Chapter 1

Introduction to International Regulatory Affairs

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OBJECTIVES

☐ Extend understanding of international regulatory requirements
☐ Explain the importance of harmonization
☐ Expand understanding of current harmonization initiatives

LAWS, REGULATIONS, AND GUIDELINES COVERED IN THIS CHAPTER

☐ The Apothecary Wares, Drugs and Stuffs Act
☐ Pharmacovigilance Planning E2E

Introduction

Regulations and regulatory authorities' primary purposes are to protect public safety by preventing unsafe healthcare products from being marketed. In fact, the development of modern regulations has been influenced heavily by instances of public tragedy arising from the dissemination of false or misleading information and the commercialization of harmful products.

To minimize public exposure to unsafe products, regulatory authorities often require the submission and approval of data demonstrating the product’s safety and efficacy prior to market introduction. However, product approval does not signify that a product is free from risk, but rather ensures that current information indicates the benefit-risk ratio is satisfactory and acceptable. Therefore, ongoing product monitoring is required to ensure the product safety profile is kept up to date and any identified quality and safety issues are reviewed and corrected in a timely manner, as applicable. In many cases, manufacturers are required to submit new applications to competent authorities for reapproval, i.e., renewal, at regular intervals or when changes that may impact product safety or effectiveness are being proposed (postapproval change management). Manufacturers also are responsible for pharmacovigilance and postmarket surveillance (PMS) activities, such as adverse event reporting and field safety corrective actions (FSCAs).

Regulations vary greatly by region and may vary further depending on various factors, such as the product’s risk profile and the regulatory system’s maturity. The US and EU have some of the longest regulation histories and, therefore, have well-documented requirements that are enforced readily. Many countries, such as Australia, China, and Turkey, include aspects of the US and EU regulatory frameworks or regulatory approval processes. In developing markets, regulations may be less clear and evolving or may not be well supported or enforced, further creating challenges for manufacturers and increasing the public’s risk of exposure to unsafe products.

With the continuous development, adoption, and implementation of international product regulations, the challenges associated with regulatory compliance increase. Although regulations’ purpose is to protect the public from unsafe products, over-complicated, contradictory, or outdated regulatory requirements can
delay or prevent access to potentially beneficial products. Therefore, several harmonization groups have been established to standardize international requirements.

**Early Regulation**

The *Apothecary Wares, Drugs and Stuffs Act* was issued in England in the 1500s and is an example of early regulation on control of medicines, under which inspectors were able to regulate medicinal product manufacturing.¹ Although examples of early regulation exist, such as *The Apothecary Wares, Drugs and Stuffs Act*, the modern regulation of drugs and other critical products did not begin until the early 1900s, with the passage of the US *Pure Food and Drug Act*. Prior to this, consumers were exposed to risks posed by potentially unsafe, ineffective, and adulterated products without any protection. Incidents of public tragedy, such as the 1937 Elixir Sulphanilamide incident in the US and the thalidomide tragedy in the EU and Canada in the 1950s, fast-tracked the implementation of modern regulation.²,³

**Regulators’ Role**

Although regulations vary by region, regulators’ main intent is to protect public health. This consistent message is illustrated in the statements of responsibility by the following regulators:

- Central Drugs Standard Control Organization (India), which “safeguard[s] and enhance[s] the public health by assuring the safety, efficacy, and quality of drugs, cosmetics, and medical devices”⁴
- Therapeutic Goods Administration (Australia), which “safeguards and enhances the health of the Australian community”⁵
- Pharmaceuticals and Medical Devices Agency (Japan), which has the “obligation is to protect the public health”⁶

**Drugs**

Compared to such products as medical devices and cosmetics, drugs have a relatively long regulatory history. Although individual submission requirements vary, regulatory authorities generally require the submission and approval of information demonstrating the drug has a satisfactory benefit-risk ratio. For generic drugs, manufacturers must provide evidence the generic has the same therapeutic efficacy, safety, and performance characteristics as the innovator drug.⁷ To add to these challenges, manufacturers must be able to meet the individual requirements of each country in which the drug is intended to be marketed. In addition, manufacturers must comply with postmarket monitoring requirements to ensure critical issues are assessed against the drug’s risk profile and actioned, as required.⁸

