CHAPTER
1

The Drug Development Continuum, Preclinical to Market Access

Darlene (Dar) Rosario, MBA, BS, RAC-US; Pragnesh Donga, MPharm, MBA, RAC-Drugs;
Kathrin Schalper, PhD, RAC-Devices, RAC-US, RAC-CAN, RAC-EU

The medicinal product development process follows specific steps, from discovery through clinical investigation and ultimately to the market. 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 (chemically derived) and biopharmaceuticals (made from or containing living organisms).

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 (market exclusivity) to market the product. In addition, a health authority can grant an additional period of market exclusivity upon approval of the medicinal product in a specific country or region.[3]

The five steps in the development continuum are illustrated in **Figure 1-1**. 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 participants (i.e., patients, subjects, volunteers) 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, for example, current good manufacturing practices (cGMPs) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines.

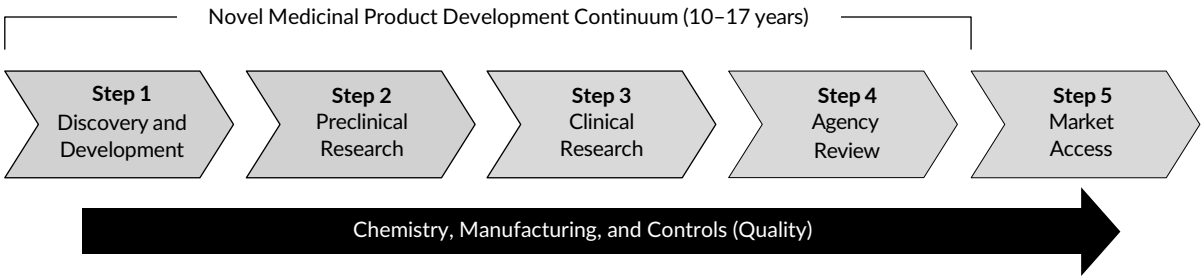
CMC development has its own continuum, timeline, resources, and cost that run in parallel with the clinical activities in the development continuum. CMC development begins in Step 1, discovery and development, after a compound (drug or biologic candidate) is identified. The CMC continuum is phase-appropriate and becomes more complex and costly through the product development continuum, because CMC activities continue through every stage of development, commercial launch, and postauthorization. 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 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 GMP requirements 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 focused on different approaches to traditional drug discovery and development once the patent/exclusivity period expires. Such approaches include generic medicines, biosimilars, and repurposing/repositioning of existing drugs. Except for biosimilars, these approaches develop the same active ingredient or previously approved active ingredient to identify opportunities to expedite drug development using a 505(b)(2) or 505(j) regulatory pathway[4] in the US and Article 8(3) "Mixed Use" or Article 10 of Directive 2001/83/EC[5] in the EU.

Generic medicines and therapeutic protein biosimilars are examples of product development approaches that do not follow the traditional de novo product development continuum. When the innovator's patent(s) or other periods of exclusivity expire, generic medicines and biosimilar manufacturers can submit applications 505(b)(2) new drug application (NDA) and abbreviated new drug application (505(j) pathway, ANDA) in the US, an abbreviated new drug submission (ANDS) in Canada, an MAA in the EU, or a 351(k) Biologics License Application (BLA) in the US to the respective regulatory agency to seek authorization for their generic or biosimilar version. A generic drug/medicine is identical – or bioequivalent – to the brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use.[6,7] For example, gefitinib tablets were authorized originally for

Purchased from RAPS Library (library.raps.org) for the exclusive use of unknown.
© 2026 RAPS Library. Please report unauthorized use to raps@raps.org

Figure 1-1. The Medicinal Product Development Continuum



non–small cell lung cancer (NSCLC) under the brand name Iressa (AstraZeneca) in the US on 13 July 2015. As of March 2025, it is approved as the generic medicine gefitinib tablets manufactured by six manufacturers in the US. In the EU, Gefitinib Mylan tablets were approved in 2018 and withdrawn in 2024 for commercial reasons.

In the EU, a therapeutic biosimilar is not regarded as a generic medicine of a biological medicine. It is defined as a biological medicine highly similar to the reference product, an already approved biological medicine, in terms of structure, biological activity and efficacy, safety, and immunogenicity profile.[8] In the US, a biosimilar is also defined as a biological product that is highly similar to and has no clinically meaningful differences from an existing Food and Drug Administration (FDA)–approved reference product. Minor differences between the biosimilar product and the reference product in clinically inactive components are acceptable and must demonstrate no clinically meaningful differences from the reference product in terms of safety, purity, and potency (safety and effectiveness).[9]

Europe has led the way in biosimilar authorizations. In April 2006, Sandoz received marketing authorization (MA) for Omnitrope (somatropin),[10] a biosimilar to Pfizer's Genotropin (somatropin), from the European Commission (EC), becoming the world's first biosimilar. Japan and Canada followed with authorizations in 2009. On 6 March 2015, Sandoz received authorization for the first US biosimilar, Zarxio (filgrastim-sndz), a biosimilar to Amgen's Neupogen (filgrastim).[11]

These above approaches leverage the information previously submitted for pharmacology, formulation, safety (toxicology), and previous human experience, thereby reducing development time, cost, and resources and reducing the risk of product failures in clinical development. The two approaches do not require the company to repeat nonclinical (Step 2) research. Instead, a biosimilar usually requires an abbreviated nonclinical program only. For a generic approach, clinical research (Step 3) is not repeated on inactive ingredients or formulations already authorized for safety and effectiveness. The generic medicine must be bioequivalent to the innovator reference product. For a biosimilar approach, new clinical trials to demonstrate similarity to the reference medicine are conducted to determine human pharmacokinetics (exposure) and pharmacodynamics (response), and clinical immunogenicity. In addition, a regulatory agency may require a new abbreviated clinical trial for safety and effectiveness for the biosimilar to be authorized.

Another effective alternative approach to traditional drug development is drug repurposing (DR). These medicines generally share a similar active substance with an already authorized product but may differ significantly in their formulation, strength, route of administration, or indications. Such differences introduce additional value, enhancing therapeutic outcomes or addressing patient needs that existing generics may not fully meet.

DR identifies new uses for existing drugs and finds new therapeutic uses for new drugs other than the disease for which they were initially intended. DR is also known as repositioning, recycling, rescuing, and reprofiling.

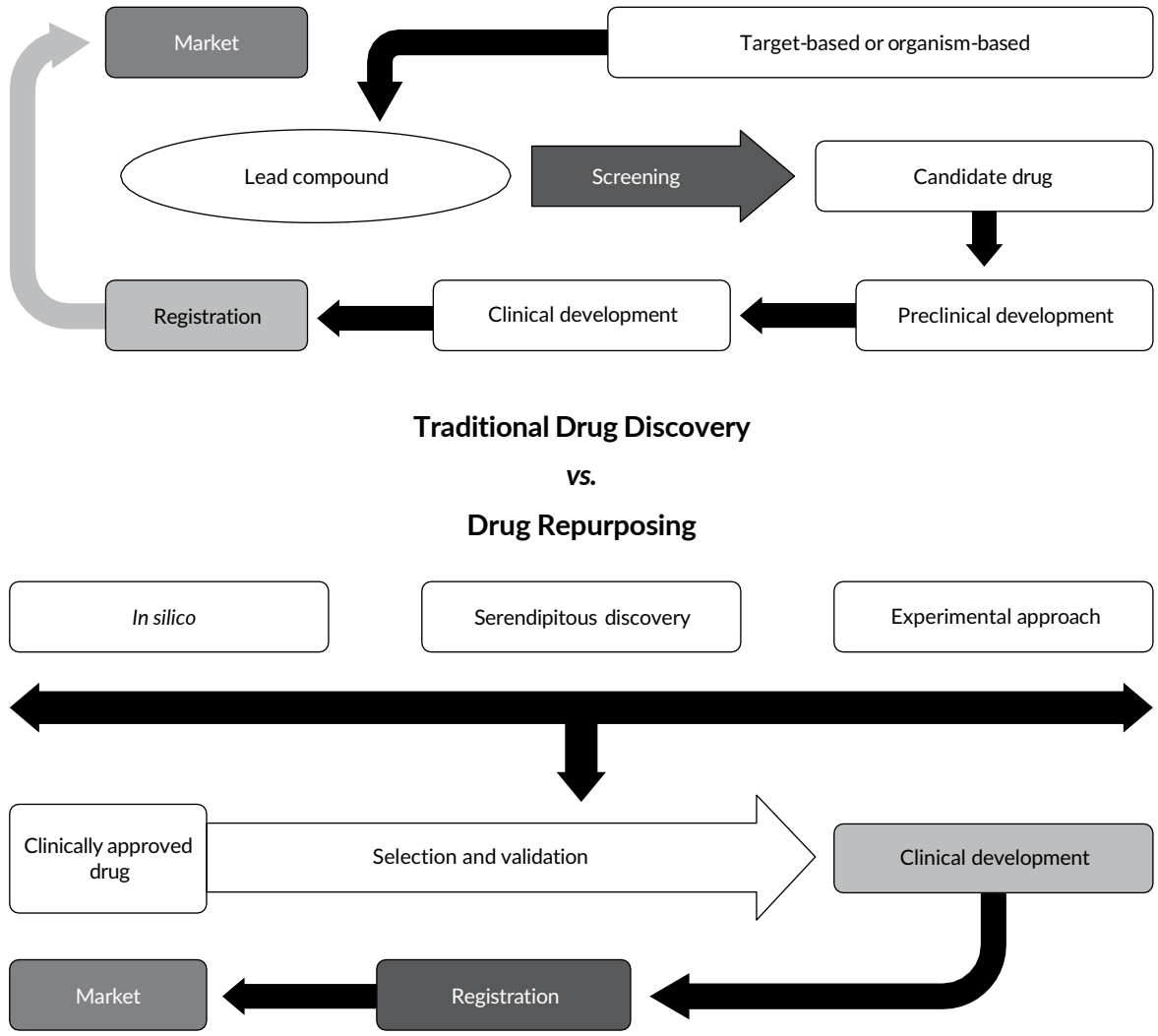
Two well-known success stories of DR are sildenafil, marketed as Viagra, and thalidomide. Viagra represents unintended or accidental repurposing. During a clinical trial for a potential new drug to treat angina, Pfizer observed that many male participants reported unusual side effects, erections.[12] Before Viagra was approved in 1998, there was no oral treatment for erectile dysfunction. Originally developed as an anti-hypertensive, sildenafil has been repurposed to treat erectile dysfunction and pulmonary arterial hypertension. Thalidomide, a widely used drug in Europe in the 1950s and 1960s for the treatment of nausea in pregnant women, was connected to serious birth defects (fetal limb) and removed from the market in 1961.[13] Recently, research has shown it to be an effective treatment for leprosy and multiple myeloma.[14]

A more recent example of DR – more specifically, repositioning – is Keytruda (pembrolizumab), an anti–PD-1 antibody originally approved in 2014 to treat advanced or unresectable melanoma. Keytruda subsequently has been approved for additional indications, in combination with approved therapies/treatments, and for use in different treatment settings.[15] As of this writing, Keytruda was indicated to treat 20 different cancers.

While the de novo development process has five steps, the DR process has four steps: compound selection and validation, clinical development, regulatory authority review and authorization, and market access, including postmarketing safety monitoring and reporting.[15]

Purchased from RAPS Library (library.raps.org) for the exclusive use of unknown.
© 2026 RAPS Library. Please report unauthorized use to raps@raps.org

Figure 1-2. Traditional de Novo Product Development Process Versus Product Repurposing



As with generic medicines and biosimilars, DR leverages previously generated pharmacology, toxicology, and clinical and safety data to identify potential DR opportunities, reducing development time, cost, and rate of product failures in clinical development.

When comparing the de novo medicinal product development program against a DR program, there is a substantial reduction in research and development time. In the de novo approach, it is estimated that it can take 10-17 years to develop a new drug compared with 3-12 years for authorization from the FDA or European Medicines Agency (EMA) using the DR approach. The costs are also significantly different, approximately $1.6 billion for DR versus $12 billion for de novo development.[16] **Figure 1-2** compares the de novo development process versus repurposing, illustrating the 5 and 4 steps, respectively.

