



DEVELOPING A CULTURE OF PHARMACOVIGILANCE Towards International Best Practices

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LIST OF ABBREVIATIONS

ANDA	Abbreviated New Drug Application
ANVISA	Brazilian National Health Surveillance Agency
API	Active Pharmaceutical Ingredient
ASEAN	Association of Southeast Asian Nations
CADREAC	Collaboration Agreement of Drug Regulatory Authorities in European Union Associated Countries
CDSC	Central Drugs Standard Control (India)
CGMP	Current Good Manufacturing Practice
CIOMS	Council for International Organizations of Medical Sciences
CLs	Compulsory Licenses
CMC	Chemistry, Manufacturing and Controls
COFEPRIS	Commission for Protection against Health Risks (Mexico)
EMA	European Medicines Agency
FDA	US Food and Drug Administration
FDI	Foreign direct investment
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
ICH	International Conference on Harmonization of Technical Requirements for Registration of Biopharmaceuticals for Human Use
IND	Investigational New Drug
MERCOSUR	Southern Common Market
NDA	New Drug Application
OECD	Organisation for Economic Co-operation and Development
PAHO	Pan American Health Organization
PVP	Pharmacovigilance Plan

LIST OF ABBREVIATIONS

RMP	Risk Management Plan
QbD	Quality by Design
RDP	Regulatory Data Protection
R&D	Research and Development
SFDA	State Food and Drug Administration (China)
TÜFAM	Turkey's Pharmacovigilance Centre
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.



EXECUTIVE SUMMARY

Today the legislation and regulation of the manufacture, dispensation and use of biopharmaceutical products is vast, complex and comprehensive. Governments across the world (including developed, developing and emerging market countries) view the regulation of medicines and biopharmaceutical treatments as paramount to maintaining public health. Medicines and new medical treatments have to undergo a wide range of tests and safety procedures both before they are allowed to market and after they have been approved for sale and use.

But standards of safety control and quality are not the same or even similar throughout the world. Not surprisingly the most rigorous systems of regulation can be found in those parts of the world with the most advanced health systems: North America, Europe, Japan, Australia, and Southeast Asia. Other countries face challenges with regards to both having an adequate level of biopharmaceutical regulation in place as well as making sure it is being applied and implemented in practice.

This report examines one of the most important facets of a high quality drug regulatory structure, namely that of pharmacovigilance. 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.

As patients and healthcare professionals around the world access and use more biopharmaceutical products and technologies, the importance of maintaining and, in many cases, introducing and applying comprehensive pharmacovigilance regulations only increases. Biopharmaceutical products are today manufactured, sold, distributed and dispensed across the globe. Complex and interlinked supply and demand chains mean manufacturers, distributors, wholesalers, pharmacists, healthcare professionals and patients all make up a global network of producers, sellers and consumers of these products and technologies.

In this context introducing and applying high quality standards of pharmacovigilance is of real importance in securing the integrity of biopharmaceutical supply chains against the growing menace of substandard and counterfeit medicines and ensuring patient safety.

This report makes two key findings.

First, through an exhaustive examination of the highest standards and best pharmacovigilance practices throughout the clinical, post-marketing and post-exclusivity phases of a biopharmaceutical product's life span (from the early R&D stages all the way to the market entry of generic products) the report assembles a pharmacovigilance 'Gold Standard'. Although not purporting to be a definitive guide or one-size-fits-all solution this Gold Standard does include a number of fundamental elements any robust pharmacovigilance system must adhere to including a recognition of the different challenges in safety monitoring in each phase and corresponding sub-phase of pharmacovigilance. The 'Standard' is summarized in the table on the next page.

Second, this report examines the state of pharmacovigilance in seven emerging and developing markets. Looking at the legal and regulatory situation as well as the actual application of pharmacovigilance regulations and rules the report finds that there is considerable variation as to the extent and effectiveness of drug regulations across the world. Many countries, such as China and Brazil, have in place relatively robust regulations but face challenges with applying and enforcing those regulations. Other countries, such as Indonesia, lack the right rules and regulations themselves. Equally, it is clear that awareness of pharmacovigilance among health professionals and patients is relatively limited in all the studied countries. The survey evidence that exists suggests that knowledge about pharmacovigilance and reporting mechanisms among health professionals in the seven countries analyzed is quite limited and can

A 'Gold Standard' of pharmacovigilance

Phase I: The clinical phase

The pre-clinical stage

- Ensure safety and quality within the drug's R&D process, by implementing the Chemistry, Manufacturing and Control regulatory requirements, such as process validation, Quality by Design and Good Laboratory Practices standards.

The clinical stage

- Ensure adherence to ICH E6 Good Clinical Practices guidelines to ensure ethical and scientific quality and credibility when conducting clinical trials
- Enforce close monitoring, analysis and evaluation of AE/ADR reports within clinical/bioequivalence trials

The marketing approval and manufacturing stage

- Adopt a risk-based strategy for all new drug applications, by requiring CMC information and current Good Manufacturing Practices certificates, and by including Risk Management and Pharmacovigilance Plans

Phase II: The post-marketing phase

Establish a robust regulatory framework in order to

- Construct safety profiles for marketed drugs in collaboration with manufacturers
- Conduct phase IV clinical trials when necessary
- Ensure safety and quality in distribution and dispensation by enforcing market authorization holders adherence to ICH guidelines

Establish good practice of pharmacovigilance by

- Raising awareness of healthcare professionals and consumers on the importance of properly reporting ADRs by using ICH guidelines
- Ensure that a robust national system for the accumulation and evaluation of ADRs is in place and is operative
- Ensure that manufacturers acknowledge and complies with pharmacovigilance practices and standards, such as the submission of Periodic Safety Update Reports, risk management and pharmacovigilance plans, and upholding international standards of manufacturing
- Setting the roles and responsibilities of all actors involved, in accordance with the WHO and ICH guidelines
- Ensure the system's ability to collaborate with international initiatives

Phase III: The post-exclusivity phase

- Establish robust legal and regulatory framework and enforce international standards in manufacturing and distribution
- Ensure accurate and up-to-date product labeling for all marketed drugs, in accordance with newly-acquired safety information

vary dramatically from health institution to health institution and region to region. Surveys of patient knowledge and awareness of the importance of ADR reporting and how to report adverse events showed even lower levels of awareness.

Based on these main findings this report makes the following four recommendations:

1. Recognize the centrality of pharmacovigilance to public health

Increasingly, greater numbers and kinds of biopharmaceutical products and treatments are available to a growing number of patients across the world. Now more than ever modern medicine is relying on biopharmaceuticals to treat, cure and help patients. Particularly in the emerging world in which biopharmaceutical markets and consumption is set to outpace growth in the developed world. It is vital in this context that increased demand and supply of medicine and medical technologies is matched by an equally developed and strong safety net.

2. Measure performance

Governments and policymakers need to measure pharmacovigilance performance consistently and comprehensively with clear and transparent benchmarks and goals. Measures should be holistic including not only number of ADRs but repeated surveys and reviews of levels of pharmacovigilance awareness among health professionals, patients and other key actors.

3. Boost awareness levels

In most countries the evidence suggests that awareness and recognition of pharmacovigilance is quite limited both among health professionals and patients. While many countries are working towards raising this awareness through campaigns, seminars, workshop activity and, in some cases, the creation of online reporting mechanisms this effort needs to be intensified. Public and professional awareness of the need and importance of pharmacovigilance and making reporting as straight-forward and practical as possible should be at the forefront of any drug regulatory authority.

4. Professional training

Given the relatively low levels of awareness among health professionals in all countries the creation and inclusion of pharmacovigilance in medical training and professional accreditation courses for health professionals is an idea worth exploring.



INTRODUCTION

At their best, medicines and biopharmaceutical treatments provide a relatively cheap, mobile and highly effective method of providing medical care. Many times they do not require either a medical professional or hospital to dispense the treatment but can be administered by the patient him- or herself or by someone close to them.

Still, for all their positive attributes medical drugs and treatments are by their very nature chemical compounds which can be poisonous to the human body. They can be highly toxic, dangerous and cause great harm when not taken by the intended patient or in the correct sequence and amount. While their intended effects are always hoped to be benign, there is universal recognition that biopharmaceutical technologies and products require extensive and high quality regulation. Indeed, the regulation of medicines and biopharmaceuticals has its roots in the industrialization and modernization of Western Europe and North America during the 19th and 20th centuries.¹

Today the legislation and regulation of the manufacture, dispensation and use of biopharmaceutical products is vast, complex and comprehensive. Governments across the world (including developed, developing and emerging market countries) view the regulation of medicines and biopharmaceutical treatments as paramount to maintaining public health. Medicines and new medical treatments have to undergo a wide range of tests and safety procedures both before they are allowed to market and after they have been approved for sale and use.

But standards of safety control and quality are not the same or even similar throughout the world. Not surprisingly the most rigorous systems of regulation can be found in those parts of the world with the most advanced health systems: North America, Europe, Japan, Australia, and Southeast Asia. Other countries face challenges with regards to both having an adequate level of biopharmaceutical regulation in place as well as making sure it is being applied and implemented in practice.

This report will examine one of the most important facets of a high quality drug regulatory structure, namely that of pharmacovigilance.²

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. Conceptually, pharmacovigilance is most commonly thought of in terms of post-marketing surveillance through ADRs reporting and through so-called phase IV clinical trials.³ But as will be detailed below in section 2 the practice of pharmacovigilance is actually part of a biopharmaceutical product's entire life cycle from clinical development to the introduction of follow-on generic products.

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. Biopharmaceutical products are today manufactured, sold, distributed and dispensed across the globe. Complex and interlinked supply and demand chains mean manufacturers, distributors, wholesalers, pharmacists, healthcare professionals and patients all make up a global network of producers, sellers and consumers of these products and technologies.

On the one hand this globalization of the health care sector and the free movement of its goods and services has had enormous benefits: patients can now access medicines that were in the past either not produced locally or far too expensive to import and access.

Yet for all these positive consequences there are also significant challenges. For example, there is the very real threat of substandard and counterfeit medicines infiltrating global supply chains and reaching patients all over the world. Estimates by the WHO, the FDA and others suggest that substandard and counterfeit medicines are growing in numbers not only in developing countries but also developed nations. These bodies put the number of counterfeit drugs between 10-15% of the total drugs market, with some areas in Asia and Africa reaching levels of almost 50%.⁴ Estimating the amount of substandard drugs on the market is much more difficult. This is because so many substandard drugs are legitimately manufactured and regulatory approved medicines. However, the few studies that do exist have found that in some cases, and countries, the number of substandard drugs can be as high as 40% of the total sample size.⁵

In this context introducing and applying high quality standards of pharmacovigilance is of real importance in securing the integrity of biopharmaceutical supply chains against substandard and counterfeit medicines and ensuring patient safety.

This report is divided into four sections.

Section 1 provides an overview of the drug regulatory process and key issues facing drug regulators and marketing authorities. This includes a brief discussion of the drug discovery process, issues of quality, safety and efficacy of a drug and a basic primer on how medicines are approved, marketed and sold. The purpose of this section is to introduce and contextualize pharmacovigilance within the broader context of the biopharmaceutical ecosystem.

Section 2 is a detailed discussion of pharmacovigilance conceptually as well as existing best practices as outlined by international institutions such as the WHO, ICH and advanced drug regulatory agencies such as the FDA and EMA. Key questions this section addresses include: What is pharmacovigilance? Why is it important? What are some of the best practices in place and used and what do international institutions recommend? These questions are examined through an analysis

of pharmacovigilance as three distinct phases of a biopharmaceutical product's life cycle. As this section details pharmacovigilance procedures and best practices differ depending on which pharmacovigilance phase a given biopharmaceutical product is in.

Section 3 provides a case study analysis of existing systems of pharmacovigilance in seven emerging markets covering a range of geographically and economically diverse countries: Argentina, Brazil, China, Indonesia, Mexico, Russia and Turkey. Each case study includes a description of the pharmacovigilance system in place in the specific market as well as an assessment of how the system works in practice. This latter applicatory aspect is a point of emphasis in this section. The information garnered through pharmacovigilance can only be of use if it is, firstly, collected in a systematic fashion and, secondly, put to good use by drug regulators. Indeed, effective pre and post marketing monitoring relies on drug regulators and health systems having developed robust systems of pharmacovigilance. However, in many countries there is not the infrastructure, resources, nor basic appreciation for the importance of having a well-functioning and continuous system of pharmacovigilance in place. This includes the ability and opportunity various actors and stakeholders within a given health system to play a role within the pharmacovigilance system. For example, to what extent do physicians, healthcare professionals and patients play a role within the pharmacovigilance system? Are these actors encouraged to do so or are there mechanisms or a prevailing culture in place which hinders the effective full participation and use of these actors within the pharmacovigilance system?

Finally, section 4 will offer concluding thoughts and policy recommendations on what countries can do to improve existing systems of pharmacovigilance.



1

THE IMPORTANCE OF MONITORING THE SAFETY OF MEDICINES

Nationally and internationally the biopharmaceutical market is one of the most heavily regulated markets in the world. 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.

It should be noted that these standards vary from country to country and jurisdiction to jurisdiction.⁶ The highest and most rigorous standards are those in the most developed health systems in North America, Europe and Southeast Asia. In many other countries health, safety and quality regulations are still being introduced and/or fully implemented.

This section gives an overview of the biopharmaceutical development process, how biopharmaceutical products and technologies are regulated and an overview of relevant standards. Given that regulatory standards and practices can vary considerably from one country and legal jurisdiction to another the below description is based on the most rigorous standards and international best practices.

1.1 The biopharmaceutical R&D process

Developing new biopharmaceutical products and treatments is an expensive, risky and time-consuming enterprise. While estimates vary, various sources agree on the significant investment and time needed to develop new biopharmaceuticals with different figures ranging from 10 to 15 years and USD1.3-1.8 billion.⁷ Significant resources are invested in basic research and drug discovery as well as the approval, manufacture and post-marketing monitoring of new drugs. The initial phases involve basic research on disease processes, the discovery of new compounds with potential for treatment, development of the most promising compounds and analysis of selected compounds in test tubes and animals, which takes roughly between 3 and 6 years.

