pugatchconsilium

THE EVOLUTION OF PHARMACOVIGILANCE

Labeling, Packaging and Pharmacopeia Standards

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This report was commissioned by Novartis Pharmaceuticals Corporation.
The views represented here are those of the authors only.

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ANDA	Abbreviated New Drug Application
API	Active Biopharmaceutical Ingredient
CGMP	Current Good Manufacturing Practice
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organizations of Medical Sciences
CMC	Chemistry, Manufacturing and Controls
EMA	European Medicines Agency
FDA	US Food and Drug Administration
GCP	Good Clinical Practices
GDP	Good Distribution Practices
GMP	Good Manufacturing Practices
ICH	International Conference on Harmonization of Technical Requirements for Registration of Biopharmaceuticals for Human Use
NBCD	Non-Biological Complex Drug
NDA	New Drug Application
NTI	Narrow Therapeutic Index
OECD	Organisation for Economic Co-operation and Development
PI	Prescribing Information
PMDA	Japan's Pharmaceutical and Medical Devices Agency
PRAC	Pharmacovigilance Risk Assessment Committee
PVP	Pharmacovigilance Plan
QbD	Quality by Design

LIST OF ABBREVIATIONS

R&D	Research and Development
RLD	Reference Listed Drug
RMP	Risk Management Plan
SPC	Summary of Product Characteristics
TGA	Australia's Therapeutic Goods Administration
WHO	World Health Organization

Additional definitions

Biopharmaceutical

A term used to describe and include both chemical based medicines (which are manufactured using a chemical process and products) as well as biologics which are medicines that are inherently biological products developed with biological sources and process. Throughout the paper, the terms biopharmaceutical, drug, medicine and medicinal product are used interchangeably.

EXECUTIVE SUMMARY

The safe use of medicines is perhaps the single most important criteria that any regulatory authority within a given country has to ensure, in order both to protect public health and the integrity of its healthcare system. Pharmacovigilance is the name given to the mechanisms and tests that together map and ensure the safety of a medicine throughout its life span – from test tube to patient.

While many developing and emerging markets are still grappling with the challenges of putting in place the fundamental institutions and processes of a pharmacovigilance framework, most high income developed markets have already robust systems of pharmacovigilance in place. Still, even in developed markets challenges remain. In fact, over the last few years a number of new pharmacovigilance challenges have emerged, particularly in a given medicine's post-exclusivity phase. When an innovative medicine enters the market it has several years of exclusivity, originating from its patent and/or market exclusivity protection. Once this exclusivity period expires, new follow-on generic participants can enter the market. The expiry of this exclusivity period and subsequent time period raises several specific pharmacovigilance questions relating to manufacturing, packaging, labeling and the use of pharmacopeia standards for regulatory purposes as well as more broadly the question of how all types of products (innovative, generics, small molecules as well as big ones) should be monitored.

The purpose of this report is to examine some of these challenges in the areas of packaging and labeling, and pharmacopeia standards. This is an important topic as differences and gaps in the regulatory framework for these areas have the potential to have a significant impact on standards of quality, patient safety and incentives for biopharmaceutical innovation and R&D. The report provides a thematic discussion of these areas, the new pharmacovigilance challenges they pose and the different policies and actions taken by major DRAs in addressing (or not fully addressing) these challenges.

Overall the report finds that a more holistic approach is necessary in which standards of pharmacovigilance are applied to all types of medicines – be it innovative or generic, small-molecule or complex, chemical or biologic. Looking at the "additional monitoring" initiative taken by the EMA in 2013 as a case study example, the report finds that EMA's policy ambiguity regarding the inclusion of products with multiple manufacturers has resulted in what appears to be an inconsistency and gap between the treatment and monitoring of reference products and follow-on generic manufacturers; a significant gap which potentially raises patient safety and public health concerns. Equally with regards to labelling this report finds that the latest academic research shows how there are still serious challenges and gaps in major OECD markets. In particular, there are discrepancies in ADR reports between reference and follow-on products.

Based on these findings the report makes the following three recommendations:

1. EMA's "medicines under additional monitoring" policy should be exhaustive and account for all manufacturers
   The EU Regulation 198/2013 is a laudable pharmacovigilance initiative, yet it should be clarified that its requirements apply to all manufacturers and types of products be it innovative or generic, small-molecule or complex, chemical or biologic.

2. Pharmacopeial organizations should expedite the inclusion of new monographs
   A greater emphasis should be placed on maintaining an efficient, updated and expedited pharmacopeial workflow as it is an essential part of the pharmacovigilance framework.

3. Greater flexibility in labelling
   In light of the situation in the US after the Supreme Court ruling (*Pliva v. Mensing*), which left patients with no legal remedy in cases of injuries resulting from inadequate labeling of generic products, governments and DRAs should act to adapt the legal and regulatory frameworks accordingly and enable all manufacturers to promptly change their products' labels in accordance with the emergence of new safety information.

INTRODUCTION

Biopharmaceutical products are today manufactured, sold, distributed and dispensed across the globe. As patients and healthcare professionals around the world increase their access to and use of more biopharmaceutical products and technologies, the importance of maintaining and, in many cases, introducing and applying comprehensive pharmacovigilance regulations only increases.

Pharmacovigilance is the name given to the mechanisms and controls that together map and ensure the safety of a medicine throughout its life span – from test tube to patient. Conceptually, pharmacovigilance is most commonly thought of in terms of post-marketing surveillance through ADRs reporting and through so-called phase IV clinical trials.[1] But as is discussed below the practice of pharmacovigilance is actually an integral part of a biopharmaceutical product's entire life cycle, from clinical development to the introduction of follow-on generic products. Since the 1990s pharmacovigilance has matured, both conceptually and practically, and there have been efforts to harmonize best practice standards. While many developing and emerging markets are still grappling with the challenges of putting in place the fundamental institutions and processes of a pharmacovigilance framework, most high income developed markets have already robust systems of pharmacovigilance in place. Still, even in developed markets challenges remain.

The issue

Over the last few years a number of new pharmacovigilance challenges have emerged. This is particularly the case with comparisons and monitoring of original/reference products vis-á-vis generic products. Here, standards of comparison and monitoring that underpin pharmacovigilance structures are in some cases not up to date or in full recognition of changes in quality and composition of these products. When an innovative medicine enters the market it has several years of exclusivity, originating from its patent and/or market exclusivity protection. Once this exclusivity period expires, new follow-on generic participants can enter the market. The expiry of this exclusivity period and subsequent time period raises several pharmacovigilance issues relating to manufacturing, packaging, labeling, use of pharmacopeia standards for regulatory purposes as well as more broadly the question of how all types of products (innovative, generics, small molecules as well as big ones) should be monitored.[2]

The purpose of this report is to examine this issue more broadly as well as specifically in relation to the areas of packaging, labeling and pharmacopeia standards. A key conceptual theme in this report is how pharmacovigilance can be viewed from and practiced in accordance with a more holistic approach, which equally accounts for all types and classes of medicines, be it innovative or generic, small-molecule or complex, chemical or biologic.

This report consists of three sections.

Section 1 provides a brief discussion of pharmacovigilance conceptually, the regulatory history of pharmacovigilance and existing best practices as outlined by international institutions such as the WHO, ICH and advanced drug regulatory agencies such as the FDA and EMA.

Section 2 introduces conceptually the issue of additional safety monitoring for follow-on products versus reference products. Specifically, this section examines the issue of bioequivalence – a crucial component of the marketing approval of generic products – through a case study analysis of the 1984 American Drug Price Competition and Patent Term Restoration Act (the Hatch-Waxman Act). This act is a fundamental part of the modern drug regulatory infrastructure not only in the US, but it is also a model piece of legislation for the rest of the world. This section focuses on the Abbreviated New Drug Application which the Hatch-Waxman Act established and its influence on the approval process of generic products vis-á-vis key methodological and clinical challenges

in the bioequivalence requirement. Although this legislation is over thirty years old, lawmakers and stakeholders at the time recognized the need and importance of pharmacovigilance for all types of biopharmaceutical products whether they be innovative or follow-on generic.

Section 3 provides a thematic discussion on potential gaps in pharmacovigilance standards and procedures in the areas of labeling, packaging and pharmacopeia. It looks at the different policies and actions taken by major DRAs in developed OECD countries on addressing (or not addressing) these potential gaps. In particular, this section provides an in-depth analysis of the European Parliament's Regulation 198/2013 introducing the 'black triangle' labeling for biopharmaceuticals. This requirement for additional monitoring for certain identified products provides a good case study of a recent pharmacovigilance initiative which, on the one hand, aims to mitigate safety risks while also increasing awareness of the importance of maintaining good pharmacovigilance practice. Yet the policy faces real challenges in terms of its practical operational application. Specifically, it appears that the ambiguity regarding the inclusion of products with multiple manufacturers has resulted in a gap in monitoring which potentially raises patient safety and public health concerns.

Section 4 offers concluding thoughts and policy recommendations on what can be done to address the challenges presented in the earlier sections and to promote harmonization and ensuring that best practice pharmacovigilance standards continue to stay abreast of the most recent regulatory and medical science developments.