The World Health Organization (WHO) defines pharmacovigilance as “the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug related problems.”⁹ This definition also is referenced in the International Council on Harmonisation (ICH) guideline, *Pharmacovigilance Planning E2E*, which “describes a method for summarising the important identified risks of a drug, important potential risks, and important missing information, including the potentially at-risk populations and situations where the product is likely to be used that have not been studied pre-approval.”¹⁰ *Pharmacovigilance Planning E2E* advises, “Routine pharmacovigilance should be conducted for all medicinal products.”¹¹ The guidance recommends routine pharmacovigilance include the following, in addition to any local requirements:

- Systems and processes to ensure information about all suspected adverse reactions reported to company personnel are collected and collated in an accessible manner
- Preparing reports for regulatory authorities
  - Expedited adverse drug reaction reports
  - Periodic safety update reports
- Continuous monitoring of approved products’ safety profile, including signal detection, issue evaluation, updating labeling, and liaising with regulatory authorities¹²

**Medical Devices**

The regulation of medical devices is a vast and rapidly evolving field and is intended to protect the user against the risks associated with the design, manufacture, and packaging of medical devices. According to the 2013 *WHO Baseline Country Survey on Medical Devices*, more than 120 countries have a regulatory authority.
responsible for implementing and enforcing medical device regulations.\textsuperscript{13} The level of information required to register a medical device in these countries varies depending on such factors as the regulatory system's maturity and the medical device's risk class.

Desktop research based on the WHO's global atlas of medical devices\textsuperscript{14} summarizes the dynamic regulatory landscape. Medical device regulations not only differ by country, but are also product-specific, and there are countries without a medical regulatory approval process.\textsuperscript{15} In such countries as New Zealand, the regulatory process may be as simple as notifying the regulatory agency of the intent to market, whereas in such countries as China and India, the regulatory process may require submission and approval of a multi-sectioned submission dossier with evidence of safety and effectiveness. While there is variation in regulatory submission requirements, some standardization exists in the form of the Summary Technical Document (STED), a harmonized submission format developed by the Global Harmonization Task Force (GHTF).\textsuperscript{16}

Once a medical device is registered, manufacturers are required to notify regulatory authorities of adverse events. As with medical device registration requirements, medical device vigilance reporting requirements can vary by country. Often, manufacturers are required to report adverse events only to the regulatory authority in the region where the reported event occurred; however, regulatory authorities may share information to stay informed about potential safety issues. One such example of collaboration among regulatory authorities is the International Medical Device Regulatory Forum's (IMDRF) National Competent Authority Report (NCAR) Exchange Program, which was developed for “[exchanging] information relating to significant concerns or potential trends that individual authorities have observed in their jurisdictions but have not yet resulted in recalls or Field Safety Corrective Actions (FSCAs).”\textsuperscript{17}

**Veterinary Products**

Veterinary products are products intended to prevent, treat, or diagnose diseases in animals. As with products intended for human use, veterinary products include drugs, vaccines, devices, and food additives. Where veterinary products are regulated, it may be by a specific veterinary group, an agricultural group, or a group responsible for the regulation of equivalent human products.

Veterinary drug regulation often is similar to that for human drugs. However, veterinary drugs also may need to conform to maximum residue limits, since they can end up in the food chain.\textsuperscript{18}

**Foods, Dietary Supplements, and Cosmetics**

In general, food, dietary supplements, and cosmetic products do not require premarket approval unless the subject product is intended to treat or prevent a disease, i.e., the product meets the definition of a drug. However, manufacturers of foods, dietary supplements, and cosmetics should be able to demonstrate product safety with respect to composition (including color additives), packaging, and labeling. In addition, some countries require additional monitoring and traceability for genetically modified organisms (GMOs) entering the food chain.\textsuperscript{19}

**Harmonization**

Although international regulators have a common intent, no single regulatory scheme currently exists. Differences among regulatory schemes across markets can cause difficulties and delays for manufacturers, regulators, and patients alike. The initiation of independent regulatory schemes around the world and the public demand for the timely availability of safe and effective medical products highlighted a need for harmonized regulatory requirements. In the 1980s, the European Community (EC) came together with the goal of developing a single, harmonized market for pharmaceuticals. The success of the EC’s harmonization efforts illustrated that a reasonable level of harmonization was possible and paved the way for the formation of other regulatory harmonization groups, such as ICH, GHTF, and IMDRF.\textsuperscript{20,21}

