CHAPTER
1

Healthcare Landscape and Drug Development

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Healthcare always has been – and is even more so today – a vital aspect of human life. The healthcare landscape continues to evolve and transform hand in hand with evolution in the medicinal product development field, now highly influenced by payer reform, technology, scientific advances, consumer demand, and more.

These new realities and challenges impact how medicinal products are developed and approved. Previously, we lacked effective treatments for many life-threatening diseases; now, despite having many more treatments available, public scrutiny of healthcare has intensified. Patients and their families want new treatments sooner with accurate and understandable information on how to use them. While this has led health authorities to support innovation and advances in science and technology, it has also increased the complexity in the global regulatory landscape.

The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) often are the regulators who first review these innovative treatments and lead the way in bringing efficacious and cost-effective treatments to the general and broader population.

In addition, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) plays a critical role in global drug development by developing guidelines based on scientific discussions among regulatory authorities and the pharmaceutical industry. ICH guidelines are updated continuously and applied by an increasing number of health authorities worldwide. The mission of ICH is to achieve greater harmonization worldwide and ensure that safe, effective, and high-quality medicines are developed, registered, and maintained in the most resource-efficient manner while meeting high standards.[1]

Food and Drug Administration

FDA, an agency of the US the Department of Health and Human Services (HHS), is responsible for protecting the public health by assuring the safety, efficacy, and security of human drugs and biological products, as well as other products outside the scope of this book. FDA's mission includes advancing public health by supporting innovations that make medicines safer, more effective, and more affordable. The agency is tasked with providing the public with the accurate, science-based information they need to use medicinal products to maintain and improve their health. FDA plays a significant role in US counterterrorism efforts. The agency collaborates with other US agencies, international regulators, academia, trade associations, consumer groups, and others.[2]

Role in Global Regulatory Landscape

Many of the medicinal products consumed by people of leading nations such as the US are produced in other countries. In the US, FDA-regulated products are produced in over 130,000 facilities in more than 150 countries.[3] The agency faces challenges in determining and confirming that its standards and requirements have been applied in the manufacture, distribution, and storage of medicinal products imported into the US. Given that the manufacture of a product may involve multiple parties from different countries, there are chances for the product to be improperly formulated or packaged, contaminated, diverted, counterfeited, or adulterated. Thus, compliance and surveillance activities overseen by regulatory bodies across the product life cycle are a critical part of the drug development process.[4]

Inspections are a big part of such surveillance activities and depend on the stage of drug development. In situations where noncompliance is identified, FDA may issue one of several types of regulatory action letters, such as warning letters, administrative license action letters, and license revocation to cease practices that violate regulations and promote corrective action. If warranted, the FDA also has the authority to impose civil enforcement actions, including seizure, injunction, and prosecution.

FDA oversees the import and export of medicinal products to ensure that the FDA-regulated products comply with the requirements of the Food, Drug, and Cosmetics Act (FD&C Act) and the regulations promulgated under these statutes.[5] Imported products regulated by FDA are subject to inspection at the time of entry by the US Customs and Border Protection (CBP). Imported products not in compliance with US regulations are subject to detention. Moreover, FDA verifies with CPB a company's licensure for imports, may perform random sampling, and will issue import alerts for noncompliant products.[6] A foreign manufacturer must have a US license to import a biological product into the US.

FDA works closely with external organizations and foreign governments to promote product safety and regulatory consistency. Its efforts include:

- developing new enforcement and regulatory tools;
- conducting more foreign inspections;

- collaborating with foreign regulators and other stakeholders;
- developing harmonized standards and standards convergence;
- educating industry representatives about its requirements; and
- increasing transparency and accountability in the supply chain

Several offices within FDA address global issues. The Office of Regulatory Affairs (ORA) inspects and reviews products offered for entry into the US. The agency's product centers implement the policies and outreaches that touch their product portfolios. The Office of Global Policy and Strategy (OGPS) serves as a pan-agency coordinator, information distributor, and access point for multilateral organizations like the World Health Organization. OGPS also addresses international trade of regulated products and mutual recognition agreements, facilitates information sharing with its global counterparts, and manages FDA's foreign offices worldwide.[3]

The Office of International Products (OIP) coordinates the FDA's international work, which helps foster partnerships with counterpart foreign agencies and international organizations. OIP offices around the world focus on specific regions: Latin America (Costa Rica), Europe (Brussels, London), China (Beijing), and India (New Delhi).