Very few compounds actually make it past this stage to be tested in humans. At the other end of the pipeline, the process of market authorisation and manufacturing the drug to scale can take between 6 months to as much as 2 years, after which the drug must continue to be monitored and studied as it goes on to be used in earnest by the general public.

The testing of drug candidates in human volunteers via clinical trials,⁸ however, represents the largest and most risky investment in the R&D process. The clinical trial process represents an undertaking of 6-7 years per drug candidate.⁹ One study estimates that the clinical research phase now represents at least 65% of the total cost of the whole R&D process.¹⁰ The process includes complying with a wide range of regulations governing international best practices related to the quality, safety and efficacy of drugs including: Good Laboratory Practice guidelines on conducting toxicity studies; Good Manufacturing Practice; and protecting the rights of patients through Good Clinical Practice.¹¹ Despite the huge investment in this process, one recent analysis suggests that only 16% of candidate compounds which are tested in humans are likely to be approved by drug authorities.¹²

Figure 1 provides a basic overview of the biopharmaceutical R&D process, with a particular focus on the stages of clinical development.¹³

FIGURE 1 The biopharmaceutical R&D process



1.2 Essential pillars – safety, quality and efficacy

Safety

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.¹⁴

The safety of reference or innovative biopharmaceutical products and technologies is ensured through a system of rigorous tests and control prior to the drug being approved for public sale and marketing. As mentioned, these tests are conducted throughout the drug's R&D process, which consists of a pre-clinical stage and four clinical stages (also called "phases"). The safety of a drug within the pre-clinical stage is appraised by a series of studies, which determines the drug's toxicity, effects on and caused by the body (pharmacodynamics and pharmacokinetics), and appropriate dosage forms and levels.¹⁵ The clinical phases involve safety trials of the drug on volunteers (phase I), small patient groups, (phase II), large patient groups (phase III), and regulatory and post-marketing studies (phase IV).¹⁶ The purpose of these trials is to establish whether or not the drug proposed for approval is safe for human consumption.

However, this is not the case with generic drugs. Because they are not innovative products generics are in the most rigorous and demanding health systems required only to prove bioequivalence. Bioequivalence is defined by international best practice as at least 80% (or up to 125%) similarity to a reference product with respect to the rate and extent of the active ingredient's absorption within the bloodstream.¹⁷ It should be noted that bioequivalence requirements are not present in all regulatory systems. For example, as is detailed in section 3 for the relevant countries in most Central and Latin American countries bioequivalence is not required for registration of non-reference products. In countries such as Argentina, Chile and Colombia these non-bioequivalent tested drugs constitute a separate class of drugs called *similares*.

Quality

The term "quality" in the context of drug regulation refers both to the quality of the biopharmaceutical product itself and to the drug's manufacturing and distribution procedures and processes which can affect the quality of the drug. Generally speaking, it is the sum of all activities and responsibilities required to ensure that the medicine that reaches the patient is safe and effective. For example, manufacturers are responsible for developing and manufacturing the highest quality products and adhering to international standards of GMP. Distributors and dispensers of medicines need to ensure that the quality of a drug is not adversely affected under transportation, storage or actual dispensation. This is of particular importance in tropical countries where, unless proper storage and transportation conditions are maintained, a medicine's active ingredient can degrade rendering it either useless or, quite possibly, harmful to patients. And finally, the overarching responsibility for ensuring the quality and integrity of a medicine lies with each individual DRA. These authorities are responsible for overseeing all other actors and ensuring that the quality of a medicine is not allowed to deteriorate at any point in the long and complicated test-tube-to-patient supply chain. DRAs must ensure that GMP practices are followed by having frequent and comprehensive site inspections and through drug manufacturing, sale and processing licensing agreements. Similarly, the wholesale, retail selling and dispensation of biopharmaceutical products must be a licensed and/or regulated activity for which DRAs have ultimate responsibility. The WHO's definition of quality states that:

The quality of a drug or device is one of the criteria for market approval and is reviewed as part of the registration process. Quality assurance covers all activities aimed at ensuring that consumers and patients receive a product that meets established specifications and standards of quality, safety, and efficacy. It concerns both the quality of the products themselves and all the activities and services that may affect quality.¹⁸

The determinants of drug quality includes the chemical or biological identity of its active ingredient, a drug's purity, potency and stability, and a drug's uniformity with respect to color, shape, size etc.¹⁹ These determinants can be gravely affected by improper manufacturing, labeling, distribution and dispensation, such as the impurity within the production lines, inadequate temperature control when distributing, and improper labeling.²⁰

Upholding the highest standards of quality is crucial to the interests of patient safety and public health. However, standards of drug 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. Furthermore, while certain DRAs encourage innovative and generic drugs manufacturers to provide QbD data as a part of marketing authorization applications, as mentioned, there are DRAs which do not even require the proof of bioequivalence for generic manufacturers as in Central and Latin America.

Efficacy

Efficacy refers to the potential maximum therapeutic response that a drug can produce.²¹ In other words, efficacy is the extent to which the drug in question produces the desired therapeutic effect on a patient. The efficacy and the potency of a given drug is tested and established mainly during the preclinical and clinical trials phase, and is monitored continuously after its approval and marketing.

Just like safety and quality, the efficacy of a given drug is dependent on the processes by which it is manufactured, distributed, stored and dispensed. Indeed, efficacy is closely linked and affected by the quality of the drug. Poor manufacturing and/or distribution processes, use of substandard or even toxic ingredients and improper handling will not only affect the quality and efficacy of the drug, but could also result in serious harm to patients.²²

1.3 International standardization

Alongside the globalization of the biopharmaceutical market there has been growing international interest in establishing a global standard of the highest standards of safety, quality and efficacy in medicines through harmonization and standardization of drug regulations. In fact, since the 1980s initiatives have been taken by governments and regulators from across the world, international bodies such as the WHO, and the biopharmaceutical industry to harmonize drug regulation.²³

Perhaps the most important initiative has been that of the ICH, a joint effort actively involving regulators and the biopharmaceutical industry as equal partners in discussions of the scientific testing procedures which are required to ensure, assess and maintain the safety, quality and efficacy of medicines.²⁴ The purpose of the ICH is to develop the highest quality technical and scientific standards and harmonize these to create a global leading standard for the regulation and authorization of biopharmaceutical drugs. Since the 1990s the ICH Steering Committee has given priority to harmonizing the regulatory requirements for the technical content for the sections reporting data submitted in the EU, US, and Japan. Below Table 1 lists the guidelines agreed to and implemented in partnering jurisdictions.



TABLE 1 ICH Guidelines by main topic and classification codes²⁵

Quality	Safety	Efficacy	Multidisciplinary
Stability Q1A - Q1F	Carcinogenicity Studies S1A - S1C	Clinical Safety E1 - E2F	MedDRA Terminology M1
Analytical Validation Q2	Genotoxicity Studies S2	Clinical Study Reports E3	Electronic Standards M2
Impurities Q3A - Q3D	Toxicokinetics and Pharmacokinetics S3A - S3B	Dose-Response Studies E4	Nonclinical Safety Studies M3
Pharmacopoeias Q4 - Q4B	Toxicity Testing S4	Ethnic Factors E5	Common Technical Document M4
Quality of Biotechnological Products Q5A - Q5E	Reproductive Toxicology S5	Good Clinical Practice E6	Data Elements and Standards for Drug Dictionaries M5
Specifications Q6A- Q6B	Biotechnological Products S6	Clinical Trials E7 - E11	Gene Therapy M6
Good Manufacturing Practice Q7	Pharmacology Studies S7A - S7B	Clinical Evaluation by Therapeutic Category E12	Genotoxic Impurities M7
Pharmaceutical Development Q8	Immunotoxicology Studies S8	Clinical Evaluation E14	Electronic Common Technical Document (eCTD) M8
Quality Risk Management Q9	Nonclinical Evaluation for Anticancer Pharmaceuticals S9	Pharmacogenomics E15 - E16	
Pharmaceutical Quality System Q10	Photosafety Evaluation S10		
Development and Manufacture of Drug Substances Q11			

While not seeking to harmonize regulations like the ICH, other international bodies have developed similar sets of best practice advice and guidelines for emerging market and developing countries. Indeed, the WHO has for many years been arguing for the necessity of high quality and comprehensive drug regulation across the world. In 2001 the WHO published the second edition of *How to develop and implement a national drug policy*. As the title suggests the purpose of this document is to provide a step-by-step guide to drug regulations and the establishment of a national drugs policy. *How to develop and implement a national drug policy* makes clear that this is an issue that affects all countries around the world; developing countries in particular.

There have also been several important regional efforts towards biopharmaceutical harmonization. Often these have taken place within existing regional trade or security organizations. CADREAC, which includes Turkey and most

Eastern European countries, allows products approved within the EU to be recognized in other CADREAC countries. MERCOSUR has also adopted quite a lot of drug regulatory harmonization although implementation is more of a challenge with as the WHO has put it, "difficulties lie in the adoption and implementation of MERCOSUR agreements and resolutions by participant countries."²⁶

As the next section will detail, pharmacovigilance is a key part of these international efforts with the WHO, ICH and other international bodies and institutions having issued guidelines and reports on regulatory requirements and best practices for pharmacovigilance.



2

CAPTURING THE ESSENCE OF PHARMACOVIGILANCE

The WHO defines pharmacovigilance as “the science and activities concerned with the detection, assessment, understanding and prevention of adverse reactions to medicines”.²⁷ 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 drug or treatment.

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, from test-tube to patient. As such, an effective pharmacovigilance system necessitates the active involvement of regulatory authorities, manufacturers and distributors, healthcare institutions and professionals, as well as patients.

2.1 Background

The history of international pharmacovigilance goes back as much as fifty years, with 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.²⁸ As a result, the Sixteenth World Health Assembly in 1963 adopted a resolution (WHA 16.36)²⁹ that reaffirmed the need for early action with regard to the rapid dissemination of information on adverse drug reactions. This resolution led to the creation of the WHO Pilot Research Project for International Drug Monitoring in 1968. Its purpose was to develop an internationally-applicable system for detecting previously unknown or poorly understood adverse effects of medicines.³⁰ Since its inception, the project has evolved into the WHO *Program for International Drug Monitoring*, which is coordinated by the Uppsala Monitoring Centre in Uppsala, Sweden, and has 118 official member states, and 29 associate member states.³¹

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.³²

Pharmacovigilance has also evolved as a regulatory activity with an increased international emphasis through, for example, the launch of the CIOMS program on drug 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.³³

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, can spread rapidly and are difficult to refute in the absence of good data.³⁴

In many respects pharmacovigilance should be viewed as an arm of patient care.³⁵ Indeed, as stated in the Erice Declaration (a product of the 1997 “International Conference on Developing

Effective Communications in Pharmacovigilance” organized and supported by the WHO and Uppsala Monitoring Center) 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.”³⁶

This section provides the framework for a comprehensive understanding of pharmacovigilance, by providing a broad and extensive review of pharmacovigilance 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 drug;

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 drug regulatory authorities, health care professionals, manufacturers, patients and other relevant stakeholders.



Together the best practices (drawn from international institutions as well as stringent drug regulatory agencies such as EMA and FDA) described within each of these phases of pharmacovigilance combine to form a ‘Gold Standard’ of a robust pharmacovigilance system. This standard is summarized below.

2.2 The clinical phase

As described in section 1 prior to being approved for market, a new medicine must undergo a complex and lengthy process of selection, testing and development in order to make it safe for human use and therapeutically effective. 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.

As outlined in section 1 a typical biopharmaceutical R&D project consists of a pre-clinical stage, and a clinical stage. At the pre-clinical stage scientists attempt to isolate new chemical or biological entities using advanced screening and synthesizing techniques. At the clinical stage, scientists perform safety trials on healthy volunteers (phase I), small patient groups, (phase II), large patient groups (phase III), and regulatory and post-marketing studies (phase IV). These stages establish the safety, quality and efficacy of the tested drug.

The practice of pharmacovigilance takes place throughout the latter parts of a drug's R&D process. However, the safety and quality of the drug are constructed within each of the above stages. The marketing approval and manufacturing stages also influence the drug's safety and quality. Therefore, keeping to the highest standards and best practices within each of these stages is essential to ensuring that pharmacovigilance is established and maintained throughout the drug's R&D process. Below is a description of the best practices of pharmacovigilance procedures within the pre-clinical, clinical, marketing approval and manufacturing stages, which together constitute the *clinical phase* within the pharmacovigilance framework.

Pharmacovigilance within the pre-clinical stage

The pre-clinical stage consists of *in vitro* and *in vivo* tests, which help establish a proposed product or technology's toxicity and proper dosing levels.³⁷ Pharmacovigilance under this phase is achieved by ensuring the developed drug's safety and quality. This can be achieved by adhering to the highest standards and best practices of research and development, mainly GLP and QbD, which is a part of CMC process validation (described below).

GLP embodies a set of principles within which studies are planned, performed, monitored, recorded, reported and archived. Studies are undertaken to generate data which aid in the assessment of the hazards and risks of biopharmaceutical products to patients. GLP helps assure regulatory authorities that the data submitted are a true reflection of the results which are obtained during the study and can therefore be relied upon when making risk/safety assessments.³⁸

Quality by Design is a concept which refers to the planning and design of the development and manufacturing processes of a drug, in a way which minimizes risk and assures quality. Its underlying premise is that quality cannot be tested into products and instead should be built-in to existing processes and through design.³⁹ It is a concept developed through international efforts and is actively in use by stringent regulatory agencies including the FDA and EMA.⁴⁰ For instance, in the past decade the FDA's Center for Drug Evaluation and Research has implemented a special program which allows innovative biopharmaceutical companies to submit QbD information under the category of CMC.⁴¹ CMC is a concept which amalgamates the processes of creating and optimizing a chemical substance for massive manufacturing, and ensuring its safety. Thus, the regulatory authorities can better evaluate the application and be assured that the drug's safety and quality are maintained in the manufacturing process.



However, this standard is only relevant for innovative drugs. In order to maintain the quality production of generic drugs, the FDA's CDER has introduced a question-based review process, which "serves a dual purpose of providing guidance to reviewers in preparing consistent and comprehensive evaluations of Abbreviated New Drug Applications while assessing critical formulation and manufacturing process variables and providing industry with guidance on which issues need to be addressed in applications where QbD is being implemented".⁴² The pharmacovigilance measures that relate to generic medicines are discussed in detail below under phase 3, the post-exclusivity phase.

