding of the individual's psychological profile, social context, and cultural background. An integrative approach, which fuses biomedical knowledge with a deep appreciation of these factors, paves the way for genuine therapeutic engagement away from plain, dogmatic and insensible medicating. In light of this *gestalt-switch*, the 'application' of a pharmaceutical product moves from merely a biomedical act to a multifaceted decision, intricately woven with the individual's social milieu, psychological particularities, and traditional ethos and pathos. Recognizing and addressing these dimensions ensures a more comprehensive, patient-centric approach to therapeutic care. More on this in the following sections.

5.2. The Application of Therapeutics: A Brief Historical Account

Counteracting pathology and understanding pathogenesis have been one of the main objectives of the application of therapeutics. It is widely accepted that clarifying the origin of disease, its prognosis, causes and manifestation represent the right way to health. From the dawn of civilization, humanity's pursuit of health has been inextricably tied to the way treatments, remedies and medications are understood and subsequently applied. Over millennia, the spotlight has been slowly shifting from the therapeutic mixtures themselves to the sensitivity and selectivity of their application, evolving in harmony with technological and scientific breakthroughs which constitutes the role of pharmacy and pharmacists.

The Sumerians, flourishing around 3000 BC in present-day Southern Iraq, were meticulous record-keepers. On their clay tablets, one find both descriptions of symptoms for various ailments and also a list of remedies [500]. There is, for instance, a notable reference to the application of the “*bara*” plant (similar to contemporary *licorice*) to alleviate digestive issues. The application here was not a mere consumption of the plant, but a methodical preparation involving boiling and then drinking it as a medicinal liquor.

Meanwhile, by the banks of the Nile, around 1500 BC, the Egyptians took a slightly different yet equally fascinating approach. The revered Ebers Papyrus, one of the most informative and extensive of its kind, comprises over 700 remedies for various conditions [501]. Honey, for instance, today recognized for its antiseptic properties, was frequently applied to open wounds and cuts to prevent infections. There are also mentions of applying moldy bread, perhaps an early nod to penicillin, placed on injuries to stave off bacterial contaminations.

Yet it was not simply the therapeutic mixtures which intrigued these ancients but also the vessels containing them. The Egyptians are credited for inventing containers made of alabaster, glass, and other materials specifically designed to preserve their medicinal mixtures, emphasizing the significance of proper storage in application. Imhotep, an Egyptian mathematician who lived around 2650–2600 BC, is often also credited as one of the earliest physicians in recorded history [502]. He championed many therapeutic approaches, moving away from purely spiritual treatments to more tangible, trial and error-based applications. One example includes applying the extract from the willow plant, a precursor to modern-day aspirin, to alleviate pain and fevers. The application of treatments in this era was sometimes rooted in

trial and error, but primarily it was based on observations. Healers often relied on observing the texture, color, and smell of substances to deduce their medicinal properties. A vibrant yellow plant, for instance, might be prescribed for jaundice because of its color resemblance to the ailment's symptoms. Such practices highlighted the overarching belief in “signatures³²” by which the visual traits of a substance indicated therapeutic uses [503].

At the heyday of ancient Greece, around the 5th century BC, the pursuit of treatments took a more analytical turn. At the forefront was Hippocrates (c. 460 BC – c. 370 BC), often hailed as the “Father of Medicine” [504]. Born on the island of Kos, he began revolutionizing medicine by veering away from supernatural explanations and grounding it in observation and reasoning. Under the shadow of the Asclepieion temples, early precursors to hospitals, Hippocrates and his followers embraced a new philosophy. They posited that the path to wellbeing was not simply about identifying the right medicinal mixtures, but it was equally, if not more, about understanding their applications. He emphasized diet, the environment, and living habits, *i.e.* life-style, as essential elements in achieving and maintaining health [505].

For Hippocrates, the modality of application was paramount. A poultice³³ might be best for a wound, a warm herbal drink for a cold, or inhalation of vapors for certain respiratory issues [506]. He was among the pioneers to document such practices, penning several works, with “Airs, Waters, and Places” being a notable one. Here, he explored how different environments such as swampy areas *versus* dry highlands, affected health, and how remedies should be altered accordingly. His beliefs became the bedrock for the famous Greek theory of humourism [507]. Rooted in the idea that four main humours, *i.e.* bodily fluids, namely, blood, yellow bile, black bile, and phlegm, determine a person's temperament and health, this theory held sway over European and Middle Eastern medicine for centuries. An imbalance among these humours, according to this philosophy, was the root cause of illnesses. An excess of phlegm in the body, for instance, was thought to result in cold and damp ailments such as a cold, leading to practices like steam inhalation.

³² The Doctrine of Signatures posits that plants exhibit specific traits, such as color or shape, which hint at the ailments they can heal. Historically, humans have turned to plants, minerals, and animals to remedy conditions when they notice visual resemblances between the source of treatment and the manifestation of disease.

³³ A poultice, also called a cataplasm, is a soft moist mass, often heated and medicated, that is spread on cloth and placed over the skin to treat an aching, inflamed, or painful part of the body. It can also be used on wounds, such as cuts.

To address these imbalances, various procedures, including bloodletting, were endorsed [508]. Although today seen as archaic and often harmful, bloodletting became a standard practice, later championed by physicians like Galen (c. 129 AD–c. 216 AD) in Roman times [509]. Tools like the scarificator were invented for this very purpose, showcasing the lengths to which ancient physicians went to *rebalance* the humours [510]. The convergence of the application-centered approach of Hippocrates and the humoral theory provided a foundation upon which many medical practices of the time were grounded. Even as new milestones were achieved, with contributions from other notable figures such as Avicenna (980-1037 AD) in the Islamic Golden Age, the essence of their teachings echoed through the following ages. The imprint of this era remains evident even today, as modern pharmacy values both the formulation and its application in the therapeutic process.

Between 762 AD and 1258 AD, an intellectual and cultural renaissance was flourishing in the Islamic world, now commonly referred to as the Islamic Golden Age [511]. The cities of Baghdad, Damascus, and Cordoba became vibrant hubs of knowledge, where scholars translated ancient Greek, Persian, and Sanskrit texts, furthering the foundations of medicine and pharmacy. In this era, scholars such as Al-Razi (Rhazes, 865 AD–925 AD) rose to prominence [512]. Hailing from Persia, Al-Razi was an accomplished physician and a pioneering alchemist. He penned the “Kitab al-Hawi” (The Comprehensive Book), which was among the earliest to make distinctions between the manifestations of measles and smallpox [513]. More notably, Al-Razi introduced the use of alcohol (ethanol) in medicine as an antiseptic, showcasing a deep understanding of the importance of application. Apart from constantly drinking it, Al-Razi, recognized the potential of ethanol to cleanse and to prevent infections. He also detailed methods on how it should be applied to wounds or used in surgical procedures.

Another towering figure of this period was Ibn Sina (Avicenna, c. 980 AD–1037 AD). Originally from Bukhara (today’s Uzbekistan), his monumental work, “The Canon of Medicine” (Al-Qanun fi’t-Tibb), became a reference in both East and West for several centuries [514,515]. In this comprehensive tome, Avicenna catalogued diseases and their treatments, as well as, meticulously how each remedy should be applied. He discussed, for instance, how the extraction method of certain plants could impact on their potency and effectiveness. Additionally, he developed guidelines on the timing of drug administration, such as recommending some remedies to be taken on an empty stomach, while others after meals,

understanding that the body's absorption and reaction could vary based on these factors. Another notable scholar was Al-Zahrawi (Abulcasis, 936 AD – 1013 AD), often considered the father of surgery [516,517]. Based in Al-Andalus (modern-day Spain), Al-Zahrawi's encyclopaedic work "Kitab al-Tasrif" (The Method of Medicine) introduced various surgical instruments and their specific applications, emphasizing the importance of precise tools for particular procedures.

The Renaissance³⁴ in Europe, spanning roughly from the 14th to the 17th century, was an active era of rediscovery and innovation. European cities emerged as crucibles of learning, and among them, German cities such as Trier, Münster and Augsburg which played an influential role in the field of pharmacy [518]. Trier was a pioneer. Renowned as one of Germany's oldest cities with great Roman heritage, it witnessed the establishment of the first public pharmacy in 1241 [519]. This institution has represented a cornerstone for the city's inhabitants, serving as both a provider of remedies and a source of medicinal knowledge. If one suffered from digestive ailments, for instance, the pharmacist might prescribe a blend of herbs, such as mint and fennel, while advising on how it should be steeped and consumed. Not so far behind, pharmacies opened their doors in Münster in 1267 and in Augsburg in 1285.

The establishment of the University of Heidelberg in 1386 also expanded the study and teaching of pharmacy in Germany [520]. As one of Europe's oldest universities, it set the foundation for advanced studies in both medicine and pharmacy. Students were trained not only to identify and prepare medicines but also in understanding their therapeutic properties and potential interactions. With this knowledge they gathered, these early pharmacists could advise patients on the particularities of medicinal applications, such as when to take a drug, food interactions to be wary of, or side effects to watch out for. As the Renaissance progressed, the pharmacist's role expanded from merely dispensing medicines to being an integral part of a patient's healthcare journey, ensuring that the application of medicines was optimized for each individual's well-being.

A crucial figure during this era was Paracelsus (1493-1541). Born in Switzerland, he traveled around various European cities. Paracelsus challenged the prevailing medical practices derived from ancient Greek traditions, emphasizing the application of chemicals and minerals

³⁴ Renaissance is originally a French word meaning "rebirth", from *re-* 'back, again' + *naissance* 'birth' (from Latin *nascentia*, from *nasci* 'be born').

in medicine [521]. He is often remembered for his belief that “All things are poison, and nothing is without poison; the *dosage* alone makes it, so a thing is not a poison” [522]. This statement emphasizes the role of the pharmacist in ensuring that medicines were provided in the correct dose, highlighting the delicate balance between remedy and poison.

The late 19th and early 20th centuries were golden ages of scientific and medical advancements. As the boundaries of knowledge expanded, there was a rising emphasis on precision in the application of pharmaceuticals. One of the significant figures from this epoch was Charles Gerhardt (1816-1856), a diligent French chemist working in Strasbourg. In 1853, he successfully synthesized acetylsalicylic acid for the first time, which became later widely known as aspirin [523]. Interestingly, aspirin was left almost forgotten for around 50 years and its mechanism of action was not established until 1971 by the British pharmacologist and Nobel Prize winner John Vane (1927-2004). Yet perhaps another important figure in popularizing and establishing the application of aspirin has been Felix Hoffmann (1868-1946), the discoverer of the infamous diacetylmorphin or heroin, who was working for the company Bayer at the time. Hoffmann’s work, together with Bayer’s rigorous approach, underscored the importance of standardized dosages, ensuring that each pill contained an exact and consistent amount of the active ingredient. This consistency has been a major step forward in ensuring patient safety and therapeutic effectiveness.