1 CAPTURING THE SCOPE OF PHARMACOVIGILANCE

The safe use of medicines is perhaps the single most important criteria that any regulatory authority within a given country has to ensure, in order both to protect public health and the integrity of its healthcare system. Pharmacovigilance is the name given to the mechanisms and tests that together map and ensure the safety of a medicine throughout its life span – from test tube to patient.

The WHO defines pharmacovigilance as "the science and activities concerned with the detection, assessment, understanding and prevention of adverse reactions to medicines".[3] Broadly speaking, pharmacovigilance under this definition is a system having the capacity to, firstly, detect adverse effects from a medicine or medical treatment and, secondly, having detected adverse effects, prevent the further use of the affected medicine or treatment. Indeed, pharmacovigilance is most commonly thought of in terms of post-marketing surveillance through ADRs reporting and through so-called phase IV clinical trials.[4]

However, pharmacovigilance is a much wider practice than simply monitoring ADRs. In fact, pharmacovigilance encompasses all the aspects within a biopharmaceutical product or technology's life-cycle which concerns its safety and quality. As such, an effective pharmacovigilance system necessitates the active involvement of regulatory authorities, manufacturers and distributors, healthcare institutions and professionals, as well as patients.

1.1 Background

Over the past 50 years, pharmacovigilance has evolved as an international initiative as well as a scientific practice. Indeed, in many respects pharmacovigilance should be viewed as an arm of patient care.[5] The Erice Declaration, issued during the 1997 "International Conference on Developing Effective Communications in Pharmacovigilance" organized and supported by the WHO and Uppsala Monitoring Center, states that pharmacovigilance is a "public health activity with profound implications that depend on the integrity and collective responsibility of all parties — consumers, health professionals, researchers, academia, media, biopharmaceutical industry, drug regulators, governments and international organisations — working together".[6]

The international recognition of the pressing need for worldwide collaboration on medicines safety monitoring came about largely as a result of the thalidomide tragedy in the early 1960s, in which many thousands of congenitally deformed infants were born as the result of in *utero* exposure to a medicine.[7] Following this tragedy, the Sixteenth World Health Assembly in 1963 adopted a resolution (WHA 16.36)[8] that reaffirmed the need for early action with regard to the rapid dissemination of information on ADRs. This resolution led to the creation of the WHO Pilot Research Project for International Drug Monitoring in 1968, which purpose was to develop an internationally-applicable system for detecting previously unknown or poorly understood adverse effects of medicines.[9] The initiative currently has 118 official member states, and 29 associate member states.[10]

As a scientific practice, pharmacovigilance gained professional interest in the 1980s, with the creation of the International Society of Pharmacoepidemiology in 1984 and of the European Society of Pharmacovigilance (later the International Society) in 1992, which marked the formal introduction of pharmacovigilance into the research and academic world, and its increasing integration into clinical practice.[11]

Pharmacovigilance has also evolved as a regulatory activity with an increased international emphasis through, for example, the launch of the CIOMS program on medicine development and use, in 1986. The CIOMS

initiatives (known as the CIOMS working groups) have provided a forum for policy makers, biopharmaceutical manufacturers, government officials and academic scholars to make recommendations on the communication of safety information between regulators and the biopharmaceutical industry, and promoted the harmonization of international pharmacovigilance practice.[12]

The last few decades have also seen a major increase in the public availability and access to medical and biopharmaceutical information, primarily through technological development and the globalization and increased use of the internet. In addition to increasing the amount of information and ease of access these changes have given rise to new public and regulatory concerns regarding the safety and quality of medicines, such as the circulation of counterfeit and substandard medicines, particularly over the internet. Moreover, rumors and disinformation regarding the adverse effects of medicines, such as the *Eltroxin* controversy,[13] can spread rapidly and are difficult to refute in the absence of good data.

Indeed, as biopharmaceutical products are today manufactured, sold, distributed and dispensed across the globe introducing and applying high quality standards of pharmacovigilance is of real importance in securing the integrity of biopharmaceutical supply chains and ensuring patient safety.

1.2 Pharmacovigilance best practices throughout a medicine's life-cycle

During development, prior to market approval and subsequent to approval for public use biopharmaceutical products and technologies need to meet strict safety, quality and efficacy standards. The safety and quality of reference or innovative biopharmaceutical products and technologies are ensured through a system of rigorous tests and controls prior to the medicine being approved for public sale and marketing. These tests are conducted throughout the biopharmaceutical's R&D process, which consists of a pre-clinical stage and four clinical stages (also called "phases"). Crucially this process is conducted within a highly controlled and studied environment where all aspects of a tested biopharmaceutical product or technology are monitored, recorded and subject to high levels of scrutiny and evaluation.

Pharmacovigilance procedures and best practices differ depending on which pharmacovigilance phase a given biopharmaceutical product is in. While the safety and quality of a biopharmaceutical are constructed throughout its R&D process, these properties are also highly susceptible to the marketing approval and manufacturing stages. Thus, pharmacovigilance is established and maintained throughout the biopharmaceutical's entire life-cycle by keeping to the highest standards and best practices within its three main phases. These phases are:

1. The clinical phase
   This encompasses safety and quality issues within the R&D process and the manufacturing process of a biopharmaceutical;

2. The post-marketing phase
   This encompasses pharmacovigilance activities relating to the distribution and dispensation of medicines, the local and international monitoring of ADR's, and the establishment of a national pharmacovigilance monitoring system; and

3. The post-exclusivity phase
   This encompasses the safety and quality issues arising from the entry of generic products. As in phase 2, pharmacovigilance in this phase includes both the institutionalized procedures and regulatory framework in place as well as actual use and application of those procedures by DRAs, health care professionals, manufacturers, patients and other relevant stakeholders.

The purpose of the following sub-section is to zoom-in on the final phase of pharmacovigilance, the post-exclusivity phase.

1.3 The post-exclusivity phase and pharmacovigilance

When an innovative medicine enters the market it has several years of exclusivity, originating from its patent and/or market exclusivity protection. Once this exclusivity period expires, new follow-on generic participants can enter the market. The expiry of this exclusivity period and subsequent time period raises several pharmacovigilance issues relating to manufacturing, packaging, labeling, use of pharmacopeia standards for regulatory purposes as well as more broadly the question of how all types of products (innovative, generics, small molecules as well as big ones) should be monitored.

The commercial manufacturing of a biopharmaceutical requires that all of its properties, such as purity, potency and stability, are maintained through the entire manufacturing process. However, even the best practices necessitate a legal and regulatory framework in place which sets these responsibilities and also the presence of regulators capable of enforcing them. Most obviously the lack of robust manufacturing and pharmacovigilance regulations and enforcement can contribute to the circulation of substandard medicines and pose a serious threat to public health. While recent studies estimate that the prevalence of substandard and counterfeit medicines in low and lower-middle income countries was close to 30% in 2013,[14] it also evident in developed countries, such as the US and the EU. For example, India supplies about 40% of generic and OTC medicines in the US, and serious quality-related concerns have recently been raised about some of India's largest biopharmaceutical firms, most notably with regards to manufacturing and quality control procedures at Ranbaxy.[15]

In addition, there is also the issue of different excipients used by generic manufacturers versus a reference product. While generally these differences are minor and have a negligible therapeutic impact on the patient, there have been multiple cases where the effect of a switch from a reference product to a generic (or from one generic to another) has caused unwarranted clinical outcomes, such as weakened efficacy, an increase in ADRs and even toxicity.[16] This especially concerns follow-on products for 'high alert' medicines, such as NTI medicines, whose characteristics and sensitivities necessitate closer monitoring in order to avoid unnecessary safety risks.[17] For example, generic versions of the NTI anticonvulsant medicines *carbamazepine* and *gabapentin* have caused increased seizures in patients and more neurological side effects.[18] Additionally, the generic versions of the NTI antipsychotic medicine *clozapin* have resulted in relapses or exacerbations after generic substitution.[19]

As the following sections discuss, the differences between generic and reference products and (the regulatory implications this has for pharmacovigilance) is beginning to be recognized by drug regulators in the most advanced health markets. Still, there remain gaps in the current regulatory framework, particularly in the areas of labeling, packaging and pharmacopeia standards. However, before zooming in on these challenges, the paper provides a case study example of a piece of legislation that while being over thirty years old, provides some telling examples that many of these debates are not new.

2 BIOEQUIVALENCE IN RETROSPECT – A CASE STUDY OF THE HATCH-WAXMAN ACT

Passed in 1984 the Drug Price Competition and Patent Term Restoration Act (the Hatch-Waxman Act) has served as the cornerstone for the establishment of the generic drug products industry in the US, which nowadays encompasses some 80% of the American prescription medicines market.[20]

The main goal of the Act was to balance two conflicting yet desired purposes: rewarding pharmaceutical innovation while simultaneously expediting the market entry of cheaper generic versions of innovative products.[21] In order to achieve this goal, the Act granted extended protection to innovative products on the one hand while establishing the regulatory framework for a quick and easier approval of generic products.[22] Indeed, what contributed most to the following proliferation and growth of the generic industry was mainly the ANDA process which enabled generic manufacturers to rely on bioequivalence tests in order to prove their safety and efficacy.