Pharmacovigilance within the clinical stage

The clinical stage is where a product or technology's efficacy is tested and determined by a set of trials on human subjects. It is the longest and most expensive stage within the biopharmaceutical R&D process, and, due to the low success rate, often referred to as 'the death valley' of a tested drug.⁴³

With the exception of phase IV, pharmacovigilance within the clinical stage is expressed through the adherence to recommended standards and practices which aim to ensure safety when designing and conducting trials on human subjects.

Clearly, testing a product or technology under investigation on human subjects bears the risk of harm. Therefore, regulatory authorities must ensure that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible and accurate.

Crucially international institutions have played an important role in contributing to such standards and international best practices. These include standards for medical research, clinical trials and safety monitoring. Most notable is perhaps that of the World Medical Association and the "WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects".⁴⁴ First announced in the mid-1960s the Declaration has become a cornerstone in medical research and ethics guiding medical researchers all around the world. In 1996 the ICH issued GCP guideline E6 with the intention to provide "an international ethical and scientific quality standard for designing,

conducting, recording and reporting trials that involve the participation of human subjects".⁴⁵ The ICH further states that "compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected... and that the clinical trial data are credible".⁴⁶

Compiling a safety report and systematically monitoring and recording the incidence of AEs and ADRs with each biopharmaceutical being investigated is a fundamental part of the clinical pharmacovigilance process. While on the surface an elemental part of pharmacovigilance at the clinical phase, there are significant challenges in AE and ADR reporting. For example, as part of this safety reporting process it is important to distinguish between cases of adverse events in which there is a stronger association with the investigational product and a less strong association. Looking for example at FDA regulations in place until recently, sponsors investigating a drug submitted an IND safety report which included "any adverse experience associated with the use of the drug that was both serious and unexpected, and any finding from tests in laboratory animals that suggested a significant risk for human subjects".⁴⁷ However, according to the FDA, safety reports submitted included individual cases of serious events which were less likely to be associated with the drug (such as manifestations of the underlying disease, or common events related to the study population). Given the difficulty in determining a clear association between the safety event and the product under investigation the FDA has come to view submission of single events without context as "uninformative" and not always contributing to developing the safety profile of the investigated product.⁴⁸ Based on this the FDA has revised its requirements so as to "distinguish circumstances in which it is appropriate to submit individual cases and circumstances in which cases should be aggregated and compared to cases in a control group and submitted only if the event occurs more frequently in the drug treatment group".⁴⁹

Pharmacovigilance within the marketing approval and manufacturing stage

A given drug regulatory authority that evaluates the submission of a NDA for marketing approval must be ensured by the information provided by the manufacturer 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. In this context it is appropriate that regulatory authorities adopt a risk-based strategy. Once implemented, such a strategy helps assure that the highest standards of safety and quality are incorporated into the product under investigation's development, manufacturing and post-marketing stages. Key parts of such a strategy include process validation and CMC, CGMP, risk management and the submission of a pharmacovigilance plan.⁵⁰

Process validation and CMC provide scientific evidence which assures the regulatory authority that each process within the development of the drug is capable of consistently delivering a quality product.⁵¹ The commercial manufacturing of a drug requires that all of its properties, such as purity, potency and stability, are maintained through the scaling-up process.

The CGMP standard provides a minimum requirement for the establishment of a formal system of controls at a biopharmaceutical manufacturer, which, if stringently applied and put into practice, helps to prevent instances of contamination, deviations, failures, and errors. 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.⁵² The reason for upholding the CGMP standard is that testing alone does not ensure quality. In most instances, testing is done on a small sample (e.g. testing 100 tablets from a batch of 2 million). Maintaining and enforcing CGMP standard assures that drug products meet their quality standards.

A RMP is an integral part of a drug's development and manufacturing processes. Incorporating rigorous analyses of these processes helps identifying, managing, and mitigating risks. In addition, the implementation of a risk-based quality assessment system within the review process can reduce the need to submit manufacturing supplements and increase first-cycle approval of new drug applications, thereby making drug products available to patients in a timelier manner.⁵³

Both the FDA and EMA encourage biopharmaceutical manufacturers to provide (as part of the RMP or by itself) a PVP for the approval-pending drug. The PVP presents the regulatory authorities with information regarding the identified risks of the drug, and the potential risks from off-label use by populations for which the drug has not been clinically studied. In addition, the submission of a PVP plan to regulators enables a dialogue between the authorities and manufacturers to discuss the best course of pharmacovigilance actions, such as setting the timeframe for the submission of specific serious ADRs in an expedited manner, active surveillance to identify adverse events in different settings, and the performance of pharmaco-epidemiological trials.⁵⁴

2.3 The post-marketing phase

The post-marketing setting is where the actual practice of pharmacovigilance as most commonly understood takes place. In order to maintain the best practice (as defined by the WHO) of "detection, assessment, understanding and prevention of adverse effects or any other drug-related problem",⁵⁵ a robust post-marketing system of pharmacovigilance needs to be in place. This system requires that all the actors involved understand the importance of their roles and responsibilities. Examples of such roles and responsibilities include:

1. A well-understood practice of collecting and reporting AEs and ADRs by healthcare professionals;
2. a biopharmaceutical manufacturing industry which acknowledges and complies with pharmacovigilance practices and standards;
3. a robust, effective and well-developed regulatory capacity including a designated national database which enables the construction of a given product's safety profile; and
4. an acknowledgement of the crucial role patients and the public can play in reporting and providing information.⁵⁶



In other words, pharmacovigilance in this phase encompasses the institutionalized procedures and regulatory framework in place as well as the actual use and application of those procedures by drug regulatory authorities, health care professionals, manufacturers and patients.

Constructing a safety profile

When a new medicinal product is submitted for marketing approval the demonstration of its efficacy and the evaluation of its safety are based at most on several thousand patients. The limited number of patients included in phase I-III clinical trials and the lack of significant long-term treatment experience per definition does not allow for a complete evaluation of a product's safety profile. International best practices recognize that under such circumstances, the detection or confirmation of rare adverse reactions is particularly difficult, if not impossible.⁵⁷

In order to develop a more comprehensive picture of clinical safety, medicinal products are closely monitored, especially during the first years of commercialization. Within this context, it is the responsibility of the competent authorities to ensure the establishment of a robust regulatory framework that enables DRAs to collaborate with manufacturers and market authorization holders

in order to establish a drug's safety profile. This can be done through i) the conducting of phase IV clinical trials when necessary, and ii) the submission of Periodic Safety Update Reports. Periodic Safety Update Reports are utilized both by the FDA and EMA and have been codified into an ICH guideline (EC2, R2).⁵⁸

Phase IV trials are clinical trials which are conducted after a drug has been approved for marketing, in order to provide additional details regarding the drug's safety and efficacy profile. Since the drug is now under more wide-spread use, its effects on different populations (as well as its interactions with other drugs) can be better understood. These trials can be observational in nature (designed to monitor deficiencies and ADRs) or experimental (for example, in order to provide data for extrapolation of indications for the drug).⁵⁹

Indeed, phase IV trials are not a must, and are required mostly for special populations or where the clinical benefit needs further demonstration.⁶⁰ However, by their very nature, clinical trials cannot account for the tested drug's interactions with various populations in the real world. Certain risks can be foreseen within the approval stage, and require further attention, if by post-marketing surveillance or by a clinical trial. Many drug regulatory authorities have taken this into account

when developing new regulations. For instance, the FDA in the last few years has strengthened its regulatory framework by implementing section 505(o)(3), which permits the agency to require certain post-marketing studies and clinical trials for prescription drugs, in order to assess known serious drug-related risk and to identify an unexpected serious risk when available data indicates the potential for a serious risk.⁶¹

As mentioned the submission of Periodic Safety Update Reports is an essential part of constructing a drug's safety profile. DRAs and manufacturers record information on a product's safety from different sources and procedures have been developed to ensure timely detection and mutual exchange of safety data. Because all information cannot be evaluated with the same degree of priority, regulatory authorities have defined the information to be submitted on an expedited basis; in most countries this rapid transmission is usually focused on the expedited reporting of adverse reactions that are both serious and unexpected.⁶²

Since re-evaluation of the benefit/risk ratio of a drug is usually not possible for each individual ADR case, even if serious, the Periodic Safety Update Reports present the world-wide safety experience of a medicinal product at defined times after a product has been marketed. At these times, marketing authorization holders are expected to provide a critical evaluation of the risk-benefit balance of the product. Such an evaluation provides a basis on which to determine whether further investigations need to be carried out and whether changes should be made to the marketing authorization and product information.⁶³

Ensuring quality within distribution and dispensation

Once a drug has been approved for marketing it becomes part of the biopharmaceutical supply chain and other important actors become involved in the distribution and dispensation of the product. Typically, the biopharmaceutical supply chain involves four actors: the manufacturer, the distributor/wholesaler, the pharmacy/dispenser and the patient. The type of procedures and regulations relating to distribution and dispensation are an important part of maintaining the safety and integrity of an approved biopharmaceutical and hence a given system of pharmacovigilance.

There are a number of examples in place of international best practices with regards to distribution and dispensation regulations. For example, two decades ago the European Commission published guidelines on Good Distribution Practice. These guidelines were recently revised in order to account for advances in practices for appropriate storage and distribution of medicinal products.⁶⁴ These EU guidelines provide a strict standard of practice for "all activities consisting of procuring, holding, supplying or exporting medicinal products",⁶⁵ including micro-level operational procedures in place (such as hygiene and temperature control) as well as other more over-arching elements including quality and risk management.

Worth noting is how guidelines and policies such as these on distribution practices are becoming part of a wider strategy of combating counterfeit and substandard medicines. For example, recognizing the increase in sub-standard or falsified medicines and the trend of their circulation via the legal supply chain, the 2011/62/EU Directive imposes several obligations on all supply-chain actors involved i.e. biopharmaceutical manufacturers, importers, distributors, wholesalers and brokers. This includes obligations to obtain manufacturing or distributing authorization, and abiding with GMP and GDP standards.⁶⁶

Establishing the practice of pharmacovigilance

The practical aspect of monitoring the safety and efficacy of a newly-marketed drug relies heavily on healthcare professionals such as physicians, nurses and pharmacists. Indeed, ADRs are a common cause for emergency room visits and hospitalization.⁶⁷ The reporting of ADRs signals potential safety risk, which, after evaluation, could result in action taken to ensure public health.⁶⁸ An effective pharmacovigilance system will have a direct and clear process in which healthcare professionals are aware of the importance of monitoring for and reporting ADRs and the relevant structures are in place that encourage and allow such reporting to take place.

However, as is detailed below in section 3 and the individual country case studies, it is clear that in many countries a high number of healthcare professionals are, firstly, not aware of the importance of pharmacovigilance or, secondly, the

manner in which ADRs can be reported.⁶⁹ For example, medical service providers and health care institutions in the sampled countries are often not required or encouraged to have in place designated and effective pharmacovigilance units charged with the collection and submission of AE and ADR reports and training and internal awareness raising.

In addition to basic reporting, the second facet of the actual practice of pharmacovigilance is a system which, firstly, accumulates and evaluates AEs and ADRs reports at a national level, and, secondly, collaborates closely with the biopharmaceutical industry and international pharmacovigilance centers. A pharmacovigilance monitoring system can be centralized, with one national center for collecting reports, or decentralized, with a national center functioning as a focal point for regional and/or local centers. Whether or not the monitoring system is centralized or decentralized is less important than the given system being supported by the relevant regulations and authorities.⁷⁰ The regulatory body provides the backbone of any pharmacovigilance system in that it sets the roles and responsibilities of all the actors involved including the regulatory authority itself. This has been highlighted by many international institutions including the WHO. A 2006 WHO paper identifies the roles and responsibilities for patients and the public; healthcare workers; district investigation team; a national pharmacovigilance coordinator; the medicines regulatory authority; the biopharmaceutical industry and manufacturers and even the media.⁷¹

An important aspect of pharmacovigilance practice is a given system's compatibility with international initiatives, such as the WHO supported Uppsala Monitoring Centre.⁷² To be of most use international databases (like the Vigibase) require uniformity in data input and there is a compelling need for international harmonization with regards to the reporting of ADRs and AEs. This has been a key topic in international harmonization initiatives for a number of years. Consequently, the ICH has since the 1990s issued a series of guidelines on how pharmacovigilance data submitted to the regulatory authorities from the biopharmaceutical industry and healthcare professionals is recorded and submitted.⁷³

2.4 The post-exclusivity phase

When an innovative drug enters the market it has several years of exclusivity, originating from its patent and/or market exclusivity protection. Once this exclusivity period expires, new generic participants can enter the market. The entry of these generic products raises several pharmacovigilance issues centering primarily on manufacturing and labeling.⁷⁴ As section 3 will illustrate these issues are especially important in emerging markets in which health systems and regulators are still moving towards international best practices.