**International Council for Harmonisation (ICH)**

Established in 1990, ICH aims “to make recommendations toward achieving greater harmonization in the interpretation and application of
technical guidance and requirements for pharmaceutical product registration, thereby reducing or obviating duplication of testing carried out during the research and development of new human medicines.”22 ICH’s founding members were regulatory and pharmaceutical industry representatives from the EU, Japan, and the US. Membership now has expanded to include Canada, Switzerland, Brazil, China, Singapore, and the Republic of Korea, with other countries and organizations holding observer status.23

The Pharmaceutical Inspection Co-operation Scheme (PIC/S)
PIC/S was established in 1995 as an extension to the Pharmaceutical Inspection Convention (PIC) of 1970. It is a non-binding, informal co-operative arrangement between regulatory authorities in the field of good manufacturing practice (GMP) of medicinal products for human or veterinary use, whose mission is “to lead the international development, implementation and maintenance of harmonized GMP standards and quality systems of inspectorates in the field of medicinal products.” PIC/S is open to any authority having a comparable GMP inspection system. PIC/S presently comprises 54 participating authorities from all over the world (Europe, Africa, America, Asia, and Australasia).24

Global Harmonization Task Force (GHTF)
GHTF was founded in 1992 (though the first formal meeting only took place in 1993) by the regulatory authority and industry representatives from the EU, US, Canada, Australia, and Japan. GHTF was intended to “achieve greater uniformity between national medical device regulatory systems.”25 and to encourage a convergence in standards and regulatory practices related to the safety, performance, and quality of medical devices.26

In 2012, GHTF disbanded. A new group, the International Medical Device Regulators Forum, has assumed GHTF’s mission. Prior to disbanding, however, GHTF developed the STED format to help standardize medical device submission requirements globally.27

International Medical Device Regulators Forum (IMDRF)
Established in October 2011, IMDRF is building on GHTF’s foundation to “accelerate international medical device regulatory harmonization and convergence.”28 Unlike GHTF, IMDRF is comprised solely of medical device regulators and does not include industry representatives. Current IMDRF members are Australia, Brazil, Canada, China, Europe, Japan, Russia, Singapore, South Korea, and the US. The World Health Organization (WHO) is an official observer. The Asian Harmonization Working Party (AHWP), Pan American Health Organization (PAHO), and APEC LSIF Regulatory Harmonization Steering Committee are IMDRF’s Regional Harmonization Initiatives.29

IMDRF is implementing one notable example of harmonization, the Medical Device Single Audit Program (MDSAP) Pilot. The MDSAP Pilot, which began 1 January 2014, was “intended to allow MDSAP recognized auditing organizations to conduct a single audit of a medical device manufacturer that will satisfy the relevant requirements of the medical device regulatory authorities participating in the pilot program.”30 On 29 June 2017, a report summarizing the outcomes of prospective “proof-of-concept” criteria was released. Based on its evaluation of the MDSAP Final Pilot Report, the MDSAP Regulatory Authority Council (the international MDSAP governing body) determined the MDSAP Pilot had satisfactorily demonstrated the MDSAP’s viability.31 Australia, Brazil, Canada, China, Europe, Japan, and the US were the official observers and active participants in the MDSAP Pilot.32 More information can be explored at https://www.fda.gov/MedicalDevices/InternationalPrograms/MDSAPPilot/.

International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH)
VICH is a trilateral program (EU, US, Japan), launched in 1996, to harmonize technical requirements for the registration of veterinary products. VICH’s objectives
are similar to those of ICH and, where possible, VICH adapts ICH guidelines for veterinary products.\textsuperscript{33}

**International Pharmaceutical Regulators Forum (IPRF)**

The purpose of IPRF, which met first in 2013, is “to create an environment for members to exchange information on issues of mutual concern and regulatory cooperation.”\textsuperscript{34} IPRF “will facilitate the implementation of ICH and other internationally harmonized technical guidelines for pharmaceuticals for human use and will contribute to the coordination of a range of international efforts related to the regulation of medicinal products for human use.”\textsuperscript{35} Current IPRF members are regulatory authorities and agencies from Australia, Brazil, Canada, EU, Japan, Republic of Korea, Mexico, Russia, Singapore, Switzerland, and the US.\textsuperscript{36}

**Eurasia**

**Association of Southeast Asian Nations (ASEAN)**

ASEAN was established in 1967 by the Foreign Ministers of Indonesia, Malaysia, the Philippines, Singapore, and Thailand, and has since expanded to include the following additional member states: Brunei, Cambodia, Laos, Myanmar, and Vietnam. ASEAN collaborates in the areas of cultural, economic, and political development, including work in the area of regulatory harmonization.\textsuperscript{37}