However, both preceding and in the years following its enactment, the Hatch-Waxman Act faced much debate and has undergone several amendments. While most of the amendments concerned patent-related issues,[23] some of the focus has been on the safety requirements of generic products, and more specifically bioequivalence standards and the determination of therapeutic equivalence.

This section provides a general review of the Hatch-Waxman Act followed by a more thorough analysis of the safety issues and potential concerns which arise from the application of the bioequivalence concept within the FDA's regulatory framework.

2.1 Background

The Hatch-Waxman Act has its roots in the later years of the Carter Administration, when a team of experts ordered by President Carter reviewed domestic policy on industrial innovation and recommended that any patentable product which necessitates regulatory review – pharmaceuticals included – be given a term of patent restoration to compensate for the patent period lost during regulatory review.[24] This recommendation was later approved by the US Senate yet failed to receive assent in the House of Representatives. However, the issue was taken up by then-Chairman of the Health Subcommittee, Congressman Henry Waxman – co-sponsor of the Drug Price Competition and Patent Term Restoration Act.

Prior to the Hatch-Waxman Act, the US generic biopharmaceutical market was relatively small. Up until 1962, manufacturers of generic products had to submit a 'paper' NDA to the FDA, which provided proof of safety only by relying on scientific literature regarding the chemicals used in the drug.[25] However, the *thalidomide* tragedy in the early 1960s prompted a set of amendments to the Food, Drug & Cosmetic Act most notably adding a requirement for proof of efficacy.[26] This required generic manufacturers to undergo clinical trials, since the FDA regarded the innovator's scientific literature as proprietary.[27] As a result, the generic market share was only 13% in 1983 and generic products required a particular prescription in order to be dispensed.[28]

The Hatch-Waxman Act was enacted on September 24th, 1984, after it received overwhelming support in the House of Representatives.[29] By amending section 505 of the Federal FD&C Act, Hatch-Waxman established the ANDA process to enable quicker approval of generic products based on bioequivalence tests. Fundamentally, the Act balances two conflicting desires: to ensure the continuity of pharmaceutical innovation while promoting affordable care.

Key provisions of the Act include:

- Generic manufacturers are permitted to rely on the proven safety and efficacy of the RLD when filing for a marketing application under the ANDA process, provided that the generic drug candidate was proven to be bioequivalent;
- Generic manufacturers may begin the development process for their products prior to the patent expiry of the reference product, and the innovator must share relevant research data (this is known as the Bolar exemption);
- Generic companies may challenge an existing patent by filing a paragraph IV specification to the FDA. In turn, the innovator has 45 days to file a patent infringement lawsuit. If the innovator loses the case, the first generic product to enter the market (either by the filing company or by another) receives an exclusivity period of 180 days;
- Innovators may apply for patent term restoration which compensates for time lost during the innovative product's extensive R&D process, under the formula of half a day restoration for every day of clinical trials and a day of restoration for every day the product was under regulatory review. However, the maximum period of restoration permitted is five years, and the total effective patent term after restoration must not exceed 14 years;
- A five-year period of data exclusivity, i.e. five years will elapse between the approval of the original drug and the approval of a generic version that is based on the ANDA procedure;[30]
- Innovators may request an additional period of market exclusivity for new indications or where improvements to the product's safety or efficacy were made.[31]

Below Table 1 provides a summary of the Act's key provisions for innovators and generic manufacturers.

TABLE 1 Key provisions of the Hatch-Waxman Act

Innovators	Generic manufacturers
• Grants patent term restoration - 50% for clinical trials duration - 100% for regulatory review duration - Up to 5 years	• Establishment of the bioequivalence-based ANDA pathway and the waiver of clinical trials
• Defines the process for patent challenging (paragraph IV filing)	• Permits generic product development prior to patent expiry of the reference product (Bolar exemption)
• Provides period of data exclusivity (and additional exclusivity for new indications and modifications)	• Grants incentive of 180-days exclusivity for first successful patent challenge

Source: Boehm, G. et Al. (2013)

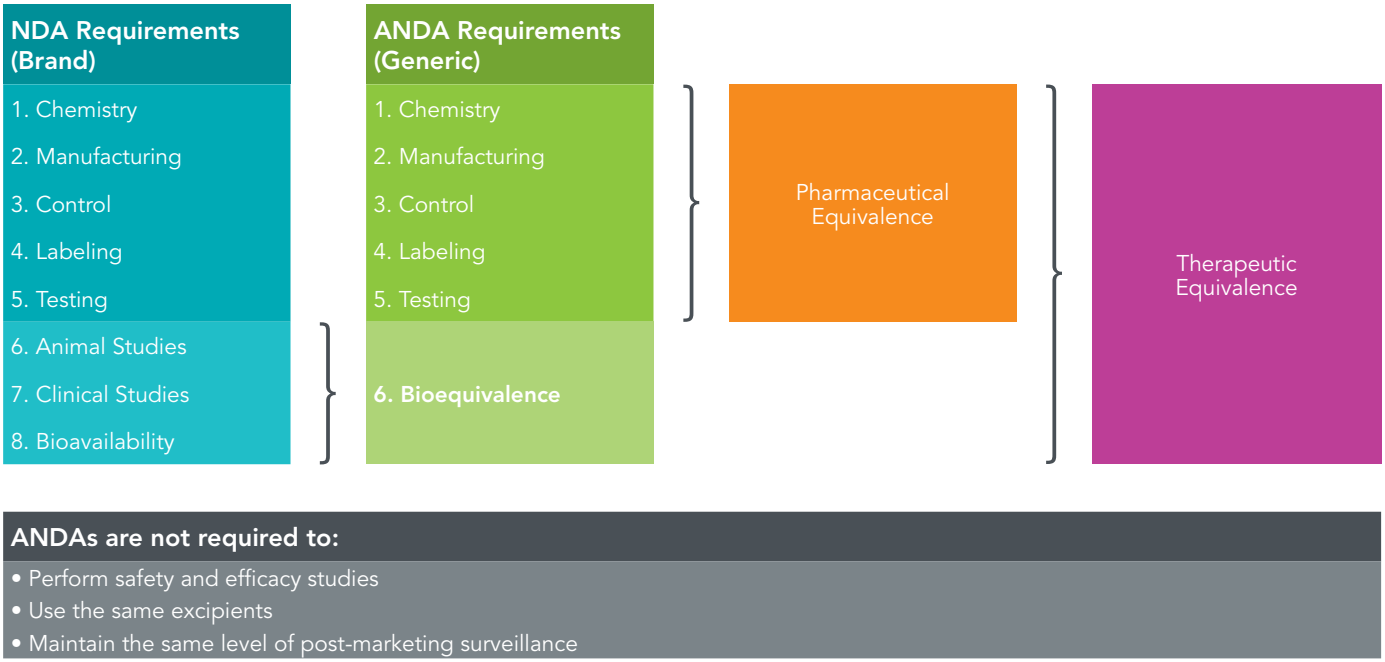
2.2 The ANDA pathway and the bioequivalence requirement

One, if not the, key feature of the Hatch-Waxman Act was the creation of the ANDA pathway. Under this pathway generic manufacturers are exempt from performing clinical research on their products. Instead generic manufacturer are required to provide "information to show that the active ingredient of the new drug is the same as that of the listed drug" and that the generic drug candidate is bioequivalent to the reference product and "can be expected to have the same therapeutic effect".[32] The FDA has further strengthened the requirements from generic drug candidates, which must also "contain the same active ingredient(s)…same dosage form, route of administration and… [be] identical in strength or concentration".[33]

The FDA has since 1980 issued a list which is formally known as the *Approved Drug Products with Therapeutic Equivalence Evaluations*. Since 1984, the list is updated on a monthly basis. In its compendium form the list is printed with an orange cover, which has given it its informal yet most commonly used name: the Orange Book.[34] Generic products on the list are categorized by their equivalence grade. There are two general codes – A and B – where A is given to generic products which the FDA considers to be therapeutically equivalent, and B is given to generic products which are, at the time of publication, not considered by the FDA to be therapeutically equivalent.[35] Following the first letter is another which represents the dosage form. In cases where a drug is labeled with AB, this means that actual or potential bioequivalence issues were discovered during the product's evaluation, and were resolved after supportive evidence from additional bioequivalence tests were submitted, as a prerequisite for receiving FDA's approval.[36]

Figure 1 shows the requirements from a generic drug candidate for attaining marketing approval.

FIGURE 1 Comparing FDA approval process requirements for NDAs and ANDAs



Source: Johnston, A. (2013), Martin, C. (2011)

As Figure 1 shows, the approval process for generic drug candidates is composed of two levels: First, generic drug candidates must exhibit pharmaceutical equivalence to their reference product, which means that they must contain the same active ingredient(s), consist of the same dosage form, route of administration and be identical in strength or concentration, according to the FDA's definition.[37] Pharmaceutical equivalence is determined through meeting pharmacopeial standards and having the same labeling standards; both of which are subject to a separate discussion below in section 3.