Manufacturing

The commercial manufacturing of a drug requires that all of its properties, such as purity, potency and stability, are maintained through the entire manufacturing process. As discussed, this can be done by implementing standards of best practice such as process validation and CGMP. However, without a legal and regulatory framework in place which sets these responsibilities (and regulators capable of enforcing them) standards are very likely to lag behind. Most obviously the lack of robust manufacturing and pharmacovigilance regulations and enforcement can contribute to the circulation of substandard drugs and pose a serious threat to public health. Recent studies estimate that substandard and counterfeit drugs were being sold in at least 124 countries in 2011 primarily developing and emerging market,⁷⁵ and that their prevalence in low and lower-middle income countries was close to 30% in 2013.⁷⁶ But substandard and counterfeit drugs are prevalent also in more mature markets such as the US and the EU. For example, India supplies about 40% of generic and OTC drugs 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.⁷⁷



There is also the issue of different excipients used by generic manufacturers versus a reference product. In most cases these differences are minor and have a negligible therapeutic impact on the patient but there have been a number of cases where the effect of a switch from a reference product to a generic (or from one generic to another) has caused unintended consequences due to the different products containing different excipients. For example, research into biopharmaceuticals used by a sample of Dutch hospital pharmacies found that switching to an infusion concentrate of gemcitabine (a chemotherapy drug) had the effect of leaving patients with symptoms similar to intoxication.⁷⁸ Upon investigation it was found that the new concentrate used contained ethanol as a solvent with the dosage being the equivalent of two glasses of beer.⁷⁹ Similarly, issues have been identified with other 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.⁸⁰

Labelling

From a pharmacovigilance perspective, the issue of drug labeling is of critical importance. A biopharmaceutical's label and leaflet contain prescription of use and safety information. If the information is misleading or misbranded the public's trust in biopharmaceuticals and in the health system is eroded. This is true for both

reference and generic products. In stringent regulatory systems generic drugs are required by law to issue the same labels as their reference products.⁸¹ The rationale behind this is that the main effects of a generic drug (including potential ADRs) are related to its active ingredient and rate of absorption, which is per definition identical to the reference product's active ingredient and (under international bioequivalence requirements) within a pre-defined absorption range. Still, this does not account for the fact that generic drugs can differ in form, excipients and impurity levels. Drug regulators are starting to acknowledge this fact. For example, in 2014 the FDA issued a proposed rule to amend its regulations regarding the labeling of generic drugs. The FDA justifies 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".⁸² The proposed rule permits generic drug application (ANDA) holders to revise a drug's labels in accordance to newly-acquired safety information which may differ in certain aspects from the reference drug's label.⁸³ This amendment is "intended to improve the communication of important drug safety information about generic drugs to both prescribers and patients".⁸⁴

2.5 A 'Gold Standard' of pharmacovigilance?

This section has described the three phases of pharmacovigilance and the different safety aspects characterizing each phase. The individual sections and sub-sections have detailed how pharmacovigilance procedures and processes differ from phase to phase depending on the different requirements of each phase. This discussion has relied on international sources and guidelines of pharmacovigilance best practices. Below Table 2 summarizes this discussion in a table overview which provides a 'Gold Standard' of international pharmacovigilance. Although not purporting to be a definitive guide or one-size-fits-all solution this Gold Standard does include a number of fundamental elements any robust pharmacovigilance must adhere to including a recognition of the different challenges in safety monitoring in each phase and corresponding sub-phase of pharmacovigilance.

TABLE 2 A 'Gold Standard' of pharmacovigilance

Phase I: The clinical phase**The pre-clinical stage**

- Ensure safety and quality within the drug's R&D process, by implementing the Chemistry, Manufacturing and Control regulatory requirements, such as process validation, Quality by Design and Good Laboratory Practices standards.

The clinical stage

- Ensure adherence to ICH E6 Good Clinical Practices guidelines to ensure ethical and scientific quality and credibility when conducting clinical trials
- Enforce close monitoring, analysis and evaluation of AE/ADR reports within clinical/bioequivalence trials

The marketing approval and manufacturing stage

- Adopt a risk-based strategy for all new drug applications, by requiring CMC information and current Good Manufacturing Practices certificates, and by including Risk Management and Pharmacovigilance Plans

Phase II: The post-marketing phase**Establish a robust regulatory framework in order to**

- Construct safety profiles for marketed drugs in collaboration with manufacturers
- Conduct phase IV clinical trials when necessary
- Ensure safety and quality in distribution and dispensation by enforcing market authorization holders adherence to ICH guidelines

Establish good practice of pharmacovigilance by

- Raising awareness of healthcare professionals and consumers on the importance of properly reporting ADRs by using ICH guidelines
- Ensure that a robust national system for the accumulation and evaluation of ADRs is in place and is operative
- Ensure that manufacturers acknowledge and complies with pharmacovigilance practices and standards, such as the submission of Periodic Safety Update Reports, risk management and pharmacovigilance plans, and upholding international standards of manufacturing
- Setting the roles and responsibilities of all actors involved, in accordance with the WHO and ICH guidelines
- Ensure the system's ability to collaborate with international initiatives

Phase III: The post-exclusivity phase

- Establish robust legal and regulatory framework and enforce international standards in manufacturing and distribution
- Ensure accurate and up-to-date product labeling for all marketed drugs, in accordance with newly-acquired safety information



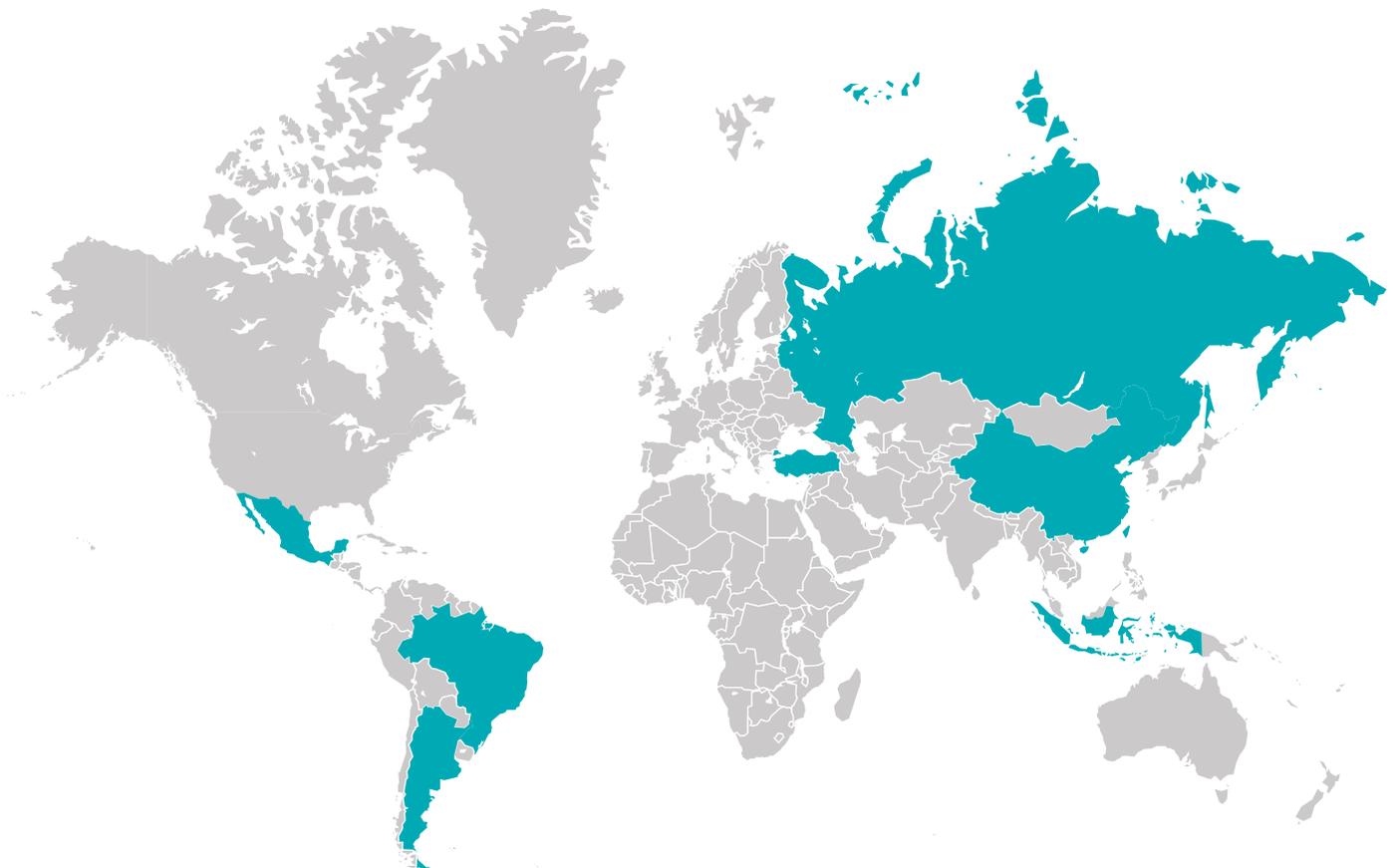
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THEORY VERSUS PRACTICE – COUNTRY CASE STUDIES

This section provides a case study analysis of existing systems of pharmacovigilance in seven emerging markets covering a range of geographically and economically diverse countries: Argentina, Brazil, China, Indonesia, Mexico, Russia and Turkey.

Each country analysis includes an overview of the pharmacovigilance system, scope of existing regulations, the involvement of the biopharmaceutical industry and health care professionals, patient awareness, a discussion of substandard and counterfeit medicines and overall evaluation of the pharmacovigilance system. Emphasizing the fact

that this section focuses not only on the legal or regulatory framework in place but also on the actual application and implementation of pharmacovigilance laws and regulations at the end of each country analysis a table is provided summarizing the legal and regulatory framework in place compared to the application or on-the-ground experience.



3.1 Argentina

Pharmacovigilance framework

The National System of Pharmacovigilance in Argentina (*Sistema Nacional de Farmacovigilancia*) is a decentralized system, which consists of the centralized authorities at ANMAT (divided into two divisions: *Departemento Farmacovigilancia and Servicio de Información de Medicamentos*) and over sixty regional centers.⁸⁵ This system was established under MoH resolution No. 706 from 1993.⁸⁶ A year later Argentina joined the WHO International Drug Monitoring Program.

The method of ADR reporting in Argentina is that of spontaneous reporting. The SNFVG receives ADR reports from the biopharmaceutical industry, public and private institutions (referred to as “peripheral effectors”), healthcare professionals, and now also from patients.⁸⁷ These reports are evaluated and classified according to the WHO-UMC standards by the pharmacovigilance department, and relevant information is disseminated via press releases, national and professional bulletins, annual reports, and by occasional workshops.⁸⁸

In 2013 ANMAT introduced a system for electronic submission of ADR reports.⁸⁹ The system consists of an online form accessible from the website of the SNFVG and was developed from the ICH-E2B international standards, “Transmission of Individual Case Safety Reports”.⁹⁰ The system is intended for the professional use of the biopharmaceutical industry as well as for public use by individual healthcare professionals and patients. However, the high rates of ADR-related hospitalization compared to the low rate of voluntary ADR reporting by healthcare professionals, suggests that even with this new reporting system in place there are significant challenges to expanding the reach and coverage of Argentina’s pharmacovigilance system.

Scope of regulation

An important step in defining the scope of Argentina’s pharmacovigilance regulations was taken in 1999, with provision No. 3870. This requires that the biopharmaceutical industry (i.e. manufacturers and market authorization holders) appoint a professional staff-member to serve as liaison with the regulatory authorities.⁹¹ A year later, ANMAT published a set of guidelines for the integration of the local biopharmaceutical industry within the SNFVG, under provision No. 2438/2000.⁹² These guidelines included the encouragement of local manufacturers to detect and share information regarding ADRs, and to determine national pharmaco-epidemiological profiles of drug-related AEs. This provision also set the standard for ADR reporting by the biopharmaceutical industry in Argentina. Significantly, these proposals stipulated that manufacturers’ pharmacovigilance actions are altogether considered voluntary.⁹³

Important changes were made to Argentina’s pharmacovigilance regulations with the issuance of provision No. 5358 in 2012. This provision, which is mandatory for market authorization holders in Argentina, sets the responsibilities of the biopharmaceutical industry with regards to pharmacovigilance planning and actions, such as the submission of Periodic Safety Update Reports, RMPs, and good pharmacovigilance practice in vaccines.⁹⁴ Further changes were made in 2013 including the introduction of provision No. 2175/2013 which states that every person or body part of the marketing, distribution and dispensation biopharmaceutical products should have in place a system of traceability and monitoring.⁹⁵ Together with provision No. 727/2013 which states that medical products are to be sold only to healthcare professionals,⁹⁶ and provision No. 753/2012 which defines the proper labeling of OTC drugs,⁹⁷ these regulations strengthened Argentina’s drug regulatory framework. However, the successful enforcement and application of these provisions remains to be seen.

Other steps have also been taken to improve the safety and quality of medicines. For instance, under provision No. 3266/2013 ANMAT requires the local biopharmaceutical industry to implement GMP standards.⁹⁸ However, this provision is a ratification of the MERCOSUR resolution No. 20/11, which does not fully comply with the ICH's international GMP standard.

Biopharmaceutical industry's scope of involvement

Local manufacturers account for more than 50% of Argentina's biopharmaceutical industry.⁹⁹ The biopharmaceutical industry (local and multinational) contributes the highest share of ADR reports in Argentina: of 5,582 reports submitted in 2012, 4,505 (80.7%) originated from industry.¹⁰⁰ However, this does not necessarily mean that local manufacturers have developed international standards of pharmacovigilance. Given that the majority of multi-national biopharmaceutical companies that operate in Argentina have in place highly robust and comprehensive systems of pharmacovigilance it is a fair assumption that their share of ADR submissions is greater than that of the local companies. As described above, the responsibility of manufacturers for pharmacovigilance has only recently been expanded from voluntary submission of ADR reports to include the submission of RMPs and the requirement to manufacture under a localized version of GMP. Moreover, as of 2014 manufacturers are to establish a traceability system which allows for the tracking and monitoring of products and batches.¹⁰¹

Healthcare institutions and professionals scope of involvement

The voluntary reporting of adverse reactions amongst healthcare professionals in Argentina is very low. In 2012, of the total of 5,582 ADR reports submitted only 982 were from health professionals and institutions. Out of these 57% were by hospitals, 22% by universities, and 10% by the MoH. Recent research suggests that this low rate of reporting is due to a number of factors including: confusion over reporting and ignorance of the pharmacovigilance system; failure to appreciate the necessity and importance of ADR reporting; and even personal factors such as fear and guilt.¹⁰²

While the rate of reports by healthcare professionals is low, the rate of emergency room visits and hospitalization due to ADRs in Argentina is similar to the rate found in other developing and developed countries. Studies estimates that at least 10% of the admissions to all of the Internal Medicine wards in Argentina are ADR-related.¹⁰³

In order to raise awareness and knowledge about pharmacovigilance among healthcare professionals, ANMAT and the College of Pharmacists and Biochemists Federal Capital have collaborated in order to promote the creation of a Network of Pharmacovigilance for pharmacies in Buenos Aires, which aims to strengthen the role of the pharmacist.¹⁰⁴ Moreover, the College of Pharmacists is also launching a pharmacovigilance network that will include free training for professionals who want to join.¹⁰⁵

Patient awareness of pharmacovigilance

Patient awareness of the SNFVG as the competent authority for reporting ADRs is very low. In 2012, only 95 ADR reports originated directly from patients or relatives. This low rate could be the result of a number of factors. First, patients might still be accustomed to communicate any adverse events to their physicians, which might not always submit a formal ADR report. Second, patients may be confused and face difficulties filling in and submitting the relevant forms. For example, the issue of proper labeling gained attention recently with the entry into force of the registration and labeling requirements described in annex I of the provision No. 753/2012.¹⁰⁶

As mentioned, during 2013 ANMAT introduced an electronic system for ADR report submission, which is intended also to be used by patients. No statistics on the system's performance and usage has yet to be published. Nevertheless, the available data on submissions suggests that unless awareness of the pharmacovigilance system, existing and new ADR reporting mechanisms and the importance of reporting is raised among health professionals and patients it is unlikely that there would be a significant increase in the number of reports submitted even with a new reporting system.