**Association of Southeast Asian Nations Pharmaceutical Product Working Group (ASEAN PPWG)**

ASEAN’s PPWG was established in 1999 to develop “harmonisation schemes of pharmaceutical regulations of the ASEAN member countries to complement and facilitate the objective of AFTA (ASEAN Free Trade Area), particularly, the elimination of technical barriers to trade posed by regulations, without compromising on drug quality, efficacy, and safety.”\textsuperscript{38} PPWG works on harmonization efforts for new chemical entities (NCEs), biotechnological products, major and minor variation products, and generic pharmaceutical products.\textsuperscript{39}

**Asian-Pacific Economic Cooperation (APEC)**

APEC was founded in 1989 by representatives from Australia, Brunei, Canada, Indonesia, Japan, Korea, Malaysia, New Zealand, the Philippines, Singapore, Thailand, and the US and has since expanded its membership to include China, Hong Kong, Chinese Taipei, Mexico, Papua New Guinea, Chile, Peru, Russia, and Vietnam.\textsuperscript{40} APEC’s primary goal “is to support sustainable economic growth and prosperity in the Asia-Pacific region.”\textsuperscript{41}

**APEC Life Sciences Innovation Forum (APEC LSIF)**

APEC recognized the importance of life sciences innovation on economic development and, in 2002, formed APEC LSIF to lead health and health sciences innovation. APEC LSIF engages representatives from government, industry, and academia.

In 2013, the APEC LSIF Regulatory Harmonization Steering Committee (RHSC) was established to “achieve regional convergence on regulatory approval procedures for medical products by 2020.”\textsuperscript{42}

One of the projects currently being implemented under APEC LSIF RHSC is the Roadmap to Promote Multi-Regional Clinical Trial (MRCT). Championed by Japan, MRCT aims to “facilitate multi-regional clinical trials (MRCT) and the acceptance of these clinical trial results for review by regulatory authorities.”\textsuperscript{43}

**Asian Harmonization Working Party (AHWP)**

AHWP was formed in 1996–97 to achieve greater regulatory harmonization in Asia.\textsuperscript{44} AHWP’s goals are “to study and recommend ways to harmonize medical device regulations in the Asian and other regions and to work in coordination with the GHTF, APEC, and other related international organizations aiming at establishing harmonized requirements, procedures and standards.”\textsuperscript{45} AHWP currently is comprised of representatives from regulatory authorities and the medical device industry from 31 member economies.\textsuperscript{46}

Most recently, following the pre-announcement issued in March 2020, the AHWP leadership is preparing the transformation of the Asian Harmonization Working Party (AHWP) into the Global Harmonization Working Party (GHWP).\textsuperscript{47}
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**Eurasian Economic Union (EAEU/EEU)**

EAEU was established by the Republic of Belarus, the Republic of Kazakhstan, and the Russian Federation to create "an economic union that provides free movement of goods, services, capital, and labor and pursues coordinated, harmonized, and single policy in the sectors determined by the document and international agreements within the Union." Since its establishment in 2014, the membership of the EAEU has expanded to include the Republic of Armenia and the Kyrgyz Republic. EAEU harmonization efforts currently are in progress.

**The Americas**

**Pan American Network for Drug Regulatory Harmonization (PANDRH)**

PANDRH was established in 1999 and officially recognized by the Pan American Health Organization (PAHO) in 2000. PANDRH’s mission is to “promote drug regulatory harmonization for all aspects of quality, safety, and efficacy of pharmaceutical products as a contribution to the quality of life and health care of the citizens of the Member Countries of the Americas.”

Current PANDRH members are “drug regulatory authorities of all PAHO member states, representatives of the regional pharmaceutical industry associations (ALIFAR, FIFARMA), academia, consumer groups, professional associations, and representatives from the five sub-regional trade integration groups within the Americas, such as the Andean Community, CARICOM, SICA, MERCOSUR, and NAFTA.”

PANDRH’s pharmaceutical harmonization efforts include prescription and over-the-counter medicines, generic products, ‘similar’ biologics, vaccines, and herbal medicines.