Second, generic drug candidates must demonstrate surrogate therapeutic equivalence, which requires that the generic drug candidate will also undergo bioequivalence studies. These studies provide the FDA with proof that the generic drug candidate "can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling".[38]

Bioequivalence between a generic drug candidate and its reference product is demonstrated when, according to the FDA, "the rate and extent of absorption of the test drug do not show a *significant difference* from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions".[39] [Emphasis added]

Within many DRAs, such as the FDA and the EMA, this "significant difference" is defined in cases where the bioavailability (the rate and extent to which the API is absorbed within the bloodstream) of the generic drug candidate differs from that of the reference product by more than 20%. In other words, a generic drug candidate is typically considered to be bioequivalent to the reference product if its bioavailability rate is within the similarity limits of 80-125% of the reference product's bioavailability.

However, while requiring bioequivalence tests to fall within the limits of 80-125% has become standard practice in many DRAs across the world, accumulated evidence from clinical and pharmacological research suggests that, in practice, even within these limits a generic version of a given product can vary significantly from other versions of the same generic product as well as from the reference product. For example, one generic product can be absorbed into the bloodstream at the lower range of the acceptable similarity limit of 80% of the reference product, whereas another generic product can be absorbed at the higher range of the acceptable similarity limit of 125%. Both products are considered as bioequivalent yet a patient that is moved from one generic product to the other will see a significant difference between the rates of absorption and could potentially experience unwanted side effects due to these differences.

This is not a new issue. Indeed, concerns regarding the adequacy of the bioequivalence test methods in providing sustainable proof of bioequivalence were raised as early as four decades ago. In 1974 the US Office of Technology Assessment was charged by the US Congress to "examine the relationship between the chemical and therapeutic equivalence of drug products and to assess the capability of current technology…to determine whether drug products with the same physical and chemical composition produce comparable therapeutic effects".[40] The report concluded that "current standards and regulatory practices do not ensure bioequivalence for drug products"[41] (It is interesting to note in this regard that some forty years later the FDA has also expressed its concerns regarding the rapid evolvement of innovative pharmaceutical technology and the applicability of bioequivalence standards).[42]

However, while technology has advanced, similar concerns are still being raised nowadays. These concerns question the adequacy of bioequivalence methods as a basis for demonstrating safe and effective use of generic products, including prolonged use and use by various populations.

From a pharmacovigilance perspective this is an important point. Safety monitoring procedures of medicines are largely built on an assumption that standards for determining regulatory bioequivalence are sufficient to base monitoring decisions on. As will be discussed in detail in section 3 pharmacovigilance regulations of all facets of medicines monitoring – from labeling and packaging to requirements of additional monitoring – while questions are beginning to be raised by regulators about this assumption, this paradigm remains influential on the pharmacovigilance

processes and guidelines in place in even the most advanced DRAs including the US and EU.

Following is an overview of the key challenges in ensuring generic products safety and efficacy in the approval process and the manner in which there remains gaps in the bioequivalence model.

2.3 Methodological challenges to the bioequivalence model

The ANDA pathway for generic drug candidates, which mainly relies on bioequivalence, involves three methodological issues that in certain respects may pose a challenge for ensuring safety and efficacy.

First, as mentioned above, is the case in which the BE range between two products may actually be larger than the accepted range of 20%. Since BE limits are set at 80%-125%, there is significant room for difference between the reference product and generic product, as well as between two generic products determined to be bioequivalent to a reference product. To illustrate, consider two generic products, one which is bioequivalent to the reference product at 86% and another at 119%. Both are bioequivalent to the reference product, as they reside within the 80%-125% BE limits. However, if they were to be compared between themselves in a BE trial (where one of the generic products is the reference product), the difference in bioavailability between the two products would be larger than 20%. In this case, the two generic products would not be bioequivalent.[43] This phenomenon is known as "generic drift".[44]

Second, is the fact that BE trials design often does not capture whether a given product has different clinical outcomes depending on the type of patient and the timeframe of usage. As mentioned, BE trials are usually conducted in the form of a randomized and controlled clinical trial on 15-50 healthy volunteers. In these trials a set of parameters is tested in order to compare the relative bioavailability of the generic drug candidate to that of the reference product. However, under this design, BE trials do not consider several factors which may affect the product's safety and efficacy in prolonged use and which may not be derived from reliance on the reference product. For example, different populations, such as children and women, are generally not considered in full, nor are factors such as age and co-morbidities.[45] Additionally, since these trials are conducted within a relatively short period of time and are based on a single-dose design, long-term effects that may occur with chronic dosing may not be adequately captured.[46]

Third, and finally, is the growing recognition that small and seemingly insignificant changes in the manufacturing process of medicines (such as different oils for liquid and capsule forms of the same product) can affect a medicine's efficacy and safety, causing undesirable clinical outcomes. For example, in a multinational survey of epileptic patients conducted in 2005, 23% believed that treatment with generic products had caused an increase in breakthrough seizures (seizures which occur despite ongoing treatment in anti-epileptic medicines).[47] Additional research covering 550 epileptic patients and 606 physicians found that two-thirds of the physicians and 34% of the patients linked the increase in breakthrough seizures to a switch to a generic product.[48] This phenomenon led

the American Academy of Neurology to publish a position statement in 2007, in which it "oppose[d] the generic substitution of anticonvulsant drugs for the treatment of epilepsy without the attending physician's approval".[49] The statement goes on: "The Food and Drug Administration has allowed for significant differences between name-brand and generic drugs…For anticonvulsant drugs, small variations in concentrations between name brands and their generic equivalents can cause toxic effects and/or seizures when taken by patients with epilepsy."[50] Additionally, clinical outcomes may differ between patients who receive the same medicine, due to the use of different excipients or interactions with food and other medicines.[51] A 2011 study conducted on 75 cancer patients revealed that of 213 drug interactions, 12.6% were clinically-significant drug-drug interactions.[52] Indeed, there have been cases where these differences have resulted in ADRs,[53] unwarranted clinical outcomes such as organ rejections in transplant patients,[54] and even increased symptoms of toxicity.[55] Moreover, the product actually sold and used by patients may differ from the product tested during the approval process, due to changes in formulation that are sometimes needed to scale-up the medicine's production. Indeed, 62% of new oral agents approved by the FDA between 1981 and 1990 were marketed in a different formulation from that which was used during clinical trials.[56] Such was the case with eltroxin, a medicine intended for thyroid disorders, which was found to cause severe ADRs on a global scale after its formulation was modified due to a change in manufacturing site.[57]

2.4 Summary

As this section has illustrated there is a growing debate over the current bioequivalence test methods and model to ensure the safety, quality and efficacy of generic products throughout their entire life-cycle.[58] This discussion is increasing in importance especially with respect to the growing complexities of new medicines and technologies in which it may not be possible to determine true bioequivalence using current methods and standards.[59] Thus, the debate over bioequivalence standards constitutes an important part of the modern pharmacovigilance infrastructure. Indeed, the discussion of this standard provides the conceptual backdrop for many of the challenges and potential gaps in pharmacovigilance which today exist in the areas of biopharmaceuticals labeling, packaging and pharmacopeia standards; the topic of the next section.

3 MAINTAINING A CULTURE OF PHARMACOVIGILANCE IN THE AREAS OF PACKAGING, LABELING AND PHARMACOPEIA

Since the 1990s pharmacovigilance has matured, both conceptually and practically. Today the most advanced DRAs continuously engage in further improving and strengthening their legal and regulatory frameworks. Relevant regulations are in place and many standards and rules now follow international best practice and have been harmonized through ICH guidelines.

However, given the constant evolution of pharmacovigilance and the fact that standards always need to be improved in a constantly evolving world of science and technology there are a number of new challenges that have emerged. Specifically there are two main areas of growing importance: i) packaging and labeling; and ii) pharmacopeia standards.

This is an important topic. Differences and gaps in the regulatory framework for these areas have the potential to have a significant impact on standards of quality, patient safety and incentives for biopharmaceutical innovation and R&D. This section provides a thematic discussion of these areas, the challenges they pose and the different policies and actions taken by major DRAs in addressing (or not fully addressing) these challenges. In particular, an in-depth analysis of the European Parliament's Regulation 198/2013, introducing the 'black triangle' labeling for medicines, is provided. This requirement for additional monitoring for certain identified products provides a good case study of a recent pharmacovigilance initiative which aims to mitigate safety risks and increase awareness of the importance of maintaining good pharmacovigilance practice. Yet the policy faces real challenges in terms of its practical operational application. Specifically, it is not clear how the policy applies to all types of products be they innovative, generics, small molecule or large molecule.

3.1 Packaging and labeling

As medicines become more diverse, complex and potent in nature, so increases the potential for harm from misuse.[60] In this respect, the packaging and labeling of medicines plays an increasingly significant role in conveying important safety information and safeguarding their intended use. A biopharmaceutical's package, label and leaflet contain advice on prescription use and safety information, such as boxed warnings, drug interactions and a list of serious and clinically significant ADRs. If this information is outdated or incomplete, the product's label and packaging will fail in its function and designation as a key component in healthcare decision-making. A poor or incorrect label increases the risk of otherwise preventable ADRs.

Before turning to the specific challenges and potential policy gaps in the pharmacovigilance regulations for packaging and labelling, the following subsections provide an overview of some of the major challenges and the critical role labelling and packaging play for patient safety.