Antibiotics among other drugs are also a product of this era. In the early 1900s Germany had a sort of monopoly in terms of the development of antibiotics. Right before the beginning of World War one, specifically in 1910, Paul Ehrlich (1854-1915) a Nobel prize winner, discovered the first antimicrobial, arsphenamine or salvarsan for the treatment of syphilis. Meanwhile in 1928³⁵, Sir Alexander Fleming, stumbled upon the revolutionary antibiotic properties of penicillin [524]. It was not until the 1940s, however, together with collaborative efforts of scientists such as Howard Florey (1898-1968) and Ernst Boris Chain (1906-1979), that penicillin has been mass-produced [525]. The challenge with penicillin has not just been related to its production, but also understanding the right doses, frequency, and duration of treatment to combat bacterial infections without causing harm. Establishing these parameters marked another leap in the meticulous application of pharmaceutical products. In Romania, in 1887, chemist Lazăr Edeleanu (1861 -1941) synthesized amphetamine [526,527]. Initially

³⁵ Notably, research into antibiotics received a lot of traction around this period as in 1935 sulfanilamide had been discovered by another German, Nobel Prize winner, Gerhard Domagk (1895-1964).

overlooked, its therapeutic potential became evident in the 1920s when it was used to treat nasal congestion and later, disorders like narcolepsy, hyperactivity, and depression. Similar to aspirin and penicillin, amphetamine's optimal application required a clear understanding of dosages and potential side effects [526]. Overuse could lead to amphetamine addiction, highlighting the importance of strict dosage guidelines. This era also witnessed the development of insulin for the handling of diabetes. In the 1920s, Canadian scientists Frederick Banting (1891-1941) and Charles Best (1899-1978) isolated insulin, paving the way for its use in treating diabetes [528]. It was, however, the careful calibration of doses, based on patient needs, that ensured the success of the hormone in managing blood sugar levels without causing hypoglycaemia.

The 21st century is witness to an extraordinary shift in the realm of pharmaceutical products. As technology and biology coalesce, the pharmaceutical landscape is no longer about general medicine but about catering to individual "biological" needs. At the heart of this shift lies the fusion of Artificial Intelligence (AI), rapid analytics, systems biology, systems pharmacology and the principle of personalized medicine. If one were to pose the question: are any two people completely identical³⁶? The answer would be a resounding "no!" This very rationale prompts asking, why then should their medication be any different? Previously, a "one-size-fits-all" method, necessarily with a few exceptions such as children and pregnant women, dominated the medicinal landscape [529]. Today, however, the emergence of *personalized medicine* emphasizes tailoring healthcare to accommodate the unique genetic makeup, lifestyle, present physiological state and environment of each individual [530]. By doing so, the effectiveness of the pharmaceutical product is maximized. Furthermore, standing as a testament to the potential of personalized medicine, *pharmacogenomics* blends pharmacology and genomics [531]. This union aims to design medications specifically suited to the genetic structure of individuals. By acknowledging the subtle genetic variations in every individual, targeted treatments become safer and more effective. Imatinib (or gleevec), for instance, is a revolutionary drug, approved by the FDA in 2001 [532]. It specifically targets cancer cells with distinct genetic mutations. Its introduction has significantly improved the prognosis for many chronic myeloid leukemia patients. Today, gleevec showcases that

³⁶ Here, the matter is further complicated if one were to factor in the fact that, on the molecular level, even the same person is not the same during the same day. In this context, the rapidly developing field of "chronopharmacology" focuses on examining the dependencies between the timing of drug administration and its effect.

understanding the genetic intricacies of a disease could lead to profoundly more targeted treatments.

The Human Genome Project in 2003, under the guidance of Francis Collins³⁷ (1950-), mapped all genes within human DNA [533,534]. With such a profound database, the horizons for personalized medicine were exponentially broadened. In the same year (2003), the FDA had approved its first gene therapy, Gendicine, designed for patients suffering from squamous cell carcinoma linked to mutations in the TP53 gene [535]. Moreover, establishments such as the Broad Institute in Massachusetts, founded by visionaries including Eric Lander (1957-) in 2004, are at the forefront of genomics [536]. This institution played a pivotal role in the advent of the CRISPR gene-editing technology, adding another potent tool to the personalized medicine arsenal [537].

Where does AI fit into this grand scheme? AI, with its machine-learning prowess, analyses vast genetic datasets, pinpointing patterns that might otherwise remain elusive to human researchers. In pharmacogenomics, AI's role is invaluable, offering predictions about how varied individuals might react to certain drugs [538]. Couple this with the principles of sensitivity and selectivity—where the former refers to the aptitude of correctly identifying those with a disease and the latter pertains to a drug's specific response, and AI's contribution becomes even more evident. By optimizing drug designs and predicting potential secondary effects, AI ensures the introduction of medications that are both potent and safe.

Rooted in ancient civilizations, our ancestors have been guided by a deep connection to nature and an unwavering belief in its curative powers. They employed everything from herbal pastes to therapeutic teas, and sometimes even urine, not merely relying on the healing properties of these remedies but also mastering their optimal application, setting the precedent for the meticulous science of pharmacy. The dawn of the 21st century ushered in a transformative era for pharmaceutical products. Yet, for all its technical brilliance, this period also highlighted an oversight. By fixating on the pathology, the diseases themselves and their genetic underpinnings rather than the patients and their particularities, there has been a drift

³⁷ Craig Venter (1946-), founder of biotech firm Celera Genomics, was another key figure in the Human Genome Project. Unlike Francis Collins, Venter was privately funded and employed a rapid 'shotgun sequencing' technique, in contrast to Collins's more methodical clone-by-clone strategy. This race created a notable rivalry, pressuring both teams. Ultimately, their findings were published almost simultaneously, Collins in *Nature* and Venter in *Science*. This presents an interesting case of scientific pursuit in the biomedical sciences, one ought to investigate deeper, see Chapter Two.

from the holistic view of patients. Traditional beliefs, environmental factors, and sociocultural particularities still play essential roles in a patient's therapeutic journey. Nonetheless, these relevant aspects are being overshadowed. In essence, as pharmacy practice has honed its focus on disease-centric precision, the broader canvas of human experience and diversity has been risked of being sidelined.

5.3. Beyond the Pill: Societal and Psychological Aspects of Treatment Choices

The journey of understanding patients' behavior towards medication and its application is intricate and layered. It is assumed that healthcare experts, whether a physician prescribing an antibiotic, a pharmacist recommending an OTC cold medication or a government authority endorsing a country-wide vaccine, base their decisions on technological and scientific evidence. They believe that what is best for patients are the products of scientific rigor. Yet, the patients on the other side might not completely agree. This is indeed evident in issues related to patients' adherence to therapeutic regimens and even acceptance in general. Intriguingly, hesitating to accept or completely refusing a medical product or approach seems to transcend possessing a proper understanding of the disease and potential therapeutic outcomes. It is, therefore, important to delve into this complex landscape by identifying the underpinning factors which influence acceptance and examine the theories which shed light on these dynamics.

Grounded in diverse academic disciplines of social and psychological sciences, these theories enrich the current understanding in healthcare practices by addressing varying factors and dimensions which shape the treatment choices of patients. Acceptance of medication or a pharmaceutical product can be defined as a patient's willingness to receive and/or adhere to a prescribed therapeutic regimen, informed not only by the effectiveness and safety of the product being scientifically established but also accounting to a multitude of psychological, sociological, and cultural factors. Such acceptance encompasses an individual's understanding of the disease, personal beliefs about the treatment, societal influences, past experiences with medications, and the trust placed in the healthcare provider. It is a decision which emerges at the intersection of empirical science and strong personal, subjective and societal considerations. The ensuing discussion rapidly moves from the safe haven of natural sciences and enters the many and vast aspects of social, cultural, historical and environmental disciplines.

In psychology, for instance, the Health Belief Model (HBM) postulates that patients' decisions to accept a medication are influenced by their subjective perceptions. This encompasses their perceived susceptibility to and severity of the disease, together with their evaluation of the benefits and potential barriers to treatment [539]. HBM is a tool which aids in grasping why people make certain health decisions [540]. It proposes that people weigh up their risks and the benefits before taking health actions. Someone might decide, for example,

to take the new malaria vaccine if they believe they are at real risk of getting infected (perceived susceptibility), think this parasite would be serious (perceived severity), and trust that the vaccine could prevent it (perceived benefits). If they are, however, worried about potential side effects or other downsides (perceived barriers), they might simply skip it. In a nutshell, HBM suggests that health choices are a balance of how patients view the risks, the severity, the benefits, and the barriers. It is a way for health professionals to understand and address patients' concerns and motivations [541].

Closely related is the Theory of Planned Behavior (TPB), which expands on this idea by suggesting that behavioral intentions, stemming from attitudes, subjective norms, and perceived behavioral control, *e.g.* self-efficacy, are pivotal in the acceptance of medications [542]. TPB provides a simple yet insightful lens to understand why people might, or might not, accept or adhere to their medications. TPB suggests that intentions to act, such as accepting a pill or a vaccine, hinge on three things [543]. Firstly, personal views or beliefs about the action. If someone believes, for instance, a medication will truly help them, they are more likely to accept it. Yet other personal beliefs such as religious beliefs might make them decide otherwise. Jehovah's Witnesses, for instance, accept most medications but for biblical reasons they refuse allogeneic blood transfusion [544]. Secondly, what action is expected by other people within their social circle. So, if a patient feels their family or doctor strongly believes in the importance of a medicine, they might be more inclined to accept it and subsequently adhere. Thirdly, to what level is the patient confident in being able to perform this action. This concept is known as self-efficacy or in other words, it is the perceived ability to carry out an action in a specific situation. If a patient is confident, they are able to manage a medicine's schedule or handle its side effects, they are more likely to keep taking it. A patient's personal attitude towards a medication, combined with their perception of societal views of those around them and their belief in their ability to undertake the treatment, come into play.