Substandard and counterfeit medicines

Argentina (like many Latin American countries) has three drug classifications: i) innovative or original, ii) generics, iii) similars. Category one drugs are used as reference drugs for both generics and similars. The crucial difference between similars and generics is that the latter undergo bioequivalence testing and the former do not. They simply need to contain the same active ingredient, concentration, pharmaceutical form and dosage, but can differ in size, shape, packaging and period of activity. The use of similars is encouraged by the Argentine government with many health officials drawing little distinction between the similars

and bioequivalent tested generics. Argentina is only just beginning to introduce/implement regulations requiring bioequivalence testing for similars. The intention is to improve quality and safety of medicines, and align with international standards. The focus is first on certain therapeutic groups with “high health risk” including ARVs, immunosuppressants, antipsychotics, etc. Nevertheless, the large majority of biopharmaceuticals on the Argentine market are not bioequivalence tested and generics and similars are frequently referred to as being interchangeable. Consequently, there is a great risk for substandard medicines penetrating the supply chain.

TABLE 3 Argentina: Strengths and weaknesses

Pharmacovigilance aspects	Strengths	Weaknesses
Scope of regulation	<ul style="list-style-type: none"> Covers general aspects of risk profiling and monitoring activities, manufacturing and labeling 	<ul style="list-style-type: none"> Enforcement lacks funding and power No bioequivalence testing requirements; safety of non-referenced products e.g. similars remain untouched
The biopharmaceutical industry’s scope of involvement	<ul style="list-style-type: none"> Set to implement GMP and traceability system 	<ul style="list-style-type: none"> Most ADR reports originate from multinational companies Localized version of GMP, implementation is slow
Healthcare institutions and professionals scope of involvement	<ul style="list-style-type: none"> Voluntary reporting by institution or directly by professional Free training for HC professionals 	<ul style="list-style-type: none"> Very low rate of ADR reports Research suggest health care institutions and professionals are not aware of pharmacovigilance as an issue and not able to report
Patient awareness of pharmacovigilance	<ul style="list-style-type: none"> New electronic ADR submission being introduced to boost patient submissions 	<ul style="list-style-type: none"> Limited awareness of importance of pharmacovigilance and mechanisms for report submissions
Substandard and counterfeit medicines	<ul style="list-style-type: none"> Limited requirements for bioequivalence testing; third class of similars in place 	<ul style="list-style-type: none"> High rates of similars High rate of confusion between quality of generics as defined internationally and similars



3.2 Brazil

Overall pharmacovigilance framework

The national pharmacovigilance system in Brazil is a centralized one operating under the responsibility of the Brazilian health surveillance agency ANVISA. Under ANVISA, a special pharmacovigilance unit – UFARM – was created in order to establish the National Pharmacovigilance System. In 2001 the Brazilian MoH established the National Center for Drug Monitoring under the National Pharmacovigilance System.¹⁰⁷ In addition to ANVISA, some Brazilian states have established local pharmacovigilance centers, which carry out local pharmacovigilance duties.¹⁰⁸

In 2007, the National Center for Drug Monitoring implemented an automated National System for Sanitary Surveillance for receiving ADR reports from healthcare professionals and market authorization holders.¹⁰⁹ Since its establishment, the total number of ADRs received has increased steadily, from 2,200 reports in 2008 to 7,300 reports in 2013.¹¹⁰ Nevertheless, the general rate of ADR reports in Brazil is quite low.¹¹¹ To address these and other safety issues in 2013 the MoH launched the National Patient Safety Program.¹¹² This program aims to reduce the incidence of adverse events in Brazil by developing protocols, promoting training processes and the creation of a system of mandatory reporting of adverse events.¹¹³

Scope of regulation

In 2009, ANVISA issued “*Resolução – RDC n° 4*”, requiring market authorization holders to establish risk management systems, and submit RMPs, PVPs and Periodic Safety Update Reports. Taken together, these documents help ANVISA in compiling a drug’s risk profile.¹¹⁴ Furthermore, this resolution expanded the pharmacovigilance responsibilities required from the biopharmaceutical industry and market authorization holders, such as complying with GMP standards, appointing a professional responsible for establishing and maintaining a system of pharmacovigilance. The resolution also defines the enforcement actions that can be taken against companies in cases where non-compliance led to serious public health risks.¹¹⁵

In 2011, ANVISA issued further regulations which set obligations to add contra-indications and restrictions of use to drugs labels and leaflets.¹¹⁶ In addition, rules concerning health surveillance were revised by Decree 8077. Under this new rule, any AEs which occur during marketing or during clinical trials must be reported to ANVISA.¹¹⁷ However, this federal legislation does not require manufacturers and other players within the supply chain to follow specified guidelines in order to ensure their products’ safety and quality.

Biopharmaceutical industry’s scope of involvement

A study conducted in 2007 found that approximately half of biopharmaceutical manufacturers in Brazil had a pharmacovigilance system in place or were in the process of implementing one. However, most of these companies were multinationals.¹¹⁸ Indeed, the Brazilian biopharmaceutical industry is largely dominated by local companies and it is only recently that most of these companies have strengthened their pharmacovigilance activities, following the 2009 *RDC n° 4* requirements. Moreover, *Resolução RDC n° 17* stipulates that all manufacturers must comply with the minimum requirements for GMP implementation which are provided in the resolution.¹¹⁹ However, these are only partial requirements from the MERCOSUR GMP code and manufacturers are allowed to use alternative routes to ensure quality.¹²⁰

Looking at ADR reporting overall submissions by the biopharmaceutical industry is a relatively small share of total reporting. Of the 7,300 reports submitted to ANVISA in 2013 10.2% came from the pharmaceutical industry in Brazil (both local and multinational).¹²¹ Given that most multinational companies already have sophisticated pharmacovigilance systems in place it can be assumed that these companies represent a significant share of the reports submitted.

Healthcare institutions and professionals scope of involvement

In 2001, the National Center for Drug Monitoring initiated the “Sentinel Hospitals” Network, which is comprised of teaching hospitals that monitor the quality and safety of medicines, and promote the rational use of these medicines. These hospitals have become increasingly important to Brazil’s pharmacovigilance and ADR reporting infrastructure. This importance is illustrated by the growth in number of ADRs reported by these hospitals and their percentage share of total ADRs reported: in 2001 the annual sum of ADR reports for the entire population of Brazil was only 178; in 2002 the annual sum was 643, with the sentinel hospitals accounting for 36% of these reports. By 2005, the sentinel hospitals provided 50% of the total annual sum of ADR reports in Brazil; by 2010 it had reached 60%.¹²² These hospitals represent the main source of AE notifications, mainly due to their motivation and qualification in reporting on adverse events and technical complaints on health products.¹²³

In addition, a project named “Notifying Pharmacies” was created under a partnership between ANVISA and the Health Surveillance Center and Regional Pharmacy Council of each Brazilian state. The project was created with the intention to expand the number of pharmacies which will serve as an ADR reporting source.¹²⁴

The number of ADR reports has also increased as a result of the implementation of NOTVISIA, ANVISA’s electronic ADR reports submission system. Since its establishment, the total number of ADRs received by NOTVISIA is climbing steadily, from 2,200 in 2008, to 7,300 in 2013.¹²⁵

Still, recent research examining the knowledge and attitude of healthcare professionals towards suspected ADRs has concluded that the knowledge and awareness in hospital of ADRs was insufficient for almost half (43.7%) of health professionals, and that only slightly more than half of the researched professionals were able to identify and fill out reporting forms correctly.¹²⁶

Patient awareness of pharmacovigilance

The rate of ADR reports per 1 million inhabitants is low in Brazil. As mentioned, the annual sum of ADR reports for 2013 was only 7,300 for a population of over 199 million.¹²⁷ This is approximately 36.7 reports per 1 million inhabitants, which is low compared to the average rate within a sample of advanced health systems of about 300-400 ADR reports per 1 million inhabitants.¹²⁸

With regards to awareness of the online reporting system, studies examining the use of NOTVISIA by healthcare professionals and by patients found that 95% of patients and 68% of healthcare professionals were not aware of NOTVISIA. Furthermore, of those who were aware, only 1% of patients and 9% of healthcare professionals made use of NOTVISIA to report ADRs.¹²⁹

Substandard and counterfeit medicines

Up until 2003 Brazil (as in Argentina) drew a regulatory distinction between three different types of pharmaceuticals: Similar Drug Product, Generic Drug and Reference Drug Product.¹³⁰ Unlike Argentina, Brazil in 2003 introduced measures to effectively curtail the use and distribution of similars, replacing them with bioequivalent tested generic drugs by 2013-14.¹³¹ These regulations introduced in 2003 require all similar drugs to submit bioavailability data, pharmaceutical equivalence tests and a copy of GMP certificate issued by the national DRA, ANVISA. While this requirement was in 2009 somewhat watered down, phasing out the use of similar drugs is a significant achievement in the fight against substandard medicines. Indeed, the similars have long been a source of substandard and low quality pharmaceuticals. Following the introduction of the 2003 bioequivalence regulations, 21 similar products were immediately removed from the market by ANVISA.¹³² Quality studies of the similar drugs find substantial rates of low quality medicines. For instance, analysis of ferrous sulphate pills and oral solutions over a four year period found close to 40% of samples with significant discrepancies in quality, including grade of the principal active ingredient and precipitation.¹³³

TABLE 4 Brazil: Strengths and weaknesses

Pharmacovigilance aspects	Strengths	Weaknesses
Scope of regulation	<ul style="list-style-type: none"> Covers manufacturing and labeling, Risk management and profiling 	<ul style="list-style-type: none"> Safety issues with similares, generic manufacturing and counterfeits still exist
The biopharmaceutical industry's scope of involvement	<ul style="list-style-type: none"> Under current regulations, required to actively participate in pharmacovigilance activities 	<ul style="list-style-type: none"> Extremely low rate of ADR reports Manufacturers must adhere to minimum requirements of a localized GMP standard, or alternatives¹³⁴
Healthcare institutions and professionals scope of involvement	<ul style="list-style-type: none"> Establishment of "sentinel hospitals" and notifying pharmacies Increasing share of ADR reports 	<ul style="list-style-type: none"> Surveys and research finds health professional often have limited awareness of pharmacovigilance
Patient awareness of pharmacovigilance	<ul style="list-style-type: none"> Electronic ADR submission mechanism introduced to in part boost patient submissions 	<ul style="list-style-type: none"> Limited awareness of the importance of pharmacovigilance and mechanisms for report submissions
Substandard and counterfeit medicines	<ul style="list-style-type: none"> 2003 reform efforts have eliminated the similar drug class in Brazil 	<ul style="list-style-type: none"> Implementation and elimination of similares products is still ongoing



3.3 China

Overall pharmacovigilance framework

The Chinese MoH began pharmacovigilance activities during the late 1980s, with the establishment of a national center for ADR monitoring. A decade later, in 1998, China had joined the Uppsala International Drug Monitoring Program, and in 1999 the first regulations for ADR monitoring was officially published.¹³⁵ Since then China has experienced a gradual development of its pharmacovigilance regulatory framework.

The national pharmacovigilance system in China is decentralized. The SFDA is the regulatory authority under which the national center for ADR monitoring operates and supervises 34 provincial ADR monitoring centers and 333 municipal centers, which are set up in China's 32 provinces and municipalities.¹³⁶ In 2004 a pilot project for an on-line reporting system was initiated.¹³⁷ This system became operational only recently.

Scope of regulation

ADR report monitoring regulations were recently revised in 2011 by the MoH.¹³⁸ The revised regulation thoroughly expands both the scope of practice and the legal framework of pharmacovigilance in China.¹³⁹ These regulations set the roles of government bodies as well as the responsibilities of the biopharmaceutical industry and market authorization holders including the need for submission of Periodic Safety Update Reports and domestic and internationally published ADR reports within a defined timeframe. Moreover, the regulations clarify the potential liabilities of drug providers, that is, manufacturers and medical institutions. Failure to meet the minimum requirements of the defined pharmacovigilance activities can result in a fine of up to 30,000 Yuan (approximately \$4,800).¹⁴⁰ In addition, providers can be held liable in cases when a violation of pharmacovigilance provisions has resulted in harm caused to patients.¹⁴¹

With regards to manufacturing safety and quality, in 2011 the Chinese MoH issued a set of regulations for the implementation of a localized version of GMP standards, which also provided guidelines for ADR monitoring and reporting. Further measures were taken with

regards to raising quality and safety standards in biopharmaceutical manufacturing through the 2013 publication by the MoH of a "Drug Quality Management Practice".