Packaging

The proper packaging of medicines is one of the keys to successful pharmacovigilance, as packages serve the dual purpose of protecting medicines from exposure to the contaminations of the outside world while also preventing their unintentional misuse. For example, recognizing that iron poisoning was the main cause of death due to pharmaceutical poisoning in young children, the FDA issued in 1997 a regulation for unit-dose packaging (i.e. strip or blister packages)

of iron-containing medicinal products.[61] As a result, mortality from iron poisoning among US children dropped from 29 cases in the decade preceding 1997 to only 1 in the following five years.[62]

Moreover, packages can be redesigned to encourage adherence to medication as prescribed. For example, the packaging of *carbamazepine* – a medicine intended for epilepsy and psychiatric disorders whose overdose could result in respiratory depression, seizures and arrhythmias – was changed in Australia from a 200-tablet bottle to strip packaging. As a direct result, significantly fewer medicines were ingested by patients.[63] Additionally, following numerous cases of death and serious injury due to unintentional overdose of *methotrexate* (a cancer and autoimmune diseases medicine) which were suspected to result in part from improper packaging, the UK's National Patient Safety Agency funded a research program with the purpose of preventing future cases.[64]

From a pharmacovigilance perspective, two main issues relating to packaging are of particular importance: the prevention of contaminations and minimization of medication errors due to improper packaging.

The issue of preventing contamination is of obvious safety importance. The commercial manufacturing of a medicine, where the highest safety and quality standards are not strictly maintained, holds the potential for multiple possible contaminations which could result in serious health risks. For example, research conducted into the prevalence and sources of *cyclophosphamide* contamination (a carcinogenic substance) within hospital pharmacies in Sweden concluded that the source of the contamination found on packaging of antineoplastic medicines originated from the manufacture or packaging process at the pharmaceutical manufacturer.[65]

In order to prevent instances of contamination, stringent DRAs (including the FDA and EMA) require both innovative and generic manufacturers to follow the cGMP standard. The cGMP standard provides the minimum requirements for the establishment of a formal system of controls at a biopharmaceutical manufacturer. These requirements include establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories.[66]

However, standards of pharmaceutical quality and enforcement of international or even local standards varies greatly between different DRAs. Compliance with international standards of pharmacopeia, GMP and GDP are not required unanimously by all DRAs or in all countries. This especially concerns generic products, since many generic manufacturers which ship their follow-on products worldwide are located in developing countries where in some cases both quality and safety regulations are lax as is their enforcement. For example, the FDA recently blocked entire shipments of generic products which originated from India-based manufacturers due to serious shortcomings detected at inspection.[67]

The issue of similarity between medicinal products' names, also referred to as "Sound-Alike Look-Alike" (SALA) medicines, is recognized by many DRAs as a safety risk. The US-based Institute for Safe Medication Practices maintains a list of medicines with similar names, which currently has almost 400 pairs of SALA medicines.[68] The United States Pharmacopeia also maintains a list of medicines whose brand names generate confusion and currently has over 750 unique medicine names.[69] Indeed, 12.5% of medication errors – which are estimated to result in at least one death per day and 1.3 million injuries per year in the US – are attributed to confusion over medicines' names.[70]

Stringent DRAs are closely involved in the process of naming new medicines. For example, the FDA's Center for Drug Evaluation and Research conducts two proprietary name reviews for each innovative drug candidate, the first approximately halfway through the clinical stage, and another 90 days prior to the drug candidate's expected approval.[71] The primary goal of this practice is to ensure that the proposed brand name is not similar in a confusing manner to other brand names or INNs already in the market.[72]

While stringent DRAs have similar requirements regarding the choice of product names, they differ in their methods for avoiding medicine name confusion in practice. For example, the UK's MHRA, requires that only positive statements will

be used (e.g. "for intravenous use only" instead of "not for intravenous use") and that the use of the Tall-Man Lettering technique – a technique which involves the use of capital letters to highlight specific parts of the medicine's name – be used specifically for *cephalosporin* medicines.[73] The Tall-Man Lettering technique was implemented as a pilot study in Canada and in Australia,[74] yet it is not a mandatory requirement. However, Health Canada has recently issued comprehensive guidance for the biopharmaceutical industry presenting a stepwise approach in choosing and testing a product's brand name.[75]

Additionally, confusion could be the result of symbols and pictograms. For example, article 62 of the European Parliament directive 2001/83/EC permits the inclusion of symbols and pictograms,[76] which usually highlight important safety information, such as radioactivity or activities which should be avoided due to the medicine's effect. However, EU-Member States differ in their symbols and pictograms as well as country-specific labeling requirements. For instance, in Austria medicines which cause fatigue must bear a red triangle warning symbol, while in Denmark the same triangle is required for medicines which may affect the ability to drive or operate heavy machinery.[77]

Labeling

As with packaging stringent DRAs all have in place specific requirements for the types of information which should be included on a medicine's labels and leaflets, as well as the format and hierarchy of its inclusion.[78] For example, the prescribing physician must be provided with the evidence which supports the product's efficacy for its approved indications, its properties and mechanisms of action and its drug-drug interactions. For these reasons the FDA, for instance, has issued guidance which dictates the manner of selecting, emphasizing and excluding safety information involving ADRs, contraindications and warnings.[79] In addition, the attending nurse or pharmacist who dispenses the medicine to the patient must be able to read clearly the medicine's names, dosage form and strength in order to prevent medication errors. For these reasons DRAs issue requirements such as a 12-point size and different fonts for the medicine's brand name, INN and dosage form and strength.[80]

Unfortunately, biopharmaceutical labeling is not always up-to-date with the current scientific literature especially for patient sub-groups. For example, recent scientific research has found that the prescribing information for a significant number of products lacked dosing information for elderly patients.[81] Additionally, of 45 products which could potentially interact with an antidepressant medicine commonly prescribed for the elderly, the information provided in the antidepressants package covered less than half of these potential interactions.[82]

More broadly, the latest academic research shows how there are still serious challenges and gaps with regards to labeling in major OECD markets. For example, in a 2014 study of the quality and consistency of prescription medicines labeling in the US, UK and Germany for 25 of the most common medicines the overall conclusion was that the labels of the sampled products failed to provide officially authorized information for the safe prescription of these medicines.[83] Some of the findings which led to this conclusion are: "side effect information provided in SPCs is frequently clinically meaningless or even misleading",

"contraindications and warnings listed in SPCs are frequently inconsistent and/or incomplete", and that "key SPC information for the same drug varies from manufacturer to manufacturer in a way that cannot be explained by biology, excipients, or licensing issues".[84] In particular, the study found major inconsistencies with regards to the labeling of generic products. Among its key findings was that generic products' labels included inconsistencies regarding indications and contraindications. The researchers noted that for a given generic product, contraindications were identical in only 60% of cases in the US, 10% in the UK and 20% in Germany.[85] Inconsistencies were observed also in the reported frequency of undesirable effects of generic products. Finally, and perhaps most significantly, large differences were observed in the editorial age of generic SPCs. For example, the researchers found that on average, SPC updates for generic products in the sample were between 2-3 years apart in all countries with the UK seeing the longest delays where the maximum delays ranged from just over 4 years to close to 8.5 years.[86]

These are not isolated findings. Other studies have found that around three-quarters of generic products' labels differ from that of the reference product, mostly by missing information and outdated post-marketing reports.[87] Particularly, discrepancies in ADR reports were found in almost 70% of over 9,000 labels of generic, follow-on products.[88]

As this research illustrates, the subject of safety information is of special relevance to generic products. When an innovative new medicine enters the market, its MAH often conducts post-marketing surveillance, also known as a phase IV clinical trial, in which the product's safety and efficacy are monitored in real-time use and ADRs are collected and assessed. New safety information which is garnered throughout the trial is implemented into the product's leaflet and PI. However, since generic manufacturers are often required by law to issue the same labels as their reference products, a situation arises in which new and vital safety information is not, as the above cited research finds, included in a timely fashion (and sometimes not at all).[89] Including newly-acquired safety information is obviously of crucial significance, since if healthcare professionals are not aware of newly discovered ADRs, patient safety is at risk.

This issue has taken the center of a heated debate in the US, which came to the fore after the Supreme Court exempted generic manufacturers from liability over their products' labels. Briefly put, following the entry into force of the Hatch-Waxman Act, generic manufacturers were compelled under federal law to issue their products with the same label as their reference products.[90] However, the only legal recourse mechanism available for injured consumers is filing a "failure-to-warn" claim, which applies, for instance, where safety issues and warning are inadequately or improperly placed.[91] Several lawsuits on this topic have reached the US Supreme Court.

The first notable case was the 2009 US Supreme Court's ruling in *Wyeth v. Levine*, where an innovator (*Wyeth*) was sued for inadequate labeling, after an antihistamine medicine which should have been mixed with a saline solution and administered intravenously by dripping through a catheter was administered directly to a patient's vein due to unclear labeling regarding the product's proper administration method.[92] The US Supreme Court ruled in favor of *Levine*, holding that the innovator could have changed its product's label immediately without any conflict between federal laws and FDA's labeling requirements.