Furthermore, there are several similar psychological models. On one side, The Social Cognitive Theory (SCT), posits that individuals acquire and maintain particular behavioral patterns through the interplay of personal, behavioral, and environmental factors, especially *via* observational learning [545,546]. SCT emphasizes that individuals learn by watching others. Think of it as picking up habits from friends or being influenced by characters on TV, YouTube or Twitch.

The Transtheoretical Model (TM), often known as Stages of Change (SC), on the other side, elucidates the process of intentional behavior change. It suggests that individuals go through stages when making changes in a specific behavior, from merely thinking about the change to maintaining the new behavior over time [547,548]. Consider a patient opting to switch from branded medicine to a generic one: they might start by weighing the pros and cons, then try the generic, and eventually make it their regular choice if satisfied.

Additionally, the Self-Determination Theory (SDT) explores the nature of human motivation, emphasizing the importance of *autonomy*, *competence*, and *relatedness* [549]. This means that people tend to be more motivated when they feel they are making choices based on their own free will, feel competent in their actions, and feel connected to others. This theory proposes that individuals are happiest and most driven when their choices come from within, rather than from external pressures or rewards [550]. It is about finding personal meaning and satisfaction in what individuals do. Take a pharmacist who advises a patient on medication: the patient is more likely to adhere if they understand the medication, feel confident in managing their regimen, and trust their pharmacist's expertise. Together, these theories are supposed to offer insights into how and why people make decisions about their health and other aspects of life.

Shifting gears to the public health perspective, the Socio-Ecological Model (SEM) introduces other layers of complexity. It emphasizes that acceptance of medications is not just an individual's isolated choice [551]. Instead, it is a decision situated within a broader relational, community, and within societal contexts. Here, patients' immediate social circle, the beliefs and knowledge of their community, and overarching societal structures and policies intertwine to influence choices [552]. This indeed seems in line with the psychological approach yet more focused on the social dynamics of rendering a decision say, for instance, whether to accept a vaccine or not.

In a similar breath, the *sociological perspective* posits that the acceptance of medication does not operate in a vacuum. It is deeply embedded within a socio-cultural fabric. Factors such as education, socio-economic status, gender, marital status, employment and even geographical contexts *i.e.* urban *vs.* rural settings may have profound impacts [553]. An urban patient, for instance, with higher educational attainment and perhaps also a higher income, might be more receptive to newer treatments, influenced by easy access to information and healthcare facilities, while someone from a rural background might prioritize traditional

remedies, influenced by community traditional wisdom and possibly limited access to modern healthcare. Figure 26 summarizes all the approaches discussed.

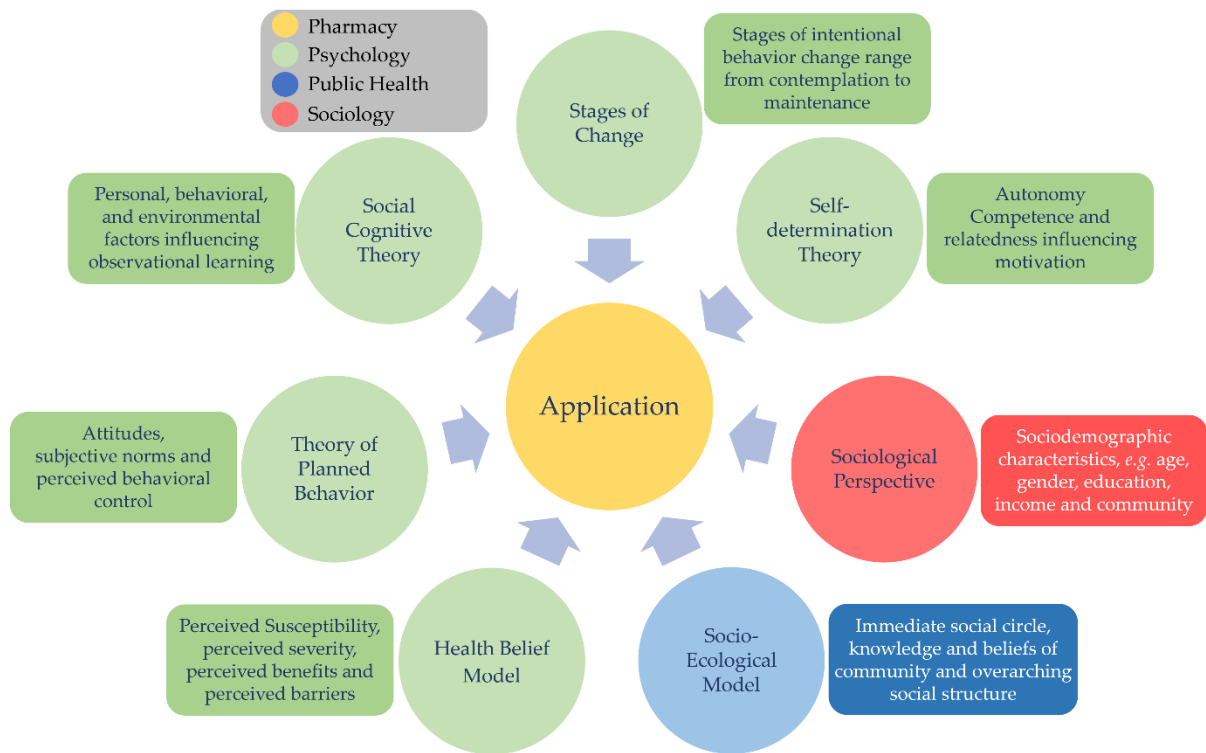


Figure 26. Summary of the theories and approaches discussed within the context of the application of pharmaceutical products.

It should be noted that discussions about different types of treatments which relate to the nature of the disease or condition at hand significantly impact a patient’s approach to medication. Chronic conditions, such as diabetes or hypertension, require sustained adherence to treatment. The challenge here often lies in maintaining consistency over long(er) periods. On the other hand, acute conditions, like malaria, present a slightly different conundrum. Here, acceptance may revolve around preferences, such as opting for synthetic over traditional herbal treatments. Then there is the realm of preventive treatments, epitomized by vaccines, such as the one for COVID-19. Acceptance in this arena can be controversial, fueled by sociocultural beliefs, misinformation, or simply fear of the unknown.

The complexities of why individuals might opt against a scientifically developed treatment, despite its rigorous foundation in research, stringent regulatory oversight, and proven efficacy, is a multifaceted dilemma. From psychology addressing personal beliefs and motivations, to sociology emphasizing cultural fabrics, the factors are vast and varied. Theories such as HBM or the SEM, offer valuable lenses through which one may understand these choices. Yet, even as they shed light on some facets, others remain unclear and perhaps inaccessible. Notably, personal and societal factors intertwine, where personal conceptions of

a patient merge with community beliefs, and broader societal structures. The acceptance of medication is, after all, a dance between the individual, their immediate world, and the larger societal framework. Chronic or acute conditions, be it diabetes or malaria, and even preventive treatments such as the COVID-19 vaccine, each have unique considerations. The complex interplay between these myriads of factors emphasizes the tremendous effort dedicated to unraveling why some might refuse a scientifically backed treatment. And yet, despite these dedicated attempts, the enigma persists. As researchers and practitioners continue to seek understanding, the overarching question looms: Why, in the face of empirical evidence establishing the safety and effectiveness of pharmaceutical products, do individuals, sometimes, opt for a divergent path? The ensuing two sections provide an account of pursuing the answer. Their results and discussions are supported by three studies conducted in 2018, 2020 and 2021.

5.4. Curbing the COVID-19 Outbreak: A Tale of Two-Nations- Syria and Ghana

The global emergence of COVID-19 introduced unforeseen challenges to healthcare systems and exposed the inherent disparities in public health responses across different nations [554–557]. As discussed in the previous section, the varied contours of national histories, socio-economic characteristics, and cultural fabrics have indeed influenced the impact of the outbreak and the effectiveness of preventive measures. Global efforts have focused on adapting a standardized approach to curb the spread of the COVID-19 pandemic [558,559]. One widely accepted approach by such health authorities has been the recommendations of the WHO [560]. Wearing of facemasks in public places, regular handwashing, maintaining “social” distance and receiving the vaccine have been preventive measures millions of people around the globe had to deal with for a span of almost three years. Yet the reception, acceptance and adherence to such preventive interventions have been polarized [561–564]. While such differences in adapting the preventive measures might not come as a surprise, they construct a hot spot for researchers aiming to explicate the underlying reasons for eluding accepting or practicing what has been deemed as the best course of action by public health experts. Put simply, why do people not practice the preventive measures set to protect them and their communities? Is a standardized approach to halting a pandemic universalizable? In this context, Syria and Ghana present uniquely contrasting landscapes, underlining the need for tailoring public health response strategies based on regional idiosyncrasies.

The destructive intersection of armed conflicts and infectious diseases has historically wrought havoc on vulnerable populations [565–567]. Syria, embroiled in a more than a decade-long war, offers a poignant example. This conflict has systematically eroded the nation’s political, economic and social infrastructures, resulting in a fragile healthcare system ill-equipped to manage pandemic-scale crises [568–570]. The repercussions of these upheavals over the past decade have dramatically affected the pharmaceutical industry and the exodus of healthcare professionals, reflecting the magnitude of structural and human resource challenges facing Syria. Additionally, the re-emergence of diseases such as cholera, hepatitis A, and polio highlights the severe healthcare inadequacies. The advent of COVID-19 only exacerbated these challenges [571–574]. Given the limited capacity for polymerase chain reaction (PCR) testing and the ongoing conflict, it has been deemed challenging to acquire reliable data on the pandemic’s progression in Syria.

In contrast, Ghana's experience with COVID-19, while rooted in its own set of challenges, was notably different [575,576]. Ghana has no military conflicts, unlike some of its neighboring countries such as Sudan and Ethiopia. Yet, unlike Syria it has a long and rich history of traditional medicine which is in some cases mixed with superstition and even magic [577,578]. Despite historically grappling with diseases such as malaria, H1N1 influenza and cholera, and the inherent limitations of healthcare resources, Ghana's official response to the pandemic has been commendably proactive [579,580]. While many African nations faced dire predictions regarding the pandemic's potential impact, Ghana managed to keep its infection rates relatively modest. Measures such as lockdowns, contact tracing, and advocating personal preventive practices have been introduced in a timely manner. Concurrently, public health campaigns emphasizing the population's knowledge about the disease have been pivotal.