However, the implementation of these standards on a national level is far from complete with enforcement activities and mechanisms lagging behind. For example, article 59 of the "Adverse Drug Reaction Reporting and Monitoring Management Approach" regulation from 2011 stipulates the minimum pharmacovigilance criteria for the biopharmaceutical industry, as follows: (a) the appointment of a part-time staff for the monitoring of ADR reports; (b) the investigation, evaluation and treatment of ADR reports, and (c) serious ADR reports. Failure to comply with these requirements can result in a fine of up to \$500,000.¹⁴² However, article 58 sets a much higher standard, such as appointing a full-time specialized member of staff for ADR monitoring, establishment of an ADR reports archive, and the submission of Periodic Safety Update Reports. Yet failure to comply with these criteria could only result in a fine of up to \$5,000.¹⁴³

Biopharmaceutical industry's scope of involvement

Up until 2011, the Chinese ADR monitoring system depended on spontaneous reporting by market authorization holders. Since reporting ADR's was not mandatory for the biopharmaceutical industry, its share in the annual sum of ADR reports was small, accounting for only 10% of the reports in 2004. Since then this share has increased significantly, accounting for 258,000 or approximately 19% of the annual sum of 1,317,000 ADR reports in 2013.¹⁴⁴ However, the SFDA considers the overall number of reports submitted by the biopharmaceutical industry to be relatively low.¹⁴⁵ Manufacturers and the local industry became more involved in pharmacovigilance after 2011. After observing high rates of ADRs in conjunction with the use of several biopharmaceutical products, the SFDA organized interviews with the relevant manufacturers, urging them to develop risk control measures. These manufacturers were incorporated into the scope of GMP inspections carried out by the provincial/municipal authorities.¹⁴⁶ Furthermore, the SFDA took relevant measures in light of potential risks, such as orders to change safety information on

drugs' leaflets, and revocation of drugs which demonstrated serious health risks.¹⁴⁷

Healthcare institutions and professionals scope of involvement

In 2012, the share of ADR reports which originated from hospitals was 74.8%. Despite this figure awareness amongst health professionals as to the importance and necessity of pharmacovigilance remains relatively limited. A number of factors have been identified as contributing to this including: lack of resources (in both funds and time) for proper training, and the lack of experts to conduct such training.¹⁴⁸ In addition, ADR reporting by healthcare professionals can also be hindered by the relevant regulations which were set to encourage them. For instance, a medical institution will be held liable for a patient who was harmed due to drug-use, if the institution did not fully comply with the requirements set in existing regulation.¹⁴⁹ Thus, paradoxically doctors might be encouraged not to rush to report ADRs experienced during hospitalization in that particular institution if there's a risk the institution could be found at fault.

Patient awareness of pharmacovigilance

Chinese patients are generally unaware as to how to report ADRs directly to the national center for ADR monitoring via the electronic system. This is illustrated by the percentage of ADR reports coming from patients. In 2012, the share of ADR reports which originated directly from patients was 0.8%.¹⁵⁰

Substandard and counterfeit medicines

The Chinese pharmaceutical market has long been associated with very high levels of both counterfeit and substandard medicines. Indeed, China is in many respects the world leader in counterfeit medicines. For instance, in 2006 close to half of all seizures of counterfeit Viagra were made in China.¹⁵¹ In addition, both substandard and counterfeit medicines manufactured in China have spread to other parts of the world, even Europe and North America. More recently the persistence of counterfeit and substandard drugs has been highlighted in numerous local news reports.¹⁵²

TABLE 5 China: Strengths and weaknesses

Pharmacovigilance aspects	Strengths	Weaknesses
Scope of regulation	<ul style="list-style-type: none"> • Generally covers responsibilities regarding manufacturing and risk profiling • Covers non-compliance 	<ul style="list-style-type: none"> • Implementation is very slow • Enforcement is lenient and lacks power • Many safety issues regarding substandard and counterfeits remain unattended
The biopharmaceutical industry's scope of involvement	<ul style="list-style-type: none"> • Increasing share of ADR reports • Set to implement localized GMP standard 	<ul style="list-style-type: none"> • Total number of reports still low • Many manufacturers enter the list of constant inspection by the SFDA
Healthcare institutions and professionals scope of involvement	<ul style="list-style-type: none"> • Provide the highest share of ADR reports 	<ul style="list-style-type: none"> • Lack of funds for training • HC institutions and professionals held liable for drug-use related harms – may actually discourage reporting
Patient awareness of pharmacovigilance	<ul style="list-style-type: none"> • Electronic ADR submission mechanism introduced 	<ul style="list-style-type: none"> • Limited awareness of importance of pharmacovigilance and mechanisms for report submissions • Low levels of ADR reporting from patients – less than 1%
Substandard and counterfeit medicines	<ul style="list-style-type: none"> • A number of regulations in place to ensure quality and safety of medicines 	<ul style="list-style-type: none"> • China is home to the largest counterfeit and substandard market in the world



3.4 Indonesia

Overall pharmacovigilance framework

Pharmacovigilance in Indonesia is still in its infancy, with basic regulations only having been introduced in recent years. Currently the national pharmacovigilance system is centralized under the authority of the National Agency of Drug and Food Control. Founded in 2001, this agency is responsible for the implementation of a national pharmacovigilance policy, as set out in its five years (2010-2014) “Strategic Objectives”.¹⁵³

The policies which concern pharmacovigilance contain a wide variety of actions, such as: the expansion of control over therapeutic products; the implementation of international standards; the development of monitoring tools; the dissemination of pharmacovigilance guidelines through workshops and symposiums; and the development of an electronic system for the analysis of signals.¹⁵⁴

The task of controlling and monitoring the safety of drugs falls on the Sub-Directorate of Surveillance and Risk Analysis of Therapeutic and Household Healthcare Products within the Distribution Control of Therapeutic and Household Healthcare Products Directorate.¹⁵⁵

The drug safety review process (which the Sub-Directorate of Surveillance and Risk Analysis of Therapeutic and Household Healthcare Products is responsible) consists of a number of pharmacovigilance related activities including: the collection and the review of all the data from the different reports (AEs/ADRs, risk-benefit ratio reviews, proposed actions); signaling and characterization of risk; issuing of statements to physicians and the biopharmaceutical industry; and recommendation for regulatory action.¹⁵⁶

In 2011 an electronic system for ADR report submissions was launched in a test phase.¹⁵⁷ At the beginning of 2014 the system was publicly launched, with a dedicated site which allows the online submission of ADR report by healthcare professionals and the biopharmaceutical industry, and the presentation of drug-related safety issues

and updates.¹⁵⁸ Efforts are also being taken to upgrade the reporting format into E2B (ICH standardized format), thus enabling the sharing of pharmacovigilance information with international drug monitoring programs.¹⁵⁹

Scope of regulation

Indonesia’s first pharmacovigilance regulations were introduced in 2008. Article 22 of the MoH decree No. 1010/Menkes/Per/XI/2008 on Drug Registration states that re-evaluation of a marketed drug will be performed if post-marketing surveillance demonstrates that (1) the risks outweighs the benefit from the drug; (2) the drug shows no significant effectiveness; (3) the drug does not meet bioequivalence requirements; (4) there is a need to improve the drug’s composition and reformulation.¹⁶⁰

In 2010 further measures were introduced with the issuing of the MoH decree No. 1799/Menkes/Per/XII/2010. Article 9 of this regulation stipulates that the biopharmaceutical industry must meet the requirements for CPOB (a localized and much simplified version of the GMP standard), and also “must conduct pharmacovigilance”. Pharmacovigilance is here defined in accordance with the WHO definition.¹⁶¹

In 2011 the National Agency of Drug and Food Control issued decree “HK.03.1.23.12.11.1.10690”, which serves to implement the MoH regulation from 2010. This regulation broadens the scope of pharmacovigilance activities as defined in the 2010 regulation, to include the surveillance and reporting on changes in the benefit-risk profiles of drugs and quality issues that may impact the safety of drugs.¹⁶²

The agency also issued guidelines for the implementation of GDP in 2012.¹⁶³ Implementation of these standards is far from complete, but overall the trend is positive and up from 5% of market authorization holders which had implemented the localized GDP standard in 2010 to 30% in 2012.

Biopharmaceutical industry's scope of involvement

The biopharmaceutical industry in Indonesia, largely composed of local generic manufacturers, has been slow in implementing pharmacovigilance standards and activities. The average of ADR reports submitted to the National Agency of Drug and Food Control is low at approximately 550 annual reports. About 50% of these originate from the biopharmaceutical industry. However, 70% of these reports are international reports compiled from international sources with only 30% being strictly local.¹⁶⁴

One reason for this is that pharmacovigilance standards and activities became mandatory only recently. Furthermore, the government body charged with enforcement of these MoH regulations (Sub-Directorate of Surveillance and Risk Analysis of Therapeutic and Household Healthcare Products) has been criticized for having a lack of funds and professional staff.¹⁶⁵

Healthcare institutions and professionals scope of involvement

Of the annual average of approximately 550 ADR reports, about 50% come from healthcare professionals within hospitals and pharmacies.¹⁶⁶ This means that from 2.3 reports submitted per 1 million inhabitants in Indonesia, about only 1 comes from healthcare professionals. While a share of 50% from the total sum of reports is respectable in absolute terms, this figure is very low when comparing to the international average of annual reports of around 300-400 reports per 1 million inhabitants in selection of developed health systems.¹⁶⁷

Similar to China, healthcare professionals' awareness of pharmacovigilance activities is relatively limited. This is due to both a lack of resources (in both funds and time) for proper training as well as a paucity of experts to conduct such training. Indeed, the number of physicians, midwives and beds for the Indonesian population is in itself quite low and medical staff is often under-qualified.¹⁶⁸

This challenge has been recognized by the National Agency of Drug and Food Control. The agency has placed an emphasis upon pharmacovigilance training and the dissemination of pharmacovigilance knowledge within healthcare facilities, through workshops and symposiums, periodical publication of a pharmacovigilance bulletin (Buletin Berita Meso) and the dissemination of safety issues and warnings via a designated website.

Patient awareness of pharmacovigilance

Patient awareness of pharmacovigilance activities is minimal. This is mainly the result of the lack of a national system. Patients currently do not have any direct means of contacting and reporting ADRs to the national drug authorities. The new system for the electronic submission of ADR reports is designated only for healthcare professionals and for manufacturers. Furthermore, regulation regarding pharmacovigilance in drug labeling (i.e. 'who to report to' information) is lacking.¹⁶⁹ Thus, the majority of reports of adverse reactions (if reported at all) are communicated by patients directly to healthcare professionals within institutions. However, since many Indonesians do not have easy access to health care, it is likely that under-reporting is quite significant.¹⁷⁰

Substandard and counterfeit medicines

Counterfeit and substandard medicines are a serious problem in Indonesia. Estimates by the International Pharmaceutical Manufacturers Group in Indonesia place counterfeit medicines as making up 10% of the overall market with a value of circa USD 200 million.¹⁷¹ Others have estimated that the total cost of the counterfeit drugs market to the Indonesian Government has been significant at USD 4.75 billion between 2005-2010.¹⁷²

TABLE 6 Indonesia: Strengths and weaknesses

Pharmacovigilance aspects	Strengths	Weaknesses
Scope of regulation	<ul style="list-style-type: none"> • Some improvement in implementation of GMP and GDP but these are localized not international standards 	<ul style="list-style-type: none"> • Implementation of strategic objectives is slow • Supervising department under-manned • Over-simplified definition of pharmacovigilance activities • Current regulation defines broad responsibilities for market authorization holders
The biopharmaceutical industry's scope of involvement	<ul style="list-style-type: none"> • Responsible for risk profiling 	<ul style="list-style-type: none"> • Very low rate of ADR reports, with low levels coming from local manufacturers • Lack of incentives to comply with regulations • Regulations favorable for local manufacturing
Healthcare institutions and professionals scope of involvement	<ul style="list-style-type: none"> • Health professionals responsible for circa 50% of ADRs • Awareness raising campaigns in place 	<ul style="list-style-type: none"> • Under-qualified medical staff • Low rate of awareness to pharmacovigilance in general • No relevant regulation regarding HC institutions
Patient awareness of pharmacovigilance	<ul style="list-style-type: none"> • Electronic ADR submission mechanism introduced but is not available to patients 	<ul style="list-style-type: none"> • Limited awareness of importance of pharmacovigilance • No direct mechanisms for report submissions
Substandard and counterfeit medicines	<ul style="list-style-type: none"> • Local GMP standards are a first step in focusing on quality 	<ul style="list-style-type: none"> • Counterfeit and substandard medicines estimated at making up a significant percentage of the drug market



3.5 Mexico

Overall pharmacovigilance framework

The Mexican pharmacovigilance system is decentralized. The national authority is COFEPRIS, which was founded by the Mexican MoH in 2001 and is the Mexican drug regulatory authority.¹⁷³

With regards to pharmacovigilance activities there are several important institutions including the National Pharmacovigilance Center (*Centro Nacional de Farmacovigilancia*). This center is responsible for the collection and evaluation of ADR reports from biopharmaceutical manufacturers, distributors, and healthcare professionals, as well as for providing relevant feedback.¹⁷⁴ In addition, each Mexican state has established a pharmacovigilance designated center, and many public and private hospitals have done the same.¹⁷⁵ Taken together, all the bodies which are acting to enforce and promote pharmacovigilance are referred to as the Mexican national pharmacovigilance program (*Programa Permanente de Farmacovigilancia*).¹⁷⁶

In recent years COFEPRIS has acted to promote pharmacovigilance activities by the biopharmaceutical industry and healthcare professionals. However, pharmacovigilance activities are still relatively under-developed. For example, looking at ADR reports per population Mexico has a relatively low reporting rate. Over 10 years (2001-2011), the National Pharmacovigilance Center received 132,362 notifications on adverse events; on average 13,000 per year.¹⁷⁷ Calculated on a per population basis this is 116 reports per million population. This is below the international average of 300-400 ADR reports per million population for developed health systems.¹⁷⁸

Scope of regulation

Subsequent to the establishment of COFEPRIS, the first pharmacovigilance regulation published was the *Norma Oficial Mexicana NOM-220-SSA1-2002* in 2002, which entered into force in 2005.¹⁷⁹ This regulation has set the legal framework for the national practice of pharmacovigilance, by defining the roles and responsibilities of the national authorities, healthcare institutions and professionals, clinical research units, and the biopharmaceutical industry.

A decade later the MoH published the *Norma Oficial Mexicana NOM-220-SSA1-2012*, which entered into force in 2013. This regulation has broadened the scope of the national standard for the implementation and operation of the framework introduced in 2002. More importantly, by broadening the scope of pharmacovigilance practice within hospitals, this standard has brought Mexico (at least on paper) closer to the good pharmacovigilance practice guidelines issued by PAHO in 2011.¹⁸⁰ Specifically, this regulation included the following: a requirement that hospitals establish a pharmacovigilance designated unit with a professional profile, to participate in phase IV trials ordered by the authorities, and the collecting and archiving of all ADR-related information.¹⁸¹ Furthermore, spontaneous reports by patients are allowed, although an online system for ADR reporting has not yet been established.