In 2011 a similar lawsuit (*Pliva v. Mensing*) reached the US Supreme Court, but in this case the lawsuit was against a generic company. In contrast to its previous judgment this time the Supreme Court found that a generic manufacturer cannot be held liable for "failure-to-warn" claims, since, as the Court stated, "if the manufacturers had independently changed their labels to satisfy their state-law duty to attach a safer label to their generic metoclopramide, they would have violated the federal requirement that generic drug labels be the same as the corresponding brand-name drug labels".[93] More broadly, the Court found that the Hatch-Waxman Act, a federal law, preempted lawsuits under state laws against generic companies.[94] In addition, federal courts have also dismissed claims that generic manufacturers failed to label and pack their products adequately, continued the marketing of a product which posed unreasonably public health risks, and even claims on improper design.[95]

Following these decisions, numerous lawsuits against generic companies have been dropped, as consumers were left with no option for a legal remedy. This is particularly problematic in the 39 US states which mandate generic substitution laws.[96] In such instances a patient can be dispensed with a generic product, yet left with no legal recourse mechanism in cases where the medicine has caused an injury due to inadequate labeling.

In light of this situation, the FDA in 2013 issued a proposed rule to amend its regulations regarding the labeling of generic products. The proposed rule permits generic product marketing application holders to revise a product's labels in accordance to newly-acquired safety information which may differ in certain aspects from the reference product's label.[97] This amendment is "intended to improve the communication of important drug safety information about generic drugs to both prescribers and patients".[98] The FDA justified these proposed changes on the grounds of "the obligation of all drug application holders to monitor safety information about the drugs they market and ensure that product labeling is accurate and up to date".[99] However, the FDA's proposed rule is currently in the process of public consultation,[100] and it remains to be seen whether this amendment will be implemented, and to what extent it is implemented.

Nevertheless, the issue of the differences between an innovative product and its follow-on products is not equally addressed by major DRAs or related regulatory authorities. For example, in light of the safety issues which arise with regards to automatic substitution and NTI medicines, several US States have restricted the practice of substituting an innovative NTI medicine with a generic product.[101] At the EU-Member State level, some countries permit substitution of innovative NTI medicine with a generic product albeit with additional monitoring, while others do not address this issue.[102]

In this context it is worth noting that while the discovery of serious ADRs several years after a medicine is marketed is not very common, it is not unheard of. For example, 10.2% of medicines which were marketed in the US between 1975 and 1999 have acquired a new black box warning or been withdrawn from the market amidst safety concerns; for half of these medicines this occurred 7 years or more after marketing.[103] Additionally, in 2010 the FDA withdrew a 53-year-old product from the market due to newly-found risk, and issued a black box warning for a 26-year-old product.[104]

The issue of post-marketing surveillance and the challenges in applying similar standards to all products is of particular pertinence in the case of regulations introduced in the EU for requiring additional monitoring for certain categories of medicines. The following sub-section will provide an in-depth analysis of EMA's policy on products requiring "additional monitoring".

3.2 The EU's Regulation 198/2013 – A case study

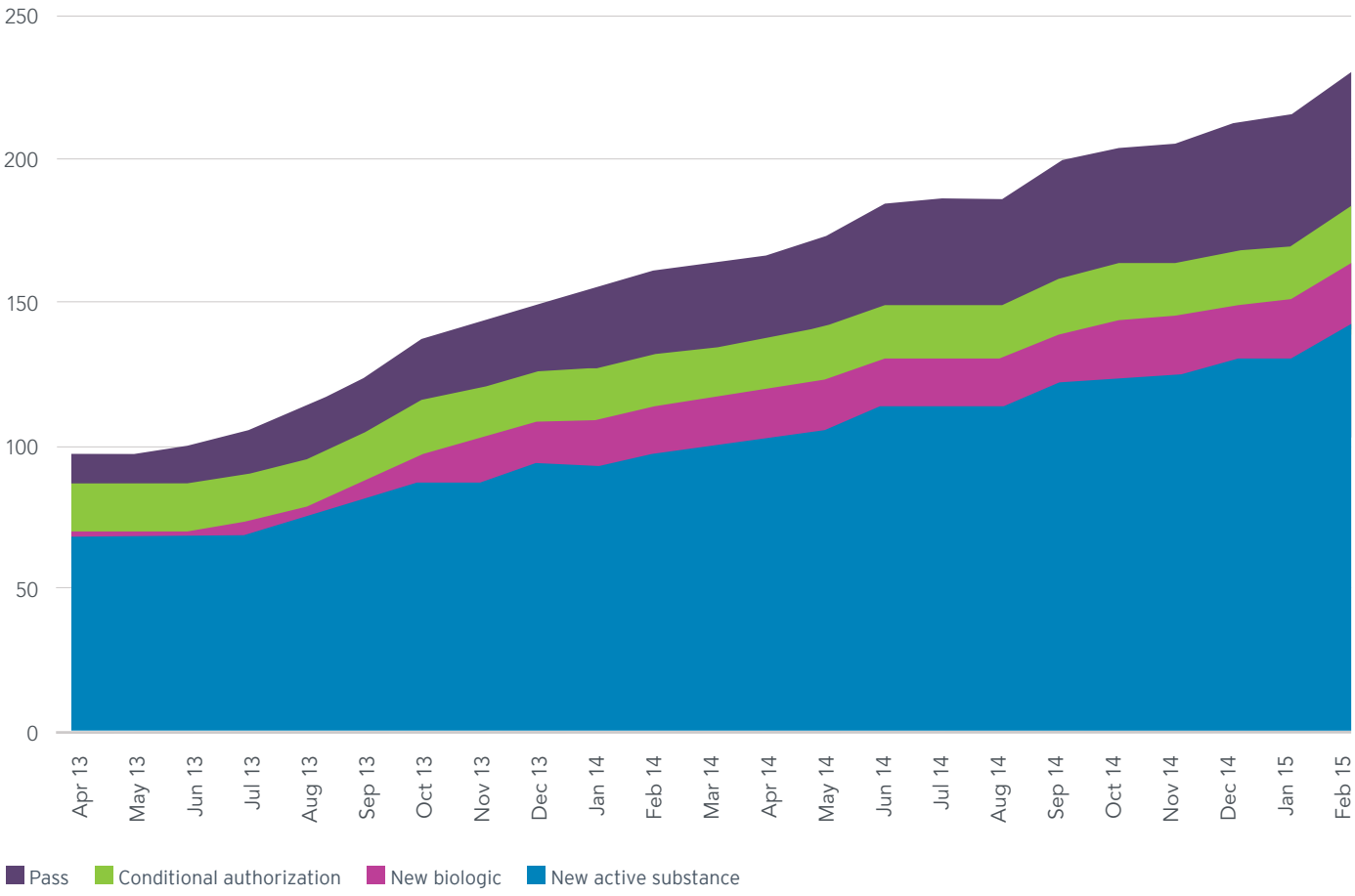
In 2012, the European Parliament introduced comprehensive pharmacovigilance legislation. One key component of this legislation is Regulation 198/2013,[105] which requires certain products to include special package labeling of a black inverted triangle on the side of the package. Products that are required to include this label on the package are known as medicinal products subject to "additional monitoring".[106]

There are four different types of products included on this list:

1. A product approved for market after 2011;
2. A product that is a biological medicine (including biosimilars);
3. A product given conditional approval or approved under "exceptional circumstances"; or
4. A product for which there is a regulatory requirement to carry out a PASS.[107] (The definition of PASS is described below.)

Since its inception in 2013 the list has grown significantly with the number of products more than doubling. There are currently (as of March 2015) 230 items on the list, consisting of medicinal products and APIs.[108] Below Figure 2 shows the growth of the list from mid-2013; and on the next page Table 2 provides the distribution of these medicines by their therapeutic class.

FIGURE 2 Growth of the additional monitoring list, distributed by reason for inclusion



Source: EMA, 2015

TABLE 2 Distribution of selected medicines under additional monitoring by therapeutic class, 2015

Therapeutic area	No. of medicines
Respiratory Diseases	12
Hematological disease	7
Musculoskeletal disease	4
Hormonal contraceptives	4
Antibacterial agents	3
Anticancer agents	2
Cardiovascular diseases	2
Gastroenterological diseases	2
Orphan designation	1

Source: EMA, 2015

TABLE 3 Distribution of medicines under additional monitoring by reason for inclusion, 2015

Reason for inclusion	No. of medicines
New active substance	104
New biologic (including biosimilars)	20
Conditional/exceptional circumstances authorization	37
Post-Authorization Safety Study (PASS)	70

The EMA is responsible for the inclusion of medicines which were authorized by the centralized procedure, while the inclusion of medicines which were authorized by the decentralized or mutual recognition procedure is under the responsibility of the relevant EU-Member State, pending consultation with PRAC.[109] For new medicines, the initial period of inclusion on the list is five years.[110]

While Regulation 198/2013 does not make a clear-cut reference to the type of medicines which are to be included on the list (i.e. innovative only or generic as well), the EMA has stated that: "A medicine can be included on this list when it is approved for the first time or at any time during its life-cycle".[111] Thus, while novel medicinal products will generally remain on the list for five years (which is usually within the period of market exclusivity and prior to any follow-on generic products having been launched), new medicines which were authorized under exceptional circumstances will remain on the list until they fulfill the conditions which brought their inclusion onto the list.[112] Opposite Table 3 gives an overview of the distribution of medicines currently included in the additional monitoring list by reason for inclusion.