The rationale behind juxtaposing Syria and Ghana lies in their contrasting socio-political landscapes and their distinctive responses to the pandemic. Both nations underscore the quintessential importance of understanding local contexts when framing health interventions. Syria's ongoing conflict, coupled with international sanctions, has rendered its healthcare system vulnerable, making its population particularly susceptible to the ravages of a pandemic. Conversely, Ghana's proactive measures, albeit within resource constraints, offer lessons on how timely interventions may curb an outbreak. These two nations, through their challenges and responses, emphasize the interplay between the diverse array of factors which influence the efficacy of pandemic mitigation efforts. The aim is to showcase the myriad of socio-cultural, economic, and political factors which influence population practices in the face of global health threats. Understanding these issues is pivotal for crafting interventions which resonate with local realities and ensuring that they are both effective, safe and sustainable.

5.4.1. Insights on Syria's Response to Covid-19

Despite the vast challenges Syria has faced over the past decade, its population has demonstrated an admirable knowledge and understanding of infectious diseases, including Covid-19. This is particularly commendable given the fragility of the nation's healthcare infrastructure [581].

Interestingly, while Syrians displayed considerable knowledge about Covid-19, this did not necessarily correlate with their understanding of other diseases like polio and leishmania, despite the recent resurgence of these diseases and also being at the forefront of awareness

campaigns in the country. What this suggests is that knowledge in one area does not guarantee comprehension in another, further supported by the observation that a mere 18.9% of an individual's knowledge about Covid-19 can be predicted based on their understanding of polio and leishmania. Additionally, there was no evident gender-based differences in being knowledgeable about Covid-19. Younger Syrians showed slightly more familiarity with the virus. Remarkably, the capital city, Damascus, displayed more knowledge about the virus compared to other cities like Aleppo and Dyer Az Zawr, barring Hama.

One uplifting finding was the direct relationship between Syrians' comprehension of Covid-19 and their adherence to WHO guidelines, *i.e.* the more a Syrian knew about the disease the more likely they would practice the preventive measures. Yet, this relationship had its limitations; not every knowledgeable Syrian necessarily practiced preventive measures consistently. This discrepancy mirrors global challenges, like the threat acknowledged of climate change *versus* limited actionable steps taken by individuals.

Another encouraging aspect was the strong sense of self-efficacy among Syrians. This idea here pertains to the health belief model discussed above. In essence, the more capable a Syrian felt about following preventive measures, like wearing a mask in the heat or maintaining distance in crowded areas, the more likely they were to do so. This confidence, however, did not always translate into action; a confident Syrian might still hesitate to get vaccinated.

Concerning visible preventive measures such as wearing masks, there was an initial concern that such measures might conflict with cultural norms, potentially leading to stigmatization. Yet these concerns have been falsified as it seems that social stigma had a negligible influence on practicing such preventive measures. The data on the actual adherence to preventive measures, however, painted a sobering picture. On average, Syrians adhered to the preventive measures of the WHO only about 52.80% of the time. Notably, hand washing has been the most practiced measure at 84.71%, and a commendable 70% wore masks. Predictably, due to limited resources, few Syrians got tested for Covid-19. Demographics also played a role. Despite their lower knowledge scores, cities such as Aleppo, Dyer Az Zawr, and Hama saw higher compliance to the preventive measure than Damascus. Surprisingly, non-urban areas lagged slightly behind in terms of these practices. An important discovery has been the significant influence of formal sector employment on compliance. Syrians working in a formal sector, both private and public, have been more likely to adhere to the guidelines and also to get vaccinated than those in the informal sector.

Perhaps most worrisome has been the moderate willingness to accept the vaccine against COVID-19. Despite the impact of war and poor living conditions, Syrians displayed similar knowledge, attitude, and practice scores towards Covid-19 as some of their regional counterparts. Yet only around 51% of the population has been reported to demonstrate willingness to get vaccinated. When viewed on a global scale, however, the pace of the vaccine rollout in Syria has been concerning. While countries such as Germany, the USA, South Korea, and China have already vaccinated around half their populations by the time this study has been conducted, Syria lagged behind with less than 5% vaccinated in late 2021. The primary vaccines available to Syrians included Sputnik V, CoronaVac, and Oxford–AstraZeneca. Priority has been given to healthcare professionals and vulnerable demographics. Was this issue with low vaccination rate related to availability and accessibility? Or is there a more profound reason underlying Syrians' hesitancy to take available vaccines. A clearer picture will transpire in section 5.4.3., after reviewing the insight from Ghana.

5.4.2. Insights on Ghana's Response to Covid-19

Ghana's widespread campaign to educate its citizens about the SARS-CoV-2 pandemic has largely been a success. From bustling cities to distant villages, most Ghanaians were informed about COVID-19. Interestingly, similar to the situation in Syria, while knowledge has been high, actual practice of protective measures in Ghana, such as wearing masks or social distancing, has not been fully followed, posing challenges, especially regarding the willingness to receive vaccination [582].

In this context, it has been found that most Ghanaians, whether urban or rural, were quite knowledgeable about COVID-19, scoring an average of 69.90%. Their understanding mirrors the results seen in neighboring African countries. Perhaps past experiences with diseases like cholera, which has a significant annual death toll in Ghana, have shaped this awareness. Additionally, knowledge about cholera and influenza represented a significant predictor of COVID-19 awareness. Yet, the puzzling mismatch transpires once again. Despite this knowledge, only about a third of the population followed the recommended safety guidelines. While being younger or residing in Accra might increase one's likelihood to accept, practice and adhere, there remained a substantial gap in understanding why most were not compliant. Economic factors, social customs, and even Ghana's tight knit, often crowded community structures might have played roles here.

Consider face masks, for instance. Only 29% of those surveyed were inclined to wear one. This reluctance might stem from their cost, especially given the average daily wage in Ghana. While local masks are more affordable, higher-grade N95 masks eat up a significant chunk of a day's earnings. And the tangible discomfort of wearing a mask on a sweltering day, combined with costs, could indeed deter many. Cultural norms too might play a part; regular hand washing might not be a frequent practice for some. The "Veronica bucket" invention, which made handwashing more accessible in public places, was a bright spot in Ghana's response. Yet, it seems that overarching societal norms, such as crowded markets and living conditions, hinder widespread adoption of preventive behaviors.

There is also a psychological angle. Fears, stigma, self-efficacy, and group dynamics shape attitudes toward COVID-19 and vaccinations. Similar to other African nations, Ghana's population could also exhibit vaccine hesitancy. Misinformation, especially on social media, might have introduced doubt about vaccine benefits. The influence of the social circle and learning by mimicking or watching what others do are important aspects emphasized by the theories discussed before such as TPB, SCT and SEM. One intriguing finding was the heavy reliance on friends' recommendations, evident from a past study where most Ghanaians preferred herbal medicines against malaria based on friends' endorsements, as will be explored in section 5.5.

The broader concern is the future. At the time of the study, developed nations had been advancing in their vaccination coverage, while Ghana, with a mere 3% of its populace vaccinated, remained vulnerable. Here, historical mistrust, such as the painful memory of the Tuskegee study, could be among the contributing factors. To counter this, it is crucial for global and local health agencies to realize that distribution of vaccines represents one part of the equation. Building trust is equally vital. Public awareness campaigns, community outreach, and involving trusted community figures could bridge this gap. Familiar faces, or "social influencers" in today's parlance, could be instrumental. Watching them getting vaccinated might alleviate widespread concerns.

5.4.3. From Knowledge to Action: Mind the Gap

Though the discussion here spans broad geographical and cultural spectra of Syria and Ghana, several relevant findings can be discerned regarding public perception and practice during the Covid-19 pandemic. The population in both nations demonstrated commendable knowledge regarding the SARS-CoV-2 pandemic. An intriguing divergence, however, was

observed in the translation of this knowledge into practical action, reflecting a gap between understanding and actionable measures. As discussed before, accepting a medication or a medical intervention transcends knowing about the disease or even the intervention itself.

Syria, while displaying a robust understanding of the pandemic, particularly in its urban sectors, highlighted the importance of broadening this knowledge base. This is especially true for non-metropolitan areas and the older populace engaged in the informal sector. Ghana, despite its population being well-informed, observed a paradoxical reluctance to adopt precautionary measures. This dichotomy of knowledge *versus* action is not exclusive to these nations; echoes of it are evident in global responses, with unrest and demonstrations across cities such as Berlin, Amsterdam, and Vienna a common sight these days. To truly combat the spread of Covid-19 and/or any other future pandemic, it is paramount to go beyond mere dissemination of knowledge and awareness campaigns. A holistic approach, intertwining comprehensive, transferable and culturally sensitive public health campaigns with positive reinforcement mechanisms appears necessary.

In addition, another alarming finding was the low willingness to be vaccinated. Bearing in mind that these two studies have been conducted right before or at the start of the rollout of the vaccines worldwide, only around 51% of the participants in Syria and 35% in Ghana demonstrated willingness to receive the COVID-19 vaccine. Initially, one may speculate that such low acceptance of the vaccine would be due to practical limitations such as availability and accessibility as around the end of 2021 less than 5% of the population in both countries had been fully vaccinated³⁸. Yet even now, in 2023, after almost two years the vaccination rate in both countries remains low with 12.4% of the population in Syria and 32.7% in Ghana, especially in comparison with other countries close to have been fully vaccinated. This alludes to a much more complex issue with accepting the COVID-19 vaccine.

Future studies³⁹ in these two countries must address such hesitancy by appropriate means. Such an approach would be to evaluate vaccination hesitancy by applying the 5Cs

³⁸ The vaccine against COVID-19 has been first introduced in Syria in April 2021 and in Ghana in March 2021. It was available for specific subpopulations such as medical workers and those of higher risk, such as immunocompromised and elderly individuals for a few months and then accessible to the general population upon registration.