**Africa**

**African Medicines Regulatory Harmonization (AMRH)**

Many African countries have insufficient legal foundations and/or lack the technical expertise to support adequate or efficient regulatory reviews. AMRH was created “to establish and improve standards and requirements related to the regulation of and access to safe, high-quality medicines for the African population.” AMRH, which has been led by African health ministers since 2014, aims to achieve its objective by overseeing “the registration of a selected list of medicines and coordinate regional harmonization systems on the continent.”

**Economic Community of West African States (ECOWAS)**

ECOWAS is made up of 15 member countries located in the Western African region. It was established in 1975 via the treaty of Lagos. ECOWAS’s mission is to promote economic integration in all fields of activity of the constituting countries. Its vision is the creation of a borderless region where the population has access to its abundant resources and is able to exploit same through the creation of opportunities under a sustainable environment.

**The International Coalition of Medicines Regulatory Authorities (ICMRA)**

ICMRA is a voluntary, executive-level coalition of key regulators from every region in the world. It provides a global strategic focus for medicines regulators and gives strategic leadership on shared regulatory issues and challenges. ICMRA was created to address current and emerging regulatory and safety challenges globally.

**International Pharmaceutical Regulators Programme (IPRP)**

IPRP was established on 1 January 2018 as a result of the consolidation of the International Pharmaceutical Regulators Forum (IPRF) and the International Generic Drug Regulators Programme (IGDRP). The IPRP strives to create an environment for its regulatory members and observers to exchange information on issues of mutual interest, enable cooperation, and promote convergence of regulatory approaches for pharmaceutical medicinal products for human use. IPRP offers tangible benefits for its members and observers and is committed to promoting information sharing and collaboration to advance public health, facilitate access to medicines, and address emerging regulatory challenges of mutual interest.

**Other**

**World Health Organization (WHO)**

Established in 1948, WHO is an agency of the United Nations (UN), whose mission is to provide global
leadership in the area of public health. WHO has staff in more than 150 country offices, with regional offices covering the WHO African Region, WHO Region of the Americas, WHO South-East Asia Region, WHO European Region, WHO Eastern Mediterranean Region, and WHO Western Pacific Region. WHO employees work in the following areas:

- Health systems
- Noncommunicable diseases
- Promoting health through the lifecycle
- Communicable diseases
- Preparedness, surveillance, and response
- Corporate services

WHO is involved with a number of harmonization initiatives including, but not limited to the following:

- ICH
- IMDRF
- AHWP

**Organisation for Economic Co-operation and Development (OECD)**

OECD is an intergovernmental economic organization with 37 member countries, founded in 1961 to stimulate economic progress and world trade. Together with governments, policy makers, and citizens, OECD works on establishing evidence-based international standards and finding solutions to a range of social, economic, and environmental challenges. It provides a unique forum and knowledge hub for data and analysis, exchange of experiences, best-practice sharing, and advice on public policies and international standard-setting.

**Organisation of Islamic Cooperation (OIC)**

OIC, formerly the Organisation of the Islamic Conference, is an international organization founded in 1969, consisting of 57 member states, with a collective population of more than 1.8 billion as of 2015, with 49 countries being Muslim-majority countries. The organization states that it is “the collective voice of the Muslim world” and works to “safeguard and protect the interests of the Muslim world in the spirit of promoting international peace and harmony.” The OIC has permanent delegations to the United Nations and the EU.

**Conclusion**

Global regulatory statutes significantly impact healthcare companies, and regulatory requirements have evolved over the time to protect the public from unsafe products. Regulations vary worldwide, based on several factors, including product type, risk profile, and maturity of the regulatory system. The requirements’ number and variations globally can create challenges in navigating the regulatory environment and increase the demand for a better regulatory framework and harmonization. Greater harmonization can reduce cost and the time to market, facilitate trade, and enhance research and development. Several groups comprising representatives from government, industry, and academia have been established to initiate harmonization objectives.

After the era of liberalization and globalization, the desires of developing economies is to ensure the safety and performance of the product brought to their markets, and harmonized regulation is an important tool for strengthening the same. All governments have a continuing responsibility to review their own regulations, regulatory structures, and processes to ensure that they promote efficiently and effectively the economic and social well-being of their people. A growing number of countries have embarked in recent years on ambitious programs to reduce regulatory burdens and improve the quality and cost-effectiveness of regulations that remain. The difficulties and complexities have sometimes been greater than expected, and many questions remain about the risks and costs of further reform, as well as continued strong opposition from vested interests.

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