In addition to novel APIs the list includes medicines for which a PASS is required. The PASS is defined in the European Parliament's Directive 2001/83/EC as:

Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.[113]

This is basically a definition of a post-marketing study, which, as discussed earlier, is often conducted on novel medicinal products by the innovator, usually during the period of market exclusivity. However, the PASS requirement differs from a typical post-marketing study in its methods, which are determined in respect to the objective of the study for the particular medicine in question. For example, a PASS can be required where safety information is lacking or missing for specific sub-groups of patients, or to add knowledge on risks and medicine-utilization patterns over long-term use.[114]

Nevertheless, from a close examination of the products on EMA's list it appears that the terms of inclusion of medicines under the PASS requirement has resulted in a discrepancy and potential gap between innovative and generic manufacturers.

The list of medicines which necessitate a PASS contains 70 entries of new active substances as well as older products which were approved as early as 2001.[115] The PASS list also includes 13 entries for groups of products which are based on particular APIs; e.g. *cilostazol*-containing medicinal products. Within 11 of these particular API groups, products are manufactured by innovator and/or generic manufacturers. Indeed, some of these APIs have been approved as early as 2000 and already have multiple generic products in the EU market.

TABLE 4 Distribution of medicines under the PASS requirement by type and status, 2015

Total No. of medicines (as APIs) under the PASS requirement	47
Number of medicines listed by one brand name	34
Number of groups which refer to a particular APIs	13
Number of groups which refer to single manufacturer	4
Number of groups which refer to multiple manufacturers	9

Source: EMA, 2015

Above Table 4 shows the distribution of medicines which are included under the PASS requirement by their type (i.e. a particular medicine or a group of medicines) and status (i.e. innovative or generic):

However, one group of products seems to be exceptional. This is a group of *teicoplanin*-containing medicinal products. *Teicoplanin* is a complex antibiotic, which was first approved for marketing in Italy in 1987 as Targocid.[116] Its first generic product was submitted for marketing approval in 2005 through the decentralized procedure, yet disagreements between countries concerning safety and efficacy issues led the CHMP to deny this marketing application in 2008.[117] However, since 2008 numerous applications for generic products for *teicoplanin* were submitted through the decentralized and national procedures. Thus, in order to address the safety risk which was created due to discord between requirements from generic *teicoplanin* products, *teicoplanin* was included in EMA's additional monitoring list by France in 2011, and the CHMP has issued new pharmacopeial requirements for *teicoplanin*.[118]

However, while generic *teicoplanin* products are marketed across the EU, the list of *teicoplanin*-containing medicinal products contains references only to Targocid, the reference product.[119] This means that only Targocid is labeled with the inverted black triangle, which alerts healthcare professionals to pay closer attention to ADRs which may result from its use, while generic *teicoplanin* products are not.

The cause for this discrepancy is particularly ambiguous when considering the fact that *teicoplanin* was included in the additional monitoring list with the intention "to achieve a consensual view on the requirements to be fulfilled to show equivalence between the generics and the reference product of this antibiotic".[120]

This appears to be a gap in the additional monitoring policy and a potential patient safety concern, especially with respect to the fact that for the 11 different APIs listed under the PASS requirement both the innovative and generic products are listed under the additional monitoring list. If the original/reference product is subject to additional monitoring, it is only logical that generic products with the same API should be monitored as well. This is particularly so for products which are manufactured by multiple generic manufacturers in different countries and in cases of products which, like *teicoplanin*, failed to achieve cross-national agreement on their safety and efficacy and were included in the PASS list for this reason.

As explained in the previous sub-section in the case where an original/reference product is monitored yet its generic counterparts are not, it is possible that a patient may be dispensed with a generic product (for example in countries that mandate generic substitution under the product's INN).[121] This can make monitoring of ADRs more difficult, since the substitution is performed at the pharmacy level while ADRs are by and large communicated by the patient directly to the attending physician.

The example of *teicoplanin* illustrates the importance of maintaining a more holistic approach towards the practice of pharmacovigilance and need to have practices which are comprehensive and cover all relevant products.

Like labeling and packaging, pharmacopeia standards is another area which is becoming a challenge to standards and existing pharmacovigilance regulatory frameworks. The following sub-section outlines these challenges and examples of where there currently are potential gaps in existing pharmacopeia standards.

3.3 Pharmacopeia standards

According to the WHO, a pharmacopoeia is "a legally binding collection of standards and quality specifications for medicines used in a country or region",[122] whose role is to maintain the quality of medicines by providing an exhaustive and detailed set of specifications which confirm the drug candidate's characteristics such as identity, strength, purity (or its impurities profile) and performance.[123]

With its roots dating back to the Middle Ages, the term *pharmacopeia* is largely defined as "a book containing a compilation of pharmaceutical products with their formulas and methods of preparation".[124] Today, it refers to an official compilation of thousands of monographs which detail the requirements and specification (i.e. the tests and acceptance criteria) for preparing a medical ingredient in accordance with the highest standard of quality.[125] Indeed, the three major pharmacopeias – the US, the European and the Japanese pharmacopeias – all contain 2,000-4,000 monographs, and are being updated by and large on an annual basis.[126]

The major pharmacopeias contain monographs for finished medicinal products and dosage forms, as well as for their components – the APIs and excipients, for which specific chapters provide "guidance about the most common properties that might be important for a particular material in a particular application".[127] These monographs play an integral and essential part in the investigation and evaluation of a new drug candidate, as they represent the current highest standard for safety and quality control of the finished medicinal product. The consequences of not abiding with these standards can be dangerous, leading to potentially substandard products.

The role of pharmacopeias in the medicines regulatory approval process cannot be overstated. They play a central role in establishing accepted standards of quality and characteristics for a given product in a given legal jurisdiction. Drug regulators such as the FDA and EMA rely on pharmacopeias in their work on evaluating and authorizing medicines for market approval, particularly with regards to generic follow-on products.[128] Yet just as with packaging and labeling there are challenges and potential gaps here as well.

A given DRA that evaluates the submission of a drug candidate for marketing approval must be assured by the information provided by the applicant that the biopharmaceutical in question is safe for public use, that it was designed to the highest quality, and that it will benefit the patients for which it is intended. However, the drug candidate's quality is not ensured just by the mere existence of the test methods provided by a monograph.[129] The pharmacopeial test methods that were developed by an originator were designed to ensnare the impurities that are most likely to occur during the particular manufacturing process of the innovative medicine.[130] These methods might not spot impurities which resulted from different manufacturing process or unpredicted contaminations which can happen with new manufacturers. Impurities in the drug candidate's API or its formulation, even by small amounts, may result in serious safety and efficacy issues.

In addition, setting compendial standards that capture all possible excipients and their risks can also be very challenging. For instance, special grades of excipients (e.g., particle size or surface area) do not have monograph specification and thus the potential effect of their interaction with the active ingredient of a given medicine is unknown. Excipient variability can also result from numerous factors, such as the use of multisource suppliers, inconsistency in the synthesis of the raw materials, and inappropriate environmental conditions during manufacturing.[131] This excipient variability is problematic since it can lead to batch-to-batch or supplier-to-supplier variability and, potentially, non-equivalent performance.[132]

Nevertheless, DRAs have no processes or mechanisms which enable independent evaluation of the safety of a given excipient; instead, excipients are reviewed as "components".[133] Since many excipients begin as raw materials made for other industries (e.g. chemical industries), they must undergo a process of adaptation and purification from industrial grade to pharmaceutical grade. Compendial standards ensure, to the fullest extent known, their rendition as safe for human consumption. Still, as was mentioned above, concerns have been raised regarding potential drug-drug and drug-food interactions, due to excipients, as well as their effect on the rate and extent of

a given medicine's absorption in the body.[134] Unwanted side effects have also been identified with known excipients such as colorants and lactose (which can cause allergic reactions) as well as preservatives such as benzyl alcohol which can be harmful for children.[135] For example, a 2012 study measuring the prevalence of using potentially harmful excipients in neonates found that 97% (339 of 348) of the treated neonates received treatment with at least one potentially harmful excipient, and 88% (307 of 348) received at least one of 8 excipients known to be harmful to children.[136] Similar research focused on the prevalence of ethanol as an excipient in commonly prescribed medicines for premature newborns found that these infants were exposed to as much as 7 alcoholic units per week, which is a third of the safe consumption threshold for an adult man.[137]

Use of different excipients is not uncommon. For example, there are cases where the drug candidate is approved for marketing, yet is later required, during the scale-up stage, for changes in the formulation. Indeed, 62% of new oral agents approved by the FDA between 1981 and 1990 were marketed in a different formulation from that which was studied in the clinical trials.[138] Often this is a constraint of the scale-up process, which can pose a need to implement changes to the product's formulation in order to improve its purity or stability. Indeed, the formulation design is closely interlinked with the product's quality and safety attributes.[139] For example, medicinal products' formulations that did not disintegrate or dissolve properly have caused ADRs such as gastrointestinal irritation and intestinal obstruction.[140] It is also not unusual for generic follow-on products to use different excipients than a reference product.