³⁹ We have indeed conducted such studies in Syria (n = 5320) and Ghana (n = 4181) as well as in Ukraine (n = 1352). The 5Cs Model has been applied in addition to surveying which possible influence the particularities about the vaccines such as brand name, country of origin or its popularity might exert. In addition, we detailed the sources of information the participants used to acquire about vaccines and levels of conspiracy mentality. We are currently in the last steps of the statistical analysis, and we hope that these manuscripts will be available during 2024.

model which dives into the psychological underpinnings of vaccination hesitancy. It explores the *confidence* in vaccine safety and effectiveness, whether individuals become *complacent* about risks of disease, the practical barriers like access, *i.e. convenience*, how much research one may personally invest in weighing vaccine pros and cons, *i.e. calculation*, and the sense of duty to the broader community, *i.e. common responsibility*. By addressing each of these five aspects, public health professionals may aim to craft more effective strategies to encourage widespread vaccination. In addition, one may also explore the perception of the brand name, the influence of sources of information and conspiracy mentality on the hesitancy towards vaccines. By addressing the unique aspects of acceptance of pharmaceutical products, health professionals and decision-makers would indeed be empowered to connect more authentically with individuals and to enhance public health outcomes.

Strategies such as vaccine passports and other mobility restrictions are controversial and have indeed sparked unrest in countries such as the USA, France and Germany. Such approaches should be adopted with caution as they clearly contradict established theories emphasizing the role of agency, *i.e.* having the power to make a decision and feeling in control in one's choices, as discussed before in the theory of planned behavior and the Self-Determination Theory. Any strategy to increase vaccination uptake must be rooted in respect for individual freedoms and democratic principles. Furthermore, harnessing the power of influencers, be it academic stalwarts, religious figures, or social media stars, can be instrumental in championing the benefits of vaccination. These voices, resonating with the public, can bolster trust and bridge the existing chasm between knowledge and action.

In light of the events in Europe and the evolving nature of pandemics, it is imperative for both Syria and Ghana to anticipate challenges. The goal is to preemptively address them, ensuring public health while averting social unrest. Further qualitative and quantitative studies, aimed at discerning the roots of hesitancy and/or refusal to practice life-sparing measures can guide future policy directions, ensuring that both nations, and indeed the global community, are better equipped to face such health crises in the future.

5.5. Ghana's Battle with Malaria: Traditional Remedies or Modern Medication?

Malaria, a formidable adversary in global health, afflicts nearly 228 million people annually, with countries such as Ghana being majorly affected. This lethal illness, brought on by the *Plasmodium* parasite and transmitted via female *Anopheles* mosquitoes, does not just claim over 400,000 lives each year but also strains healthcare systems and impinges on national economies [583,584].

While the WHO fully endorses artemisinin-based combination therapies for malaria, recommending fixed-dose combinations such as artemether–lumefantrine and dihydroartemisinin–piperaquine in malaria-prone regions [585–587], many in Ghana have a historical inclination towards indigenous herbal remedies. Popular local treatments include brands such as Taabea or Time Herbal Mixture, and more traditional concoctions such as the one derived from *Cryptolepis sanguinolenta*⁴⁰ roots [588,589]. This specific herbal potion is prepared by boiling fresh roots of *C. sanguinolenta*, capturing its active ingredients. Notably, from a scientific vantage point, this plant offers natural compounds such as cryptolepine, known to exhibit formidable antimicrobial activities against strains of *Plasmodium falciparum*, even those resistant to chloroquine [588,590–592].

The Ghana Health Service (GHS) has a pragmatic approach, allowing antimalarials to be dispensed post a positive Rapid Diagnostic Test and endorsing the treatment of uncomplicated malaria cases outside hospitals, in places such as pharmacies, licensed shops, or even herbal outlets [593]. This not only alleviates pressure on the healthcare structure, it also amplifies the accessibility of antimalarial agents. Presently, a myriad of these herbal solutions, though sometimes inconsistent in their composition, are openly available through various media channels and street vendors. Despite lacking robust scientific backing, these remedies carry the weight of age-old wisdom and experience, distancing themselves from more esoteric treatments offered by spiritual healers [594–597].

In light of this intricate landscape, this section delves into the preferences of antimalarial treatments in Ghana, probing the inclinations of the local population towards herbal or conventional "Western" medications. The aim is to discern the rationale behind these

⁴⁰ *Cryptolepis sanguinolenta* is a revered West African shrub traditionally harnessed for its medicinal properties. Predominantly found in the tropical rainforests, its roots have been employed for ages in local remedies, particularly for treating malaria.

choices, exploring the significance of side effects, the sourcing of these medicines, and the potential factors influencing the balance between traditional and modern remedies.

5.5.1. The Ghanaian Antimalarial Dilemma

Three aspects seem relevant when trying to explicate the personal preferences of choosing an antimalarial drug in Ghana. Firstly, one will want to know if Ghanaians generally opt for synthetic medication or herbal remedies. Secondly, one might wonder about the influence of sources of information, *e.g.* advertisement, and from where Ghanaians actually purchase or get their antimalarial drugs. Thirdly, how concerned are Ghanaians about potential side-effects and how does this influence their choices? [598]

Common beliefs posit that the high cost and limited availability of synthetic antimalarial drugs may push locals towards potentially unreliable herbal treatments from unconventional distributors. Current insights, however, indeed challenge this view profoundly. Findings show that one third of the population relies solely on herbal preparation, a third on synthetic drugs and the other third on combining both choices together. A significant portion of individuals lean towards herbal remedies, not primarily because of costs or access, but largely due to perceived effectiveness and fewer side effects, *i.e.* perceived safety. This suggests that the gravitation towards herbal remedies might be more complicated than mere convenience or affordability. At closer inspection, one could observe an intriguing trend: a person's education favorably level influences their inclination towards herbal treatments. Furthermore, age also plays a part; as age increases, the preference for herbal treatments follows suit. While one might assume that the medical advice of caregivers would hold significant sway, data indicates that age is a more prominent factor in determining preference to either choice.

Despite the popularity of certain herbal treatments, many of their proclaimed benefits lack rigorous scientific validation. The vast industry backing these remedies leans heavily on age-old traditions for endorsement. Furthermore, a substantial number of respondents procured these remedies not from trusted healthcare facilities but from advertised agents and unauthorized drug peddlers. Surprisingly, traditional healers, commonly associated with such treatments, constituted a negligible source. Advertising, spanning from local TV and radio spots to street banners, emerged as a dominant influencer in these choices. Recommendations from friends also held significant sway. This paints a multifaceted picture of antimalarial drug

choices in Ghana, one that extends beyond traditional healthcare channels with regard to sources of information.

Yet there remains a pressing concern here: Although these herbal treatments are popular, they can lead to detrimental side effects. A significant fraction of consumers of herbal remedies reported adverse reactions ranging from minor inconveniences such as itching to more severe symptoms necessitating hospitalization. Most of these reactions were associated directly with the duration of treatment. Somewhat surprising, has been that a considerable number of respondents persisted with the herbal treatments even after experiencing these adverse effects.

A closer examination also reveals a correlation between the source of these remedies and the likelihood of adverse drug reactions (ADRs). Remedies sourced from traditional healers and peddlers seem particularly to be associated with increased ADRs. On the contrary, those obtained based on friends' recommendations show a reduced likelihood of such reactions. Remedies from licensed pharmacies and shops had no significant correlation with ADRs in practice. Alarmingly, drugs that are marketed with claims of "fewer side effects" often resulted in increased ADRs, underscoring the need for better oversight and public awareness.

5.5.2. Bridging Heritage and Health

Antimalarial drugs in Ghana present a complex issue which contradicts initial assumptions. While it might seem likely for urbanized cities such as Accra and Kumasi to rely on formal medical channels for prescriptions, the truth deviates from this notion. In fact, the picture is more colorful and vivid and it is depicted by traditional herbal remedies playing a significant role in the antimalarial drug landscape of Ghana.

Availability is not the sole driving factor. Data highlights that *trust* plays a relevant role in influencing drug choices. For many, recommendations from friends or reliance on local recipes engraved into the traditions of Ghana hold more weight than scientifically proven alternatives. This is indeed consistent with psychological and social theories discussed before such as TPB and SEM. This trust is further reinforced by advertising which capitalizes on locally produced and recognized remedies [594,599]. In stark contrast, imported drugs, which have been scientifically vetted, are not promoted in the same manner. There seem to be a noticeable skepticism, perhaps even a level of mistrust, towards drugs produced in nations not

affected by malaria. This sentiment extends to a broader distrust of synthetic compounds compared to natural herbal treatments. This preference for local over foreign, natural over synthetic, is not exclusive to Ghana. In Germany, for instance, local products, including alternative herbal remedies, are often favored for their familiarity and trustworthiness. The same pattern emerges in Ghana, where natural remedies are perceived as superior, regardless of their actual efficacy or potential side effects [600–602].

Importantly, social considerations have a significant influence on drug choice. It should be emphasized that policy measures to tackle health challenges must acknowledge these social underpinnings. Merely supplying Ghana, for instance, with modern antimalarial medication would not be effective unless these treatments are also socially accepted and trusted. Notably, even well-educated individuals demonstrate a preference for herbal treatments, possibly due to a perceived naturalness. In terms of subjective perception of adverse drug reactions (ADRs) a concerning trend has been identified. Two thirds of the population result to herbal or a mix of herbal and synthetic treatments despite experiencing ADRs [603,604]. The source of the herbal remedies, however, significantly influence the frequency and severity of ADRs reported, be it a licensed establishment or a traditional healer.

To improve the current situation, a multifaceted approach is necessary. While promoting scientifically proven treatments is crucial, so is researching and refining local herbal remedies [595,596,605–609]. Given their longstanding application and wide societal acceptance, enhancing these remedies might provide both, health and economic, benefits to the local population. The link between the source of a remedy and ADRs associated suggests that better regulation and sourcing could lead to safer and more effective treatments. Addressing the challenges against this backdrop requires a blend of promoting scientifically backed treatments and understanding and refining local herbal solutions, for the betterment of patients not only in Ghana, but potentially in wider regions of Africa.

5.6. Chapter Conclusions

Drawing on the intricate history and multifaceted dynamics of the application of remedies and pharmaceutical products, it seems evident that the current approach to healthcare primarily targets the pathology and pathogenesis of diseases. This paradigm, although rooted in rigorous scientific evidence, seems to have deviated from a more traditional holistic practice which places the patient, with all their unique characteristics, at the forefront. The medical world has been entrenched in the pathogenic framework, primarily fixating on diagnosing diseases and prescribing treatments. This is akin to a pharmacy purely focused on dispensing medications based on the symptoms presented by the patient. But what if, instead of only mitigating symptoms, the pharmacy of tomorrow could also advise on holistic solutions which not only treat diseases but also enhance overall wellbeing?