In addition, since 2013 COFEPRIS has published seven pharmacovigilance guidelines for specific practical issues within hospitals and the biopharmaceutical industry. Among them: a guide for the integration of pharmacovigilance reports (*Guía de Farmacovigilancia para la Integración del Informe*); a guide for pharmacovigilance in clinical research (*Guía de Farmacovigilancia en Investigación Clínica*); and a guide for the establishment and operation of National Pharmacovigilance Center-coordinated pharmacovigilance centers within hospitals (*Guía para la Instalación y Operación de los Centros Institucionales (CI) y Unidades de Farmacovigilancia Hospitalarias (UFVH) coordinadas por el CNFV*).¹⁸²

Biopharmaceutical industry's scope of involvement

Since 2002, the biopharmaceutical industry in Mexico is required to: appoint a pharmacovigilance officer responsible for the registration, analysis and submission of all ADR reports from all relevant sources; creating and submitting Periodic Safety Update Reports (in accordance with ICH guidelines); and training medical representatives on the regulation, methods and objectives of pharmacovigilance.

The 2012 regulation added the submission of RMP's and safety during clinical trials reports to market authorization holder's responsibilities. In addition, in 2013 the Mexican government published the *Norma Oficial Mexicana NOM-164-SSA1-2013*, which compels all market authorization holders to comply with the requirement of the GMP standard.¹⁸³ This resolution revises and expands the decade-old *NOM-059-SSA1-1993* which established the requirements for manufacturing drugs under the localized GMP standard.¹⁸⁴ (Although a localized version, by international standards Mexico's GMP requirements are quite robust.) Currently, many local manufacturers are still in the process of implementation and compliance.¹⁸⁵

Healthcare institutions and professionals scope of involvement

Of the annual ADR reports on average 15%-20% originate from state pharmacovigilance centers and another 10%-20% originate from clinical research units with only 5%-10% from healthcare institutions via their pharmacovigilance centers.¹⁸⁶

A fundamental reason for this is the limited knowledge and awareness among medical and health professionals of pharmacovigilance in general. Research suggests that less than 40% of Mexican doctors and nurses are aware of the field of pharmacovigilance and less than 20% are aware of the need to report ADR's to COFEPRIS.¹⁸⁷

Another contributing factor is that a large percentage of ADR reports are filed by hospital pharmacies and not by medical staff. Studies show that up to 80% of the reports are attributed to pharmacies with only 15% attributed to physicians.¹⁸⁸

Patient awareness of pharmacovigilance

Mexican patient's awareness of pharmacovigilance is somewhat higher than in many of the other countries surveyed in this report. However, generally speaking it is still quite low. For example, research suggests that less than 20% of patients are aware of pharmacovigilance centers and their duties.¹⁸⁹ This low figure could be the result of a number of factors. For instance, the significant deviation in ADR reports between different hospitals suggests that while generally

quite low, medical staff's pharmacovigilance awareness levels varies greatly from institution to institution.¹⁹⁰ This variety in turn affects patient awareness and rate of reporting.

Another factor relates to the difficulty in submitting reports. For example, according to paragraph 7.4 and 7.5 of the *Norma Oficial Mexicana NOM-220-SSA1-2012*, while healthcare professionals are encouraged to submit ADR reports electronically, spontaneous reporting by patients is restricted from the electronic system.¹⁹¹ Second, regulations regarding pharmacovigilance in drug labeling such as the inclusion of ADR reporting information is lacking.⁵

Substandard and counterfeit medicines

Counterfeit and substandard medicines have long been a threat to public health and patient safety in Mexico. The Mexican Association of Pharmaceutical Research Industries has estimated that counterfeits cost the country's drug industry around USD 700million per year which is equivalent to roughly 8% of the total drug market.¹⁹³

Substandard medicines have traditionally made up a significant part of the Mexican drug market through the *similares* drug class. Like other Latin and Central American countries Mexico had a formalized regulatory class of drugs for *similares*. In 2002 this made up an estimated 60% of the drug market.¹⁹⁴ A national debate over the quality and safety of *similares* between 2002-2005 resulted in amendments to the General Law on Health. Article 376 now requires all generics to undergo bioequivalence tests and all generics registered prior to 2005 to be re-registered using bioequivalence tests by 2010. The re-registration of *similares* seems to have been completed, however complete removal from the market is still ongoing.

TABLE 7 Mexico: Strengths and weaknesses

Pharmacovigilance aspects	Strengths	Weaknesses
Scope of regulation	<ul style="list-style-type: none"> • Current regulations define the responsibilities of industry and institutions • Reporting infrastructure in place • Spontaneous reporting by patients allowed 	<ul style="list-style-type: none"> • Pharmacovigilance activities are scarce, rate of reports is low
The biopharmaceutical industry's scope of involvement	<ul style="list-style-type: none"> • Pharmacovigilance officer responsible for risk profiling by ICH standard • Should implement localized (but still quite comprehensive) GMP by 2014 	<ul style="list-style-type: none"> • GMP standard still not universal
Healthcare institutions and professionals scope of involvement	<ul style="list-style-type: none"> • Many public and private hospitals have established pharmacovigilance centers 	<ul style="list-style-type: none"> • Very low rate of ADR reporting from HC institutions • Low awareness of pharmacovigilance • Large variety in awareness and pharmacovigilance capacity e.g. between hospital to hospital
Patient awareness of pharmacovigilance	<ul style="list-style-type: none"> • Patient reporting allowed 	<ul style="list-style-type: none"> • Limited awareness of importance of pharmacovigilance • No electronic ADR reporting system in place for patients
Substandard and counterfeit medicines	<ul style="list-style-type: none"> • Law introduced requiring re-registration of all similars products • Elimination of similars class of drugs in Mexican regulations 	<ul style="list-style-type: none"> • Some similars products still on the market



3.6 Russia

Pharmacovigilance framework

The pharmacovigilance system in Russia is decentralized. The relevant regulatory authority is the federal scientific center of expertise of medical products (Roszdravnadzor), which oversees the functioning of 54 regional pharmacovigilance centers. Roszdravnadzor is responsible for the publishing of pharmacovigilance practice guidelines, issuing warnings on drug safety issues, and training of medical staff.¹⁹⁵

In 2009, Roszdravnadzor introduced an electronic ADR reports submission system (AIS Roszdravnadzor) which tripled the number of reports submitted annually.¹⁹⁶ However, the rate of ADR reports per 1 million inhabitants remains low. Although electronic reporting significantly increased the number of reports over a period of 3 years, the annual rate for 2012 was only 88 reports per 1 million inhabitants, less than a third of the international average of 300-400 reports per million population for a selection of advanced health systems.¹⁹⁷

Scope of regulation

Up until 2010, drug safety and quality control relied mainly on obligatory Periodic Safety Update Reports from market authorization holders. Yet the rate of these report submissions was low; in 2009 there were only 309.¹⁹⁸ In 2010 the federal government enacted the federal law No 61-FZ "On the Circulation of Drugs".¹⁹⁹ This law increased the responsibility of the biopharmaceutical industry over the possible adverse reaction of their drugs, and toughened Roszdravnadzor's penalties for non-compliance to its pharmacovigilance guidelines.²⁰⁰ As a result, the annual number of safety reports climbed from 309 reports submitted in 2009 to 1,231 submitted in 2011.²⁰¹

A locally adapted version of EU GMP guidelines was recently adopted,²⁰² although the implementation of this localized GMP standard has been postponed several times, most recently to 2016.²⁰³

In May 2013 a draft agreement on the circulation of medicines was proposed within the Eurasian Customs Union. This draft agreement aims at

ensuring the ability to access safe, effective and quality medicines throughout the Customs Union based on international standards. Within it significant regulatory steps are proposed within the field of pharmacovigilance, as well as in the fields of registration, pricing and manufacturing. The acceptance of this proposal by the union member states, as well as the implementation of its content, remains to be seen.

Biopharmaceutical industry's scope of involvement

Local biopharmaceutical manufacturers have been slow in implementing pharmacovigilance measures. Much of this slow progress is the result of a fast-moving legislative and regulatory environment. Since its enactment in 2010, the federal law No. 61-FZ has undergone more than 90 amendments. Measures such as GMP compliance have been postponed.

Healthcare institutions and professionals scope of involvement

In 2012, only 10,800 ADR reports were received by Roszdravnadzor, for the entire Russian population. It is estimated that the two main reasons for this low rate of ADR reporting is lack of time and insufficient knowledge.²⁰⁴ Currently, the bulk of the responsibility for reporting ADR's is placed on the biopharmaceutical industry and market authorization holders,²⁰⁵ since medical institutions and healthcare professionals are under no specific obligation to submit such reports. The MoH order No. 757 from 2010, which "establishes the rules for monitoring the safety of drugs for medical use in circulation in the territory of the Russian Federation", specifies that the monitoring is based on spontaneous reports by healthcare professionals, by patients and by distributors, and by mandatory safety reports from the biopharmaceutical industry.²⁰⁶

Health professionals' awareness of pharmacovigilance activities and the importance of ADR reporting is low.²⁰⁷ Roszdravnadzor is currently acting to improve this, mainly through workshops and publications of a special bulletin, of drug-related safety issues, warnings, and relevant scientific research in the field.²⁰⁸ However, its effect, if measured by ADR reports, has so far not been significant.

Patient awareness of pharmacovigilance

Patient awareness of Roszdravnadzor as the competent authority for drug safety surveillance is limited. Much like with Indonesia and China, patient awareness depends greatly upon the knowledge and qualifications of physicians and health care professionals. This is mainly the result of the lack of a national system. Currently patients have no means of directly contacting and reporting ADRs to Roszdravnadzor. Thus, the majority of reports are communicated to healthcare professionals within institutions.²⁰⁹ Furthermore, regulation regarding pharmacovigilance in drug labeling (i.e. 'who to report to' information) is lacking.²¹⁰ There is also significant variation between urban and rural hospitals with regards to ADR reports.

Substandard and counterfeit medicines

Substandard and counterfeit medicines are a significant challenge to drug standards as well as patient health. Estimates suggest that substandards and counterfeits account for around 12% of the total Russian drug supply.²¹¹ Public awareness of this problem is growing. For instance, a 2008 opinion poll showed that roughly 40% of Russians were concerned that they were being exposed to substandard or low quality medicines.²¹² Furthermore, in 2006 *The Lancet* described widespread Russian practices whereby

drugs manufacturers, who operate legitimate pharmaceutical production businesses by day, would dedicate time at night to "producing extra quantities of a certified drug that does not pass through quality control, or sophisticated copies of well-known drugs are produced, often with reduced levels of expensive active ingredients". It also said that 70% of substandard medicines and counterfeits in Russia were produced domestically, and an estimated 70% of them were copies of foreign medications.²¹³

These illicit practices aside, there are wider quality concerns within pharmaceutical manufacturing. To begin with, very few Russian pharmaceutical manufacturers adhere to internationally recognised standards of GMP. According to 2010 estimates out of 400 Russian pharmaceutical companies operating in the country only 40 met international GMP standards.²¹⁴ The Russian Government and DRA has recognized the quality and safety of medicines as a key issue for regulators to address yet this still remains a significant challenge to patient safety and public health.²¹⁵

TABLE 8 Russia: Strengths and weaknesses

Pharmacovigilance aspects	Strengths	Weaknesses
Scope of regulation	<ul style="list-style-type: none"> • Since 2010, increased responsibilities of market authorization holders • Covers non-compliance 	<ul style="list-style-type: none"> • Many safety issues regarding generic manufacturing remain unattended • Compliance with GMP standards postponed multiple times • Enforcement lacks funds and power • Changing legislative environment • High levels of substandard and counterfeit medicines
The biopharmaceutical industry's scope of involvement	<ul style="list-style-type: none"> • Responsible mainly for submitting periodic safety reports 	<ul style="list-style-type: none"> • Implementation and compliance with pharmacovigilance regulations is slow • Only multinational companies hold GMP certificate
Healthcare institutions and professionals scope of involvement	<ul style="list-style-type: none"> • Reporting is voluntary under regulations 	<ul style="list-style-type: none"> • Very low rate of ADR reports • Low awareness of pharmacovigilance
Patient awareness of pharmacovigilance	<ul style="list-style-type: none"> • Potential for electronic ADR mechanism to be made available for patients 	<ul style="list-style-type: none"> • Limited awareness of importance of pharmacovigilance
Substandard and counterfeit medicines	<ul style="list-style-type: none"> • Localized GMP code introduced 	<ul style="list-style-type: none"> • High levels of counterfeit and substandard medicines • High levels of locally manufactured substandards



3.7 Turkey

Pharmacovigilance framework

Pharmacovigilance in Turkey is still in its infancy, though major steps have been taken recently in establishing a legal framework. The pharmacovigilance system in Turkey is centralized under TÜFAM which is responsible for the national collection and assessment of ADR reports and evaluation of potential health risks. Turkey is also an active member of the WHO drug monitoring program since 1987.