The importance of ensuring the safety and quality of medicinal products within the scale-up and manufacturing stage has led DRAs in many developed countries to shift increasing attention to this issue. In 1993 a collaboration of three scientific and regulatory organizations – the American Association of Pharmaceutical Scientists, the FDA and the United States Pharmacopeial Convention – recognized that with regards to noncritical excipients, "certain compositional adjustments (to formulations) were determined to be acceptable, without further justification".[141] However, the FDA issued newer guidelines during the late 2000s which categorized the possible changes to the scale-up and manufacturing process in accordance with their potential to result in ADRs. According to these guidelines, formulation or excipient changes were categorized as a "major change" requiring prior-approval supplement filing.[142] Similar requirements are found in the EMA's guidelines on "post approval change management protocols".[143] However, as noted in a white paper issued by the pharmaceutical industry, the FDA's guideline "does not provide recommendations on specific information required to assess the effect of changes to identity, strength, purity, or potency of a drug product".[144]

Pharmacopeias do not always include the latest most up to date specifications of a given product nor are they always synchronized in a timely manner on a global scale. For example, under EU legislation, substances which do not have a designated monograph within the European Pharmacopeia are subject to national pharmacopeial standards of each EU-member state.[145] However, since many countries have developed their own pharmacopeias, the incorporation of regional/international pharmacopeias (such as the European Pharmacopeia or the WHO International Pharmacopeia) is also a matter of national choice and differences persist. While some countries (e.g. Sweden, Finland) have chosen to use solely the European Pharmacopeia, others countries (e.g. the UK, France and Switzerland) have opted for incorporation of the regional pharmacopeia concomitantly with the national pharmacopeia.[146] In the US (in cases where a monograph for an excipient, an API or a finished medicinal product does not exist) a manufacturer can rely on procedures set in the European, British or the Japanese pharmacopeias' monographs.[147]

Such a situation is not unprecedented, since the official acceptance and publication of a monograph for a given medicine can take years. For example, a monograph for *atorvastatin calcium* was published in the 2014 edition of the US pharmacopeia,[148] while generic products entered the market as early as 2012.[149] Additionally, while generic products for *latanoprost* entered the US market as early as mid-2011, no official monograph has been accepted to date.[150]

This gap between the period of generic market entry and the official publication of pharmacopeial monographs constitute another potential patient safety risk. For one, the monograph provided by the innovator was developed specifically for the reference product, and may not be suitable to detect impurities where different excipients and manufacturing processes are used.[151] More importantly, in cases where the reference drug has known issues, such as specific drug-drug interactions, the manufacturing of generic products without the guidance of an official pharmacopeial monograph may place patients at risk. For example, *decitabine*, an anticancer drug, is known to result in relatively high rates of ADRs such as anemia and neutropenia. However, generic *decitabine* products have entered the US market by mid-2014,[152] although a monograph for *decitabine* has not yet been officially approved.[153]

In addition, the US pharmacopeia maintains lists of missing monographs and of monographs urgently in need of modernization, which currently account for more than 1,400 substances.[154] This is potentially a serious issue as regulatory authorities rely on pharmacopeia standards throughout their review process. Pharmacopeias that are not updated or outdated are a potential gap in the pharmacovigilance framework. Indeed, these time-gaps during which a compendial standard is not up to date hold the potential for safety issues. Although the General Chapters in the major pharmacopeias provide the standard where monographs do not exist, yet compliance with the General Chapters is not mandatory, and may need additional validation by the manufacturer.[155] Thus, improvements and updates to a given product's profile and composition are not necessarily reflected in approvals that precede inclusion of the most updated profile in a given pharmacopeia.

Furthermore, pharmacopeial monographs, as noted earlier, are generally based on the specifications developed by the originator for a specific product.[156] In stringent DRAs (e.g. the FDA, EMA), one of the objectives of the regulatory approval process is to ensure that quality was built into the product throughout the manufacturing process. Thus, a generic drug candidate is expected to meet the compendial requirements of the reference product.[157] However, as mentioned, the pharmacopeial test

methods that were developed by an originator might not spot impurities which resulted from different manufacturing process or unpredicted contaminations, which could negatively affect a given product's properties and function.[158] This presents another potential gap in the pharmacovigilance framework relating to pharmacopedia standards. This especially concerns generic products of more complex and sensitive nature, such as NTI medicines and NBCDs. This is because for medicines of these types, small and seemingly insignificant changes can significantly affect their functionality, leading to unwarranted clinical outcomes, such as decreased efficiency, increase in negative symptoms, toxicity and even death.[159] For example as mentioned above, generic versions of the NTI anticonvulsant medicines *carbamazepine* and *gabapentin* have caused increased seizures in patients and more neurological side effects.[160] In addition, the generic versions of the NTI antipsychotic medicine *clozapin* have resulted in relapses or exacerbations after generic substitution.[161]

Internationalization efforts

Taken together, the lack of harmonization between national/regional pharmacopeias in terms of both content and updating times could pose patient safety risks, since conceptions of purity are susceptible to developments and improvements in technology and chemistry; what is considered pure today may be considered impure tomorrow.[162] Some forms and levels of impurity can lead to decreased stability and degradation of the product's API, which could also be harmful to patients.[163]

These potential gaps and inconsistencies have not gone unnoticed. Many countries have moved in the direction of international harmonization of their national pharmacopeias, led and coordinated by the WHO.[164] The three major pharmacopeias – the US, the EU and Japan – have already harmonized major parts of their pharmacopeias' monographs and chapters.[165] In addition, representatives from these pharmacopeias (and other countries including Mexico, Brazil, Argentina, Ukraine and Russia) are working in collaboration to develop an internationally-accepted guide to "Good Pharmacopeial Practice".[166]

The internationalization of pharmacopeial standards could have a positive effect on global access to quality medicines. The establishment of a uniform, globally-accepted pharmacopeial practice could bring about newer, more effective quality control methods for dealing with impurities, and expand global access to medicines of better quality by reducing nationally-specific requirements and by lowering national QA costs.[167] Moreover, this could encourage national and international collaboration between manufacturers, pharmacopeial organizations and DRAs, particularly for new substances/excipients/dosage forms where a standard does not exist yet.[168]

Nevertheless, the work of the Pharmacopeial Discussion Group (a collaboration of the 3 major pharmacopeias aimed at promoting compendial harmonization) has so far progressed rather slowly.[169] Although formed in 1989, the group has so far harmonized only 20 general chapters and 63 excipient monographs out of over 1,200, most of which have no public standard.[170]

4 CONCLUSIONS AND RECOMMENDATIONS

As technology and the science of medicines is constantly evolving, so too are standards of pharmacovigilance. Indeed, over the last few decades pharmacovigilance has matured as a regulatory science and operationally with well-established and comprehensive safety mechanisms and processes in place in the most stringent markets.

In countries and regions such as the US, EU, Japan, Canada and Australia, pharmacovigilance is not a new concept but an established and essential part of the drug regulatory framework. However, even for the most advanced DRAs new gaps and challenges are constantly emerging which necessitate closer attention, as these gaps potentially pose patient safety and public health concerns.

The purpose of this report has been to examine some of these challenges in the areas of packaging and labeling, and pharmacopeia standards. This is an important topic as differences and gaps in the regulatory framework for these areas have the potential to have a significant impact on standards of quality, patient safety and incentives for biopharmaceutical innovation and R&D. Preceding sections have provided a thematic discussion of these areas, the new pharmacovigilance challenges they pose and the different policies and actions taken by major DRAs in addressing (or not fully addressing) these challenges.

Overall the reports finds that a more holistic approach is necessary in which standards of pharmacovigilance are applied to all types of medicines – innovative, generics, small molecules as well as big ones. Looking at the "additional monitoring" initiative taken by the EMA in 2013 as a case study example, the report finds that EMA's policy ambiguity regarding the inclusion of products with multiple manufacturers has resulted in what appears to be an inconsistency and gap between the treatment and monitoring of reference products and follow-on generic manufacturers; a significant gap which potentially raises patient safety and public health concerns. Equally with regards to labelling this report finds that the latest academic research shows how there are still serious challenges and gaps in major OECD markets. In particular, there are discrepancies in ADR reports between reference and follow-on products.

Based on these findings the report makes the following three recommendations:

1. **EMA's "medicines under additional monitoring" policy should be exhaustive and account for all manufacturers**
   The EU Regulation 198/2013 is a laudable pharmacovigilance initiative, yet it should be clarified that its requirements apply to all manufacturers and types of products be it innovative or generic, small-molecule or complex, chemical or biologic.

2. **Pharmacopeial organizations should expedite the inclusion of new monographs**
   A greater emphasis should be placed on maintaining an efficient, updated and expedited pharmacopeial workflow as it is an essential part of the pharmacovigilance framework.

3. **Greater flexibility in labelling**
   In light of the situation in the US after the Supreme Court ruling (*Pliva v. Mensing*), which left patients with no legal remedy in cases of injuries resulted from inadequate labeling of generic products, governments and DRAs should act to adapt the legal and regulatory frameworks accordingly and enable all manufacturers to promptly change their products' labels in accordance with the emergence of new safety information.

NOTES

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