International Arrangements

FDA uses various tools to set up partnerships with other nations to promote product safety, and they fall into two categories of international arrangements: Cooperative Arrangements and Confidentiality Commitments.[7] A Confidentiality Commitment sets up the legal framework for the FDA to share certain kinds of non-public information with international organizations and regulators in other countries as part of cooperative law enforcement or regulatory activities.

A Cooperative Arrangement is a written document that describes the good-faith intentions of the FDA, other regulators, and international organizations to engage in cooperative activities.

Parallel Scientific Advice

Another globalized approach shared by the EMA and the FDA is establishing a mechanism for experts to concurrently engage in scientific discourse with sponsors on key issues during the development phase of new medicinal products (drugs, biologicals, vaccines, advanced therapies, nanotechnology, and pediatric drug development). It helps the pharmaceutical industry and regulatory agencies proactively engage early in product development.

Cluster Calls

Various health authorities, including FDA, EMA, Health Canada, the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), and Australian Therapeutic Goods Administration (TGA), also have developed a process called 'cluster calls' to allow for increased collaboration and discussion of important topics in areas such as advanced therapies (e.g., cell and tissue products), biosimilars, blood safety, oncology-hematology products and non-clinical oncology products, orphan products, patient engagement, pediatric products, pharmacogenomics, pharmacometrics (modeling and simulation), pharmacovigilance, rare diseases, vaccines, and veterinary medical products. (Not all of these agencies necessarily participate in all clusters.)

FDA also is a member or participant in several international organizations, including the International Council for Harmonisation, Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-operation Scheme, International Medical Device Regulators Forum, and Codex Alimentarius, which promotes international food standards.

In addition to its own programs, FDA collaborates extensively with other HHS and federal agencies on international issues. Within HHS, the Office of Global Affairs (OGA) works with FDA and other agencies on such issues as trade and health, emerging infectious diseases and global health security, pharmaceutical pricing and reimbursement, and tobacco control and nutrition. In their own words, "they foster critical global relationships, coordinate international engagement across HHS and the U.S. government, and provide leadership and expertise in global health diplomacy and policy to contribute to a safer, healthier world." OGA collaborates with the US Department of State and serves as the US government's liaison to the World Health Organization.

European Medicines Agency

The European Medicines Evaluation Agency (EMEA) was founded in 1995. It worked across the European Union (EU) nations to protect human and animal health by evaluating human and veterinary medicines as their primary focus. It also provided partners and stakeholders with independent, unbiased, science-based information on medicines.[8] The name was changed to European Medicines Agency (EMA) in late 2009.[9] The main objective for establishing EMA was to have a harmonized process among the regulatory bodies of different member states within the EU. The agency also is responsible for products developed in the specialized areas of medicines for rare diseases, herbal medicines, medicines for children, and advanced therapy medicines. Up until 2020, the UK hosted EMA. Because the UK left the EU on 31 January 2020, the EMA headquarters moved to Amsterdam in March 2019.[10]

What is unique about EMA is the dual nature in which a medicinal product may be authorized. In the EU, all medicines must have a marketing authorization (MA) before they can be used by patients. There are two ways of obtaining this authorization. Under the Centralised Procedure, EMA gives an opinion, resulting in a single MA for the whole of the EU. Under national MA procedures, individual member states authorize the medicines for use in their territory.[11] Most medicinal products for human and veterinary use – including those derived from biotechnology and other high-technology methods, human medicines for HIV/AIDS, cancer, diabetes, or neurodegenerative diseases, and all designated orphan medicines – are to be approved by the Centralised Procedure.

EMA is governed by an independent Management Board composed of 36 independent members. The board's role is to define EMA's budget, develop the yearly work plan and ensure the

agency works effectively with partnering organizations.[12]

EMA on the Global Regulatory Stage

Like FDA, EMA acknowledges the importance and requirement for international collaboration. It believes this will also ensure data integrity to support clinical trials and manufacturing, encourages a global approach to authorization and supervision of medicines, and avoid unnecessary duplication of efforts. Such a collaboration aims to create efficiencies by promoting the effective use of global regulatory resources.[13] Confidentiality arrangements or mutual recognition agreements (MRAs) are critical for such bilateral activities and heavily used by EMA and European Commission to work closely in all international activities. Confidentiality arrangements facilitate the exchange of confidential information between regulators. MRAs on good manufacturing practice (GMP) allow EU authorities to rely on GMP inspections performed by other regulators, waive batch testing of products on entry into the EU and share information on inspection-related information and quality defects.[14]