Since 2005 hospitals have been required to assign a healthcare professional to function as a “contact point” for pharmacovigilance activities within the hospital.²¹⁶ These contact points are responsible for the accumulation and submission of all AE/ADR reports to TÜFAM, and for the training of the hospital’s medical staff on pharmacovigilance. In 2010 there were 329 contact points working at 317 hospitals, according to TÜFAM records. Most of them are located in large cities such as Istanbul (35.26%) and Ankara (11.25%).²¹⁷ There is relatively little coverage of rural or non-urban areas. Furthermore, these contact points are also fully employed in the hospital and their pharmacovigilance duties are on top of their existing workload. Only 4.56% of adverse effects that reached TÜFAM between 2008 and 2009 were reported by pharmacovigilance contact points.²¹⁸

Up until recently, ADR reporting was compulsory for market authorization holders and voluntary for healthcare professionals. In 2012 a pilot project (sponsored by the WHO and the Uppsala Drug Monitoring Center) tested a new software module intended for spontaneous ADR reporting by patients.²¹⁹ Furthermore, in 2013 the social security agency initiated a web-based prescription system with the intention of simplifying the control over use and traceability of these drugs.²²⁰

Scope of regulation

In 2005 the Turkish Ministry of Health (Sağlık Bakanlığında) published the “Regulation on the Monitoring and Assessment of the Safety of Medicinal Products for Human Use”²²¹ and the “Pharmacovigilance Guide for Market

Authorization Holders”.²²² These regulations defined the pharmacovigilance responsibilities of all relevant stakeholders. Under this regulation market authorization holders are compelled to provide all the safety information regarding their products, such as safety reports, AE reports from clinical trials conducted in Turkey or abroad, and information from the relevant medical literature.²²³ Furthermore, biopharmaceutical manufacturers are compelled to assign a doctor or a pharmacist for the full-time position of a medicinal product safety officer, who is in charge of delivering the said information to the authorities.²²⁴

As mentioned, this regulation also compels healthcare institutions to assign a doctor or a pharmacist to a similar position, called “contact point”. This person is charged with the gathering of all the pharmacovigilance data from the hospital staff and submitting it to the authorities.²²⁵

In 2012, an amendment to regulation No. 28226 has distributed the different roles under the responsibility of the Biopharmaceutical and Medical Devices Agency (Türkiye İlaç ve Tıbbi Cihaz Kurumu),²²⁶ and contributed to the formation of a risk management department and a subordinate pharmacovigilance risk management unit, which is responsible for, amongst other items, the professional pharmacovigilance training of medicinal product safety officers and hospital contact points.²²⁷

Another major step in the strengthening of the Turkish pharmacovigilance legislative framework was taken in 2014, with the entry into force of the “Drug Safety Regulation”.²²⁸ The new regulation expands the responsibilities of the medicinal product safety officers within biopharmaceutical manufacturers, with the obligatory submission of risk management plans (which includes a safety profile of the drug), measures of risk prevention or minimization and the effectiveness of these measures.²²⁹ This regulation also stipulates that products which require additional monitoring will be labeled with a black triangle (as stated in the EU directive 2001/83/EC). In addition, directions for communicating ADR reports to TÜFAM will be added to all drug labels.

Biopharmaceutical industry's scope of involvement

There are currently more than 300 biopharmaceutical companies operating in Turkey; 52 of them are international companies. Of these international companies, 11 manufacture biopharmaceutical products in Turkey.²³⁰

Under article 27 of the latest regulation from 2014, all market authorization holders must ensure the continuous monitoring of pharmacovigilance data, the minimization of risk, and the submission of all relevant data to TÜFAM under the defined timeframe. In addition, since 2013 biopharmaceutical companies must submit a risk management plan to the Risk Management Department of the Turkish Biopharmaceuticals and Medical Devices Agency, during preauthorization and post-authorization phases or when a safety concern with a medicinal product at any stage of its life cycle is identified. Most of the generic manufacturers in Turkey comply with a localized version of the GMP standard, quality inspections and stability and bioequivalence tests.

Healthcare institutions and professionals scope of involvement

Up until 2010, Turkey's ADR report rate was extremely low, ranging from a total of only 300 in 2006 to 500 in 2009. In spite of an increase of almost 70% in the number of ADR reports in 2011, the total rate remains very low with regards to the Turkish population of 74 million, with only 14.8 reports per 1 million population.²³¹ This is very low when comparing to the international standard of 300-400 reports per million population in advanced health systems for a selection of countries.²³²

There are a number of reasons explaining this low rate of reporting. For instance, the lack of awareness to and knowledge of the practice of pharmacovigilance within healthcare facilities is in all likelihood a major contributing factor. Studies indicate that a large proportion of medical staff has encountered ADRs in patients yet very few have reported it.²³³ Moreover, although the necessity of reporting ADRs to the authorities is relatively well-acknowledged few health professionals are aware of the procedure.²³⁴ The introduction of new directions for safety information and contact information labeling on biopharmaceutical packaging is meant to help address this issue.²³⁵

In addition, Turkey has recently initiated the practice of drug safety surveillance and informed consent forms. A patient which begins a treatment with a certain drug is requested to sign on an informed consent form, which presents the patient with information regarding the known risks of the drug. The physician is required to fill out a "drug safety surveillance form" every three months during the treatment.²³⁶

Patient awareness of pharmacovigilance

Despite recent reform efforts, patient awareness of pharmacovigilance and ADR reporting remains low. One major contributing factor to this phenomenon is that until recently ADR reporting was possible only for healthcare professionals. The electronic system (supported by the WHO drug monitoring programme) is still under pilot testing. Moreover, health professionals lack of awareness of the importance of reporting ADRs to TÜFAM, and the low rate of reports by hospital "contact points", further explains the low awareness to the importance of reporting ADRs among patients.

Substandard and counterfeit medicines

Turkey too, has serious problems with counterfeit and substandard drugs. According to former Turkish policeman and Interpol operative Cengiz Gümüştü, Turkey is the fourth largest market for counterfeit medicines in the world in terms of the number of arrests.²³⁷ In fact, the problem of counterfeit drugs is so widespread that the Turkish Government in 2010 (first broached in 2009) introduced tracking and tracing system (ITS) requiring market authorization holders to place a two-dimensional barcode on their drugs.²³⁸ This system is currently operational and used by 339 manufacturers and over 24,000 pharmacies.²³⁹ Furthermore, the existence of bartering medicines between small-scale pharmacists (which make up the majority of Turkish pharmacists) makes it very difficult to track and monitor the selling and dispensation of particular medicines. This makes pharmacovigilance monitoring and follow-up exceedingly difficult. Batches which are found to have been faulty or tampered with cannot easily be tracked as their whereabouts can have changed numerous times. Similarly, many medicines and pharmaceutical drugs can be purchased without prescriptions even though this is technically illegal.²⁴⁰

TABLE 9 Turkey: Strengths and weaknesses

Pharmacovigilance aspects	Strengths	Weaknesses
Scope of regulation	<ul style="list-style-type: none"> • Defines roles and responsibilities of market authorization holders and health care professionals • Covers manufacturing, labeling and risk profiling • TÜFAM collaborate successfully with the Uppsala monitoring centre 	<ul style="list-style-type: none"> • Pharmacovigilance regulations still in its infancy • New regulations introduced but compliance and implementation still unclear
The biopharmaceutical industry's scope of involvement	<ul style="list-style-type: none"> • Provides risk management plans • Implemented tracking and tracing system 	<ul style="list-style-type: none"> • Bartering of pharmaceuticals between pharmacies traditionally a significant challenge for batch and drug traceability
Healthcare institutions and professionals scope of involvement	<ul style="list-style-type: none"> • Increase in rate of ADR reports • Required to fill a "drug safety surveillance form" during treatment 	<ul style="list-style-type: none"> • Total number of reports still very low • Limited awareness of pharmacovigilance procedures
Patient awareness of pharmacovigilance	<ul style="list-style-type: none"> • No electronic ADR submission mechanism available to patients 	<ul style="list-style-type: none"> • Limited awareness of importance of pharmacovigilance
Substandard and counterfeit medicines	<ul style="list-style-type: none"> • Track and trace system introduced • GMP in place 	<ul style="list-style-type: none"> • Enforcement challenges • Traditionally high levels of counterfeit drugs



4

CONCLUSIONS AND RECOMMENDATIONS

Whether it be securing the borders or public health maintaining the safety and security of the public in any given country requires constant vigilance and effort. In this respect ensuring the integrity of biopharmaceutical supply chains and patient safety is no different.

There is no silver bullet or quick fix to create a perfect system of pharmacovigilance. Instead, building a robust and effective system of drug safety monitoring, reporting and action requires a sustained and systematic effort that includes all key stakeholders including regulators, manufacturers, health care professionals and patients. In this respect creating a culture and awareness of pharmacovigilance is as important as having the right technical rules and regulations in place.

The purpose of this report has been twofold.

First, to provide a thorough discussion of pharmacovigilance conceptually and practically. The preceding sections have examined pharmacovigilance throughout the clinical, post-marketing and post-exclusivity phases of a biopharmaceutical product's life span – from the early R&D stages all the way to the market entry of generic products. Examining the highest standards and best practices in place internationally the report assembled a 'Gold Standard' of those procedures and processes that characterize and are crucial building blocks of an effective system of pharmacovigilance.

Second, this report examined the state of pharmacovigilance in seven emerging and developing markets. Looking at the legal and regulatory situation as well as the actual application of pharmacovigilance regulations and rules the report found that there is considerable variation as to the extent and effectiveness of drug regulations across the world. Many countries, such as China and Brazil, have in place relatively robust regulations but face challenges with applying and enforcing those regulations. Other countries, such as Indonesia, lack the right rules and regulations themselves. Equally, it is clear that awareness of pharmacovigilance among health professionals and patients is relatively limited in all the studied countries. The survey evidence that exists suggests that knowledge about pharmacovigilance and reporting mechanisms among health professionals in the seven countries analyzed is quite limited and can vary dramatically from health institution to health institution and region to region. Surveys of patient knowledge and awareness of the importance of ADR reporting and how to report showed even lower levels of awareness.

Based on these main findings this report makes the following four recommendations:

1. Recognize the centrality of pharmacovigilance to public health

Increasingly, greater numbers and kinds of biopharmaceutical products and treatments are available to a growing number of patients across the world. Now more than ever modern medicine is relying on biopharmaceuticals to treat, cure and help patients. Particularly in the emerging world in which biopharmaceutical markets and consumption is set to outpace growth in the developed world. It is vital in this context that increased demand and supply of medicine and medical technologies is matched by an equally developed and strong safety net.

2. Measure performance

Governments and policymakers need to measure pharmacovigilance performance consistently and comprehensively with clear and transparent benchmarks and goals. Measures should be holistic including not only number of ADRs but repeated surveys and reviews of levels of pharmacovigilance awareness among health professionals, patients and other key actors.

3. Boost awareness levels

In most countries the evidence suggests that awareness and recognition of pharmacovigilance was quite limited both among health professionals and patients. While many countries are working towards raising this awareness through campaigns, seminars, workshop activity and, in some cases, the creation of online reporting mechanisms this effort needs to be intensified. Public and professional awareness of the need and importance of pharmacovigilance and making reporting as straight-forward and practical as possible should be at the forefront of any drug regulatory authority.

4. Professional training

Given the relatively low levels of awareness among health professionals in all countries the creation and inclusion of pharmacovigilance in medical training and professional accreditation courses for health professionals is an idea worth exploring.

NOTES

- ¹ Beginning in the late 19th century the regional and national regulation of the safety of foods and drugs became enshrined in both European and North American law. In 1906 the United States Congress passed the Federal Food and Drugs Act which gave the United States Department of Agriculture's Division of Chemistry regulatory powers over the interstate transportation of food and drugs.
- ² A full discussion and definition of pharmacovigilance is provided below in section 2.
- ³ Torstensson, D., Pugatch, M. (2010). *Keeping Medicines Safe: A Study of the Regulations Guiding the Approval of Medicines in Emerging Markets*, The Stockholm Network, p. 18.
- ⁴ Cockburn, R. et al. (2005). "The Global Threat of Counterfeit Drugs: Why Industry and Governments Must Communicate the Dangers", *PLoS Medicine*, Vol. 2, No. 4, p. 302.
- ⁵ Shakoor, O., Taylor, R. B., Behrens, R. H. (1997). "Assessment of the Incidence of substandard drugs in developing countries", *Tropical Medicine and International Health*, Vol 2, No 9, p. 841.
- ⁶ For a full discussion of different regulatory standards across the world see: Torstensson, D. & Pugatch, M. (2010).
- ⁷ Mestre-Ferrandiz, J., Sussex, J. & Towse, A. (2012). *The R&D Cost of a New Medicine*, Office of Health Economics, p.1
- ⁸ The World Health Organization defines clinical trials as: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes". See: WHO, "Health topics: Clinical trials", http://www.who.int/topics/clinical_trials/en/
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- ¹⁷ U.S. Food and Drug Administration (FDA). (2003). *Guidance for Industry – Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations*, Center for Drug Evaluation and Research (CDER), p. 20, www.fda.gov/downloads/Drugs/.../Guidances/ucm070124.pdf.
- ¹⁸ World Health Organization. (2001). *How to develop and implement a national drug policy*, 2nd edition, Geneva, p. 52.
- ¹⁹ Management Sciences for Health and World Health Organization. (2007). *Drug and Therapeutics Committee Training Course*. Arlington, VA: Management Sciences for Health, p. 114.
- ²⁰ Ibid, pp. 113-114
- ²¹ Within medical parlance, *efficacy* refers to a drug's capacity to produce the desired therapeutic effect within a clinical trial, while *effectiveness* refers to this capacity within commercial use (See The Merck Manual Online, Patients & Caregivers, Drugs, Drug Dynamic, Drug Action, www.merckmanuals.com/home/drugs/drug_dynamics/drug_action.html?qt=&sc=&alt=). In this paper the term *efficacy* is used for both of these meanings.
- ²² Torstensson, D., Pugatch, M. (2010). *Keeping Medicines Safe...*, pp. 15-16.
- ²³ Ibid.
- ²⁴ The working parties of the ICH are: the European Commission; the European Federation of Biopharmaceutical Industries and Associations; Ministry of Health, Labour and Welfare, Japan; Japan Biopharmaceutical Manufacturer's Association; US Food and Drug Administration (FDA); and the Biopharmaceutical Research and Manufacturers of America (PhRMA). The WHO, the European Free Trade Association (EFTA), and Health Canada participate as observers.
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- ³⁷ U.S. Food and Drug Administration (FDA). (2013). *Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products*, Center for Biologics Evaluation and Research (CBER), pp. 8-9, www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM376521.pdf
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- ⁴⁰ EMA, Human Regulatory, 'Quality by Design', www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000162.jsp
- ⁴¹ Ibid.
- ⁴² Ibid.
- ⁴³ Philipson, T. J., Von Eschenbach, A., (2014). "FDA Reform can Lift U.S. Economy", *Bloomberg.com*, <http://www.bloombergview.com/articles/2013-02-28/fda-reform-can-lift-u-s-economy>.
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- ⁴⁶ Ibid.
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