Ancient civilizations valued nature and consistently acknowledged its medicinal attributes. They turned to therapeutic teas and herbal mixtures. This approach ensured that the patient's wellbeing and personal characteristics were integrated into the therapeutic process. As the 21st century is ushered in, the application of pharmaceutical products undergoes a major shift in paradigm, further gravitating towards an almost myopic view emphasizing diseases and their genetic underpinnings. While this precision is commendable, it unfortunately sidelines the broader spectrum of human experience, traditional beliefs, environmental factors, and sociocultural nuances.

To truly enhance the current healthcare paradigm towards an impactful *gestalt-switch*, one ought to embrace an approach which does not just treat diseases, yet genuinely engages with the patient. Such a *gestalt-switch* would prioritize health promotion and delve into the origins of health. Here a concept which truly lies at the heart of modern healthcare, sometimes referred to as *Salutogenesis*, comes to mind. Derived from the Latin "*salus*" for "health" and the Greek "*genesis*" for "origin", this term, coined by the American medical sociologist Aaron Antonovsky (1923-1994), highlights an approach which emphasizes factors promoting health and well-being instead of those causing disease [610,611] .

Imagine a scenario where a patient with diabetes approaches a pharmacy. While the traditional pathogenic approach would simply involve providing insulin or other antidiabetic medications, a salutogenic strategy would consider a broader view. The pharmacist, in this context, might not only supply the medicine but also provide guidance on dietary choices, stress

management techniques, and lifestyle habits which could significantly improve the patient's overall health and wellbeing. Such an approach acknowledges that health is not merely the absence of disease but a comprehensive state of physical, mental, and social wellbeing.

Antonovsky's salutogenesis is anchored in the "Sense of Coherence" (SOC) which entails *comprehensibility*, *i.e.* understanding life events, *manageability*, *i.e.* resources to cope, and *meaningfulness*, *i.e.* life's challenges are worthy of engagement. Applying this to pharmacy would mean understanding the patient's life context, ensuring they have the necessary resources, medicinal and non-medicinal, to manage their conditions, and making them feel involved and valued in their therapeutic journey [612].

Consider, for instance, the patients who are skeptical about new vaccines, such as those for COVID-19. A salutogenic approach in pharmacies would not just emphasize the scientific effectiveness of the vaccine. Instead, it would engage with these patients, trying to understand their concerns, providing information in an accessible manner, and collaborating with them, ensuring they feel understood and are actively participating in their health decisions. The same goes for the treatment of malaria and practice of preventive measure in Ghana and Syria. In the evolving landscape of healthcare, salutogenesis offers a promising paradigm, advising to holistically understand and promote health. For the world of pharmacy, this means transitioning from a mere dispenser of drugs to an active collaborator in a patient's journey towards wellbeing⁴¹.

While the safety and effectiveness of pharmaceutical products are undeniably essential, there remains an urgent need to reconsider their application. A shift from a disease-centric view to a holistic, patient-centric perspective is the way forward. One may wish for a future for modern pharmacy where precise techniques such as personalized medicine are actively combined with patients' idiosyncratic tendencies. Only by understanding and integrating the diverse aspects of an individual's life, from the molecular to the psychological, the social and environmental, into the therapeutic process pharmacy will treat patients rather than diseases.

⁴¹ Notably, data protection regulation might actually stand in the way of pharmacists trying to inquire medical information from patients though this of course might vary from country to country. It might be, therefore, advisable to check regulation and create a waiver the patient may sign if necessary.

Chapter Six

6. Discussion: “*In my quest, I find no absolute truth*”⁴²

Despite the plethora of topics left to be addressed in future research, the account established for pharmacy within the lines of this dissertation is unique and offers a distinctive and broad utility. The discourse has been anchored by the guiding questions introduced, namely, recognizing critical challenges in pharmacy through a philosophical and interdisciplinary lens and subsequently deriving practical solutions. By and large, the prime objective has been to bridge the neglected chasm between philosophy and pharmacy and to stimulate future debates within the realm of this topic, thereby unleashing a myriad of benefits contingent on their integration.

As illustrated in the various chapters, scientific practice in pharmacy carries a lot of weight. On the one side, pharmaceutical products are direct answers to societal needs and on the other side such products undergo a demanding regulatory process to ensure their safety and effectiveness. In both sides the therapeutic products and their market entry are hinging on scientific knowledge represented in evidence and proper means of drawing inference.

Scrutinizing the epistemology guiding pharmacy produced an account of knowledge which possesses the attributes of being communal, dynamic and problem-solving oriented, as opposed to the idealized, unchanging, definitive and perhaps non-attainable truth. Such an account transcends being simply grounded in a logical structure, rather it is pragmatic, relative, never permanent and adaptable to the changing societal needs and the prevailing research traditions of the era. This means that scientists active in the field of pharmacy are on a constant pursuit to find better solutions to the problems in their field. The communal and societal aspect of scientific practice is perhaps most evident in the current publishing practices celebrated with a gold standard set up to discern good science from pseudoscience, that is blind forms of peer reviews⁴³, as highlighted in Chapter Three. This finding emphasizes the anthropocentric

⁴² The Author.

⁴³ In my view, the near future may see peer review transition to an automated process, driven entirely by artificial intelligence. I say entirely because I have it on good authority that the initial scanning of manuscripts to evaluate its suitability to be published within the scope of a journal is common practice nowadays. Even the most cutting-edge AI systems currently known, however, cannot innovate or generate fresh insights. These machines are bound by pre-existing knowledge, limiting their capacity for novel discoveries. My concern is a potential stagnation in scientific advancements, as AI might inadvertently dismiss revolutionary ideas it hasn't been previously exposed to.

aspects of scientific practice in pharmacy, together with the implications of its inherent limitations, nested in social, economic, political and historical milieus.

One aspect to consider when knowledge is relative is the potential pitfalls of reductionism. In scientific practice, oversimplifying or truncating based on relative knowledge may inadvertently miss key insights, leading one down the rabbit hole of epistemological skepticism; pondering if one truly knows anything at all or will ever do so. Instead of resisting this, it is more productive to acknowledge and harness the inherently reductionist tendencies within pharmaceutical research. Here, mechanistic explanations serve as a prime example. Such explanations analyze the interactions between a drug and an organism in their mechanistic components. Scientists, however, do not randomly or arbitrarily select such components and interactions, rather they follow a rigorous empirical practice. Furthermore, mechanistic explanations facilitate both predictability and control which are indeed two paramount goals in scientific practice.

As demonstrated in Chapter Two, however, there is immense merit in adopting a complementary holistic approach. Such perspective, exemplified in the Baumkuchen Model, refines the understanding of mechanistic models and also discerns the intricate mechanisms operating at the various levels of complexity within an organism. This may steer the reductionist explorations towards groundbreaking discoveries or guide the answer to elusive questions as illustrated by revisiting the function of metallothionines and constructing the tripartite research strategy distinctions, *i.e.* upward-looking *vs.* downward-looking, mere interactions *vs.* interventions and hypothesis testing *vs.* exploratory research. Moreover, recognizing the merits of the reductionist approach in pharmacy equips experts to innovate systematic inference methodologies, such as the E-Synthesis utilized in the case of AMX and DRESS. Balancing reductionist and holistic approaches represent the optimal approach for advancing scientific research in pharmacy.

The implications of reductionism in scientific research within pharmacy extend beyond mere methodology and research, as emphasized in Chapter Five, albeit in a different flavor. The widespread understanding of the concept of application in pharmacy risks oversimplifying individuals, reducing them solely to their molecular dimensions. This pathology-medicating-driven paradigm seems to render the patients themselves as secondary. Recent public events during the COVID-19 pandemic have underscored the potential fallout of this reductionist stance. For instance, Europe's major cities have witnessed unprecedented riots against the

COVID-19 vaccine, while globally, diminished vaccination rates reflect a broader societal apprehension. Once again, the multidisciplinary, holistic approach this time adopted to address the application of pharmaceutical products may offer a fix to this reductionist stalemate. Instead of a singular focus on disease management, pharmacy ought to rally for a more comprehensive patient care model. By weaving in the unique social, psychological, and environmental aspects of individuals, a more encompassing and patient-centric form of care is presented. Insights from fields such as psychology, sociology, and public health are indeed instrumental in reshaping and refining the concept of application in pharmacy. Another important conceptual shift in this context is focusing pharmaceutical practice and application on health promotion and the origins of health as advocated for in social pharmacy and salutogenesis.

In addition, the intimate relationship between the control and the pursuit of truth within pharmacy has been identified twofold. On one side, regulatory bodies set standards for the development and production of drug products and, on the other, market entry decisions are based on the results of scientific practice in terms of knowledge or evidence of safety and effectiveness. In some cases, it might seem as a circle, *i.e.*, researchers develop the drug and the regulators who assess and evaluate its safety and effectiveness bases their decisions on knowledge from the same source⁴⁴. But again, how can safety and effectiveness be guaranteed if the knowledge stemming from scientific practice is rather relative? To this end, the inherent uncertainty is circumvented by quality assurance and risk management measures. Pharmaceutical impurities, for instance, are mitigated by adhering to cGMP and following strategies such as quality by design. Nevertheless, impurities related scandals keep persisting. At closer inspection, it seems that the current understanding of pharmaceutical impurities in regulatory texts leaves room for entities holding different epistemic attributes to be misclassified. The philosophical approach adopted has been successful in clarifying at least eight different types of impurities in one class based on the knowledge of their chemical composition, biological activity and presence in a drug sample. In some cases, however, such as the outbreak of a novel disease, uncertainty in decision-making may be inevitable and adopting a *philosophical, i.e.* ontological, epistemological and ethical, lens might not be fruitful in providing direct and immediate guidance. Yet, a philosophical reflection on aspects related

⁴⁴ This is an issue which has already been raised in Chapter Four, where the recommendation to reducing bias in drug approval should consider excluding the manufacturer from drug monitoring.

to the type of risk attitude and means for evidence production and synthesis may indeed aid experts in counteracting future challenges and augmenting pandemic preparedness.

Forecasting future outbreaks of infectious disease or public health crises might appear unduly pessimistic. There is, however, a burning concern rooted in the treatment of the environment, especially in terms of pharmaceutical waste. The traditional notion of control within pharmacy, primarily centered around patient safety, ought to evolve to encompass a broader ecological perspective. One must always remember that human health is essentially linked to the health of the environment. Living organisms, from fungi, insects, fish, reptiles to primates, are all interconnected through complex ecological networks. Hence, any environmental degradation, whether through the contamination of ecosystems by pharmaceutical products or the subsequent loss of biodiversity, has potential ripple effects. Such disturbances and constant pressure on the ecology would inevitably trigger new disease outbreaks. Given this interconnectedness, it is incumbent upon pharmacy to expand its purview, embracing a stewardship role which safeguards both human and environmental health. Addressing these ecological concerns renders pharmacy an active participant in global efforts to ensure a more sustainable and harmonious future.

Chapter Seven

7. Conclusions: Is philosophy and philosophical thinking important in pharmacy?

The answer is a resounding yes! This is indeed a fact, not only in scientific practice but also in regulations as well as the application of pharmaceutical products. The substantive insight presented by the reflections, challenges, and solutions addressed as part of this dissertation are by no means complete or exhaustive. Apart from the rich philosophical approach which could be adopted stretching from logic, philosophy of language and phenomenology to Practical philosophy and applied ethics, each step in the lifecycle of pharmaceutical products, and pharmacy in general, offers a wealth of unique phenomena anticipating investigation, analysis, and discussions. This dissertation has engaged with topics at varying levels of complexity. The discourse spans over abstract notions such as truth, knowledge, and control, to more tangible concerns such as publishing practices, the environmental footprint of pharmaceuticals, and the strategic shifts toward patient-centric health promotion.

Numerous issues, however, still command attention, for instance, the illicit distribution and consumption of drugs, such as the recent effort to regulate cannabis in Germany for recreational use, counterfeit medication challenges and the role of aesthetics in packaging of medication which could influence patient adherence. Other issues could be related to the allocation of resources in terms of equal availability and accessibility to pharmaceutical products in less fortunate countries or in cases of rare diseases. Treatment protocols and religious believes, alternative pharmacy, patent restrictions limiting access to essential medications, and the proliferation of synthetic chemical pathways within the context of dissemination, also represent compelling issues which demand attention.

Furthermore, another compelling issue is the use of language in pharmacy, switching between specialized jargon and layperson terms. This is indeed relevant in bringing the therapeutic message across and enhancing patient communication. Areas such as family planning, geriatric care, dietary and chronic disease management, and even medical insurance in this context warrants discussion. At yet another front is the growing role of computer models and AI in pharmacy. Whether in personalized medicine, systems pharmacology, drug development, modeling spread of infectious disease, robotic dispensing or online pharmacies, big data, automation and machine learning present new avenues of exploration.

Indeed, the breadth and depth of challenges within pharmacy are vast. They emphasize the necessity for an interdisciplinary, philosophical approach in research, teaching and curricula. Reducing pharmacy to its traditional academic subtopics—such as chemistry, biology, pharmacognosy, pharmacology, or pharmaceutical technology—risks overlooking its profound intersections with politics, economy, society, psychology, and history. In the advancement of the field, both as a science and a profession, embracing this encompassing, holistic outlook will undeniably benefit all stakeholders. Establishing research centres dedicated to these interdisciplinary challenges would further foster cooperation and solution-driven examination, ultimately redefining the scope and impact of modern pharmacy.

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600. Trends and Challenges of Traditional Medicine in Africa | African Journal of Traditional, Complementary and Alternative Medicines Available online: <https://www.ajol.info/index.php/ajtcam/article/view/67959> (accessed on 29 September 2023).
601. Blog - How Not to Explain African Distrust of Western Medicine Available online: <https://bioethicstoday.org/blog/how-not-to-explain-african-distrust-of-western-med/> (accessed on 29 September 2023).
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605. Boadu, A.A.; Asase, A. Documentation of Herbal Medicines Used for the Treatment and Management of Human Diseases by Some Communities in Southern Ghana. *Evidence-Based Complementary and Alternative Medicine* **2017**, *2017*, e3043061, doi:10.1155/2017/3043061.

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9. Personal Resume

AHMAD YAMAN ABDIN

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Education

SEPTEMBER 2018 – DECEMBER 2023

PhD Candidate, Bioorganic Chemistry, Saarland University, Germany

Title: *Critical Evaluation of Pharmacy: Truth, Control and Application*

JULY 2016 – JULY 2017

M.Sc. Pharmacy, Bioorganic Chemistry, Saarland University, Germany

Title: *The philosophical implication of pharmaceutical impurities*

SEPTEMBER 2008 – SEPTEMBER 2013

B.Sc. Pharmacy, Faculty of Pharmacy, Damascus University, Syria

Teaching

Teaching assistant and laboratory supervisor in the field of analytical chemistry. Taught an introductory course on philosophy of science and science communication. Supervised several Master of Science in Pharmacy students since 2017. I am also a founder and lecturer of the Global Classroom for Pharmacy and beyond.

Employment

JULY 2016 - PRESENT

Research Assistant, Bioorganic Chemistry Department, Faculty of Pharmacy, Saarland University, Germany

ERASMUS academic staff mobilities to the University of Montenegro (2017, 2017 and 2019) and Shota Rustaveli State University, Georgia (2018). Organizer of “[Meet&Greet](#)” cultural and social events for young scientists (2019). Organizer of the “International Week for Science” conference, Saarland University (2018 and 2019). Visiting researcher at the UCCS (Unité de Catalyse et Chimie du Solide) Central Lille, Lille, France (2021). Founder, organizer and lecturer at the “[Global Classroom](#)” an online international, DAAD funded teaching project (2020 and 2023).

JULY 2016 – DECEMBER 2016

Pharmacy Intern, Apotheke am Hallplatz, Zweibruecken, Germany

SEPTEMBER 2014 – NOVEMBER 2015

Community Pharmacist, Mohanad Sakhita, Damascus, Syria

SEPTEMBER 2014 – NOVEMBER 2015

Laboratory Supervisor, Faculty of Pharmacy, Damascus University, Syria

Research Interests

Scientific Communication

In the last two decades there have been an explosion in the number of scientific journals under the umbrella of Open Access (OA). While [we believe](#) that OA represents the best possible scenario towards more open and available science, we address a few issues which would render publishing more transparent and democratic. To this end we have been since 2016 working to develop our vision and were successful in 2018 in establishing two peer-reviewed journal, [Sci](#) and [Current Nutraceuticals](#). I teach workshops on oral and written scientific communication as part of my teaching supervision duties at the Saarland University and abroad during my ERASMUS+ staff mobilities. In 2021, I co-edited a [Special Issue](#) on interdisciplinary research. I am currently co-editing several Special Issues and have already co-authored four editorials.

Causality & Mechanisms

Scientists spend much time looking for causes. Finding such causes and deciding what to do about them is not easy at all. The aim is to analyze the sources of knowledge in Pharmacy and Pharmaceutical research from a philosophical perspective. We adopt notions from the New Mechanistic Philosophy and apply them to the concepts of mechanisms in pharmacology. This topic is greatly interesting from the perspective of policy making, fund allocation and pharmacovigilance.

Pharmacy & Society

Pharmacy is one of the first and most important professions in the history of human survival. Therapeutic practices utilizing plants, animals and other "things" from nature laid down the foundations of what became the largest and most influential industry in the world, the pharmaceutical industry. We operate at the interface between pharmacy and society to address in a descriptive and normative sense how to develop and support Pharmacy. One important aspect, regularly overlooked, is the relationship between pharmacy, society and the environment. Another essential element is maintaining and promoting public health, within a certain social context, especially in epidemics and pandemics. In this regard, I focused in my research on malaria, COVID-19 among other infectious disease in Syria and Ghana. I also had the pleasure of supervising four master students who carried out their research in this area.

Natural Products & Up-cycling

Utilizing nanotechnological approaches, such as particles size reduction and bio generation of nanoparticles, to unleash the biological potentials of what otherwise is considered waste materials. For more information, please see publications.

Funding

DAAD, Teaching in the Time of War Scheme, StudyBridge Ukraine-Saar for Pharmacy Students, in collaboration with Lesya Ukrainka Volyn National University, Ukraine 2022-2023

Transform 4 Europe research funding, Contraceptives in the Developing World, in collaboration with the University of Alicante, Spain 2022-2023

Förderung von Digitalen Lehr- und Lernangeboten im Rahmen des Gesamtkonzepts Global Classroom@UdS 2021, UdS-Internationalisierungsfonds, named applicant, (proposal accepted).

Digitalisierungsmaßnahmen (Ostpartnerschaften) 2020 and 2021, DAAD funding, named applicant and organizer of the project, [Global Classroom](#).

ERASMUS+ Scholarship 2021, Unit of Catalysis and Solid State Chemistry, University of Lille-Nord, Lille, France

DAAD STIBET-Program for PhD and Postdocs 2020, mentoring scholarship.

DAAD Transformation: Kurzmaßnahmen 2019, Colisa (Cooperation between Libya and the Saarland), (cancelled due to war in Libya).

COST Action NutRedOx-CA16112 supported by COST 2017 (European Cooperation in Science and Technology), <https://www.cost.eu/actions/CA16112/#tabs|Name:overview>

The “Landesforschungsfoerderungsprogramm” of the State of Saarland 2017 (Grant No. WT/2—LFFP16/01).

Conferences

[The Fourth Congress of Pharmacists of Montenegro with International Participation, May 2023](#)
Poster, title: “Pharmaceutical waste management in Montenegro: Scope, policy and implementation” Budva, Montenegro

[Salutogenesis in practice, ETC Summer courses, Valencia, Spain, July 2022](#)

[UNESCO Symposium on Social Sciences and the COVID-19 Pandemic, October 2021](#)

Speaker, talk title: “Corona in the time of war: A cross-sectional study from Syria” Paris, France (virtual)

[International Society for Philosophy of Chemistry \(ISPC\) annual conference, July 2021](#)

Speaker, talk title: “Biorefinery and biofuel in the region of Hauts de France” Buenos Aires, Argentina (virtual)

[Basel Sustainability Publishing forum, September 2019](#)

Attendee, The Center for Teaching and Research (Zentrum für Lehre und Forschung), University Hospital of the University of Basel, Switzerland

[Helmholz Institute for Pharmaceutical Research, June 2019](#)

Attendee, Saarland University, Saarland, Germany

[NutRedOx Semi-annual Conference, March 2019](#)

Speaker, talk title: “Inspired by Nature: Redox Modulators and Natural Nanoparticles” Luxembourg, Luxembourg

[Helmholz Institute for Pharmaceutical Research, May 2018](#)

Attendee, Saarland University, Saarland, Germany

[Deutsche Pharmazeutische Gesellschaft \(DPhG\) Jahresgunug, September 2017](#)

Co-organizer, Saarland University, Saarland, Germany

[NutRedOx Semi-annual Conference, September 2017](#)

Speaker, talk title: “Redox active natural products: a fountain of inspiration and inexhaustible well of well-being” European School of Chemistry, Polymers and Materials (ECPM University of Strasbourg, France

International Society for Philosophy of Chemistry (ISPC) annual conference, July 2017

Speaker, talk title: “The matter of impurities in pharmaceuticals: Substances without a name and how to handle them” ISPC at Diderot University, Paris, France

Soft Skill Courses

Teaching and Learning – Basics in English; University Didactics, Saarland University, Germany, 2021

Specific Aspects of Teaching and Learning in STEM Disciplines; University Didactics, Saarland University, Germany, 2021

Introduction to video and web-conferences; Center for Lifelong Learning, Saarland University, Germany, 2020

Cross-cultural Communication; Center for Lifelong Learning, Saarland University, Germany, 2019

First Aid; Society for Emergency Medicine, Saarland University, Germany, 2019

Professional Communication; Central Institute for Languages and Communications, Saarland University, Germany, 2018

Writing English; Central Institute for Languages and Communications, Saarland University, Germany, 2018

Editorial Duties

Special Issue, *Antioxidants*, Antioxidant Research in Germany, **Guest Editor Assistant**, 2023 (https://www.mdpi.com/journal/antioxidants/special_issues/3N4S5DXRXW)

Research Topic, *Frontiers in Nutrition*, *Biovalorization: How to Turn Food Waste into Value*, **Topic Coordinator**, 2023 (<https://www.frontiersin.org/research-topics/55701/biovalorization-how-to-turn-food-waste-into-value>)

Special Issue, *Antioxidants*, *Something is Rotten in the State of Redox*, **Guest Editor Assistant**, 2023 (https://www.mdpi.com/journal/antioxidants/special_issues/TMWCJJ2435)

Special Issue, *Sci*, Feature Papers—Multidisciplinary Sciences 2023, **Guest Editor Assistant**, 2023 (https://www.mdpi.com/journal/sci/special_issues/Y1E5UQV4W2)

Special Issue, *Sci*, Feature Papers—Multidisciplinary Sciences 2022, **Guest Editor Assistant**, 2022 (https://www.mdpi.com/journal/sci/special_issues/FPMS2022)

Special Issue, *Sci*, Feature Papers 2021 Editors Collection, **Guest Editor Assistant**, 2021 (https://www.mdpi.com/journal/sci/special_issues/Feature_Papers_Collection)

10. List of Publications

Number of citations: 242 and H-index: 9, according to Google Scholar September 2023. First publication: 2018.

1. Tiganescu, E.; **Abdin, A.Y.**; Razouk, A.; Nasim, M.J.; Jacob, C. The Redox Riddle of Selenium Sulfide. *Curr. Opin. Chem. Biol.* **2023**, *76*, 102365, doi:10.1016/j.cbpa.2023.102365
2. **Abdin, A.Y.**; De Pretis, F.; Landes, J. Fast Methods for Drug Approval: Research Perspectives for Pandemic Preparedness. *Int. J. Environ. Res. Public Health* **2023**, *20*, 2404, doi:10.3390/ijerph20032404
3. **Abdin, A.Y.**; Jacob, C. Make a Stand(ard) for Science. *Sci* **2023**, *5*, 7, doi:10.3390/sci5010007.
4. **Abdin, A.Y.**; Friend, M.; The Institutional Compass, 1st Edition; Springer Nature: Cham, Switzerland, July **2022**; Chapter 13: Regional Compass Hauts-de-France, Superimposing a Biorefinery, 161 - 173, ISBN 978-3-031-05452-5. (https://link.springer.com/chapter/10.1007/978-3-031-05453-2_13)
5. Tiganescu, E.; Lämmermann, M.A.; Ney, Y.; **Abdin, A.Y.**; Nasim, M.J.; Jacob, C. A Whiff of Sulfur: One Wind a Day Keeps the Doctor Away. *Antioxidants* **2022**, *11*, 1036. <https://doi.org/10.3390/antiox11061036>
6. Razouk, A.; **Abdin, A.Y.**; Yeboah, P.; Pitsch, W.; Nasim, M.J.; Maarouf, M.; Jacob, C. CORONA in the Time of War: A cross-sectional study from Syria. *UNESCO Books* **2022**, (forthcoming)
7. **Abdin, A.Y.**; Jacob, C. Sci: An Inclusive, Multidisciplinary Scientific Journal. *Sci* **2022**, *4*, 10. <https://doi.org/10.3390/sci4010010>
8. Hamdi, N.; Chaouch, S.; da Silva, I.; Ezahri, M.; Lachkar, M.; Alhasan, R.; **Abdin, A.Y.**; Jacob, C.; Bali, B.E. Synthesis, Structural Characterization, and Biological Activities of Organically Templated Cobalt Phosphite (H₂DAB)[Co(H₂PO₃)₄]-2H₂O. *Sci* **2022**, *4*, 5, doi:10.3390/sci4010005.
9. Jacob, C.; **Abdin, A.Y.**; Köhler, F.; Maret, W. Bert Vallee—A 20th Century Adventure(r) in Zincology. *Int. J. Mol. Sci.* **2021**, *22*, 13393. <https://doi.org/10.3390/ijms222413393>
10. Yeboah, P.; Daliri, D.B.; **Abdin, A.Y.**; Appiah-Brempong, E.; Pitsch, W.; Panyin, A.B.; Adusei, E.B.A.; Razouk, A.; Nasim, M.J.; Jacob, C. Knowledge into the Practice against COVID-19: A Cross-Sectional Study from Ghana. *Int. J. Environ. Res. Public Health* **2021**, *18*, 12902. <https://doi.org/10.3390/ijerph182412902>
11. **Abdin, A.Y.**; Jacob, C.; Kästner, L. The Enigmatic Metallothioneins: A Case of Upward-Looking Research. *Int. J. Mol. Sci.* **2021**, *22*, 5984. <https://doi.org/10.3390/ijms22115984>
12. Nasim, M.J.; Zuraik, M.M.; **Abdin, A.Y.**; Ney, Y.; Jacob, C. Selenomethionine: A Pink Trojan Redox Horse with Implications in Aging and Various Age-Related Diseases. *Antioxidants* **2021**, *10*, 882. <https://doi.org/10.3390/antiox10060882>
13. **Abdin, A.Y.**; Nasim, M.J.; Ney, Y.; Jacob, C. The Pioneering Role of Sci in Post Publication Public Peer Review (P4R). *Publications* **2021**, *9*, 13. <https://doi.org/10.3390/publications9010013>
14. **Abdin, A.Y.**; Jacob, C.; Kästner, L. Disambiguating “Mechanisms” in Pharmacy: Lessons from Mechanist Philosophy of Science. *Int. J. Environ. Res. Public Health* **2020**, *17*, 1833. doi.org/10.3390/ijerph17061833
15. **Abdin, A.Y.**; Yeboah, P.; Jacob, C. Chemical Impurities: An Epistemological Riddle with Serious Side Effects. *Int. J. Environ. Res. Public Health* **2020**, *17*, 1030 doi.org/10.3390/ijerph17031030

16. Alnahas, F.; Yeboah, P.; Flidel, L.; **Abdin, A.Y.**; Alhareth, K. Expired Medication: Societal, Regulatory and Ethical Aspects of a Wasted Opportunity. *Int. J. Environ. Res. Public Health* **2020**, *17*, 787 doi.org/10.3390/ijerph17030787
17. Yeboah, P.; Forkuo, A.D.; Amponsah, O.K.O.; Adomako, N.O.; **Abdin, A.Y.**; Nasim, M.J.; Werner, P.; Panyin, A.B.; Emrich, E.; Jacob, C. Antimalarial Drugs in Ghana: A Case Study on Personal Preferences. *Sci* **2020**, *2*, 28 doi.org/10.3390/sci2020028
18. **Abdin, A.Y.**; Auker-Howlett, D.; Landes, J.; Mulla, G.; Jacob, C.; Osimani, B. Reviewing the Mechanistic Evidence Assessors E-Synthesis and EBM+: A Case Study of Amoxicillin and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), *Current Pharmaceutical Design* **2019**, *25*: 1866. doi.org/10.2174/1381612825666190628160603
19. Kołodziejewski, D.; Koss-Mikołajczyk, I.; **Abdin, A.Y.**; Jacob, C.; Bartoszek, A. Chemical Aspects of Biological Activity of Isothiocyanates and Indoles, the Products of Glucosinolate Decomposition. *Curr Pharm Des* **2019**, *25*, 1717–1728, doi:10.2174/1381612825666190701151644.
20. Jacob, C.; Rittman, M.; Vazquez, F.; **Abdin, A.Y.** Evolution of *Sci*'s Community-Driven Post-Publication Peer-Review. *Sci* **2019**, *1*, 16, doi:10.3390/sci1010016.v1.
21. Nasim, M.J.; Alhasan, R.; **Abdin, A.Y.**; Alnahas, F.; Jacob, C. Inspired by Nature: Redox Modulators and Natural Nanoparticles. *Proceedings* **2019**, *11*, 24, doi:10.3390/proceedings2019011024.
22. Nasim, M. J.; Witek, K.; Kincses, A.; Sarfraz, M.; Alhasan, R.; **Abdin, A.Y.**; Żesławski, E.; Anna Marć, M.; Gajdács, M.; Spengler, G.; Nitek, W.; Latacz, G.; Karczewska, E.; Kieć-Kononowicz, K.; Handzli, J.; Jacob C. Pronounced Activity of Aromatic Selenocyanates against Multidrug Resistant ESKAPE Bacteria, *New Journal of Chemistry*, **2018**, Royal Society of Chemistry doi.org/10.1039/C9NJ00563C
23. Alhasan, R.; Kharm, A.; Nasim, M. J.; **Abdin, A.Y.**; Bonetti, J.; Giummelly, P.; Ejike, C. E. C. C.; Leroy, P.; Gaucher C.; Jacob, C. Flush with a flash: natural three component antimicrobial combinations based on *S*-nitrosothiols, controlled superoxide formation and 'domino' reactions leading to peroxyxynitrite, *MedChemComm*, vol. 9, no. 12, pp. 1994-1999, **2018**. doi.org/10.1039/C8MD00414E