The EU has MRAs with various countries, including Australia, Brazil, Canada, Israel, Japan, New Zealand, Switzerland, and the US. EMA also supports European Commission collaborations with Russia, India, and China through specific EU frameworks.[15]

EMA also works with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the International Coalition of Medicines Regulatory Authorities (ICMRA), the International Pharmaceutical Regulators Forum (IPRF), WHO, the Council of Europe, the Organisation for Economic Co-operation and Development (OECD), Codex Alimentarius, the Office International des Epizooties (OIE), and the European Free Trade Association (EFTA).

Additionally, EMA is involved in multiple initiatives, such as:

- EU-US Mutual Reliance Initiative on GMP inspection;
- Increasing collaboration with China and India;
- Reform of ICH governance and science;
- Common FDA-EMA application form and annual report for orphan designation;
- International Generic Medicines Assessment pilot; and
- International cooperation on approaches to Ebola treatment and prevention[16]

International Council for Harmonisation

ICH was founded in 1990 to build harmonization between regulators and the pharmaceutical industry. It was reformed into a non-profit legal entity under Swiss law in October 2015. Its mission includes promoting public health; contributing to the development, manufacturing, registration, and supervision of new medicines; and developing technical guidelines that can be implemented by the regulatory authorities. ICH[17] has grown in terms of its global membership, including members, observers, and experts. More recently, even the generic and over-the-counter industries have joined ICH. The ICH organization includes 20 members and 36 observers spread across various regulatory agencies, including the US FDA, EC, Pharmaceuticals and Medical Devices Agency (Japan), Swissmedic (Switzerland), etc., and industry members like EFPIA (European Federation of Pharmaceutical Industries and Association) and PhRMA (Pharmaceutical Research and Manufacturers of America.[18] It also has numerous working groups with many experts working towards the process of harmonization and creation and implementation of ICH guidelines. The process of harmonization and development of guidelines is a multi-step process requiring consensus between regulators on the guideline topic and content to its adoption and implementation in various ICH regions.[19] As of March 2023, over 70 ICH guidelines have been drafted on technical requirements around Safety, Quality, Efficacy, and Multidisciplinary. Some of the major advantages/successes of ICH include:

- Common Technical Document (CTD) and electronic CTD (eCTD), which brings together all Quality, Safety, and Efficacy information in a common, harmonized format accepted by regulators in all ICH regions.[20]
- Clinical trials conducted in one ICH region can be used in other ICH regions by setting the common standards on science and ethics.
- Medical Dictionary for Regulatory Activities (MedDRA) is a highly specific, standardized medical terminology used to facilitate sharing of regulatory information used for registration, documentation, and safety monitoring of medical products before and after marketing authorization.[21]

Conclusion

There is an ongoing evolution in the regulatory landscape as health authorities worldwide acknowledge the globalization of drug development processes and are working towards supporting the safe, efficacious, and cost-effective development of such products. FDA and EMA regulations and ICH guidelines continue to evolve to reflect the complexity of regulated products and fulfill public health goals. They play a key role in ensuring quality management and bias- and corruption-free approval and use of these drugs, whether being imported or exported to their specific regions.

References

All references accessed 4 March 2023.

1. International Council for Harmonisation. Mission. https://www.ich.org/page/mission
2. Food and Drug Administration. What We Do. Current as of 28 March 2018. https://www.fda.gov/about-fda/what-we-do
3. Food and Drug Administration. FDA globalization. Current as of 21 December 2022. https://www.fda.gov/international-programs/fda-globalization
4. Food and Drug Administration. Inspections, compliance, enforcement, and criminal investigation. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations
5. Food and Drug Administration. Import program – Food and Drug Administration (FDA). Current as of 15 July 2022. https://www.fda.gov/industry/import-program-food-and-drug-administration-fda
6. Food and Drug Administration. Office of Compliance and Biologics Quality (OCBQ). Current as of 10 October 2018. https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-

information-biologics/office-compliance-and-biologics-quality-ocbq
7. Food and Drug Administration. International arrangement. Current as of 13 February 2023. https://www.fda.gov/international-programs/international-arrangements
8. European Union. European Medicines Agency (EMA). https://european-union.europa.eu/institutions-law-budget/institutions-and-bodies/institutions-and-bodies-profiles/ema_en
9. PMLiVE. EMEA becomes EMA. Dated 14 December 2009. https://www.pmlive.com/pharma_news/emea_becomes_ema_197492
10. European Medicines Agency. EMA to relocate to Amsterdam, the Netherlands. Dated 20 November 2017. https://www.ema.europa.eu/en/news/ema-relocate-amsterdam-netherlands
11. Heads of Medicines Agency. Medicines approval system. https://www.hma.eu/about-hma/medicines-approval-system.html
12. European Medicines Agency. Management Board. Last updated 11 October 2021. https://www.ema.europa.eu/en/about-us/who-we-are/management-board
13. European Medicines Agency. International activities. https://www.ema.europa.eu/en/partners-networks/international-activities
14. European Medicines Agency. Mutual recognition agreements (MRA). https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/mutual-recognition-agreements-mra
15. European Medicines Agency. Bilateral interactions with non-EU regulators. https://www.ema.europa.eu/en/partners-networks/international-activities/bilateral-interactions-non-eu-regulators
16. European Medicines Agency. Multilateral coalitions and initiatives. https://www.ema.europa.eu/en/partners-networks/international-activities/multilateral-coalitions-initiatives
17. International Council for Harmonisation. Overview of ICH. Dated November 2022. https://admin.ich.org/sites/default/files/2022-11/OverviewOfICH_2022_1129.pdf
18. International Council for Harmonisation. Members & Observers https://www.ich.org/page/members-observers
19. International Council for Harmonisation. Process of harmonisation. https://www.ich.org/page/process-harmonisation
20. International Council for Harmonisation. M4: The Common Technical Document. https://www.ich.org/page/ctd
21. International Council for Harmonisation. Medical dictionary for regulatory activities. https://www.ich.org/page/meddra

CHAPTER
2

The Drug Development Continuum, Preclinical to Market Access

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The medicinal product development process, from discovery through clinical investigation and ultimately to the market, follows specific steps. The collective steps often are referred to as the product development continuum or de novo product development. This chapter will identify the steps in the product development continuum of new (novel) pharmaceuticals and biopharmaceuticals.

A Five-Step Process

All medicinal products manufactured with a new drug substance (new molecular entity) move through five steps of the medicinal product development continuum: discovery and development, preclinical research, clinical research, agency review, and market access, including postmarketing safety monitoring and reporting.[1,2] New drug substances and new medicinal products are developed under patent protection. While the patent is in effect, the application holder retains exclusive rights to market the product (market exclusivity).

The five steps in the development continuum are illustrated in **Figure 2-1**. The steps described below may proceed sequentially, and some steps will overlap. Often, the output of one step is used to make decisions to proceed to the next step, move back to the previous step to generate more information, or stop the development of the medicinal product.

An integral part of the medicinal product development continuum is the chemistry, manufacturing, and controls (CMC) process. This process ensures that the quality, consistency, and safety of the medicinal product will be evaluated in humans and ultimately approved for distribution and use. CMC development is also referred to as Pharmaceutical (Biopharmaceutical) development. The tasks include formulation development, manufacturing development, identifying product characteristics, defining critical quality attributes, product testing, and specifications that meet all global quality and regulatory requirements, e.g., current good manufacturing practices (cGMPs) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines. CMC development has its own continuum, timeline, resources, and cost that must parallel the activities in the development continuum. CMC development begins in Step 1, discovery and development after a compound (drug or biologic candidate) is identified. The CMC continuum is phase-appropriate and becomes more complex and costly through the product development continuum because CMC activities continue through every stage of development, commercial launch, and post-authorization. The CMC tasks must be identified and included in the planning of the medicinal product development continuum, or they may become a risk to the program timeline or authorization. The tasks in the CMC continuum also may occur sequentially and often overlap. The key is that CMC parallels the product development continuum to ensure the availability of an adequately characterized product manufactured according to appropriate quality standards for each stage of development.

After a new medicinal product has gone through the drug development continuum and the marketing authorization application (MAA) has been submitted to and approved by a regulatory agency, an opportunity becomes available for companies

Figure 2-1. The Medicinal Product Development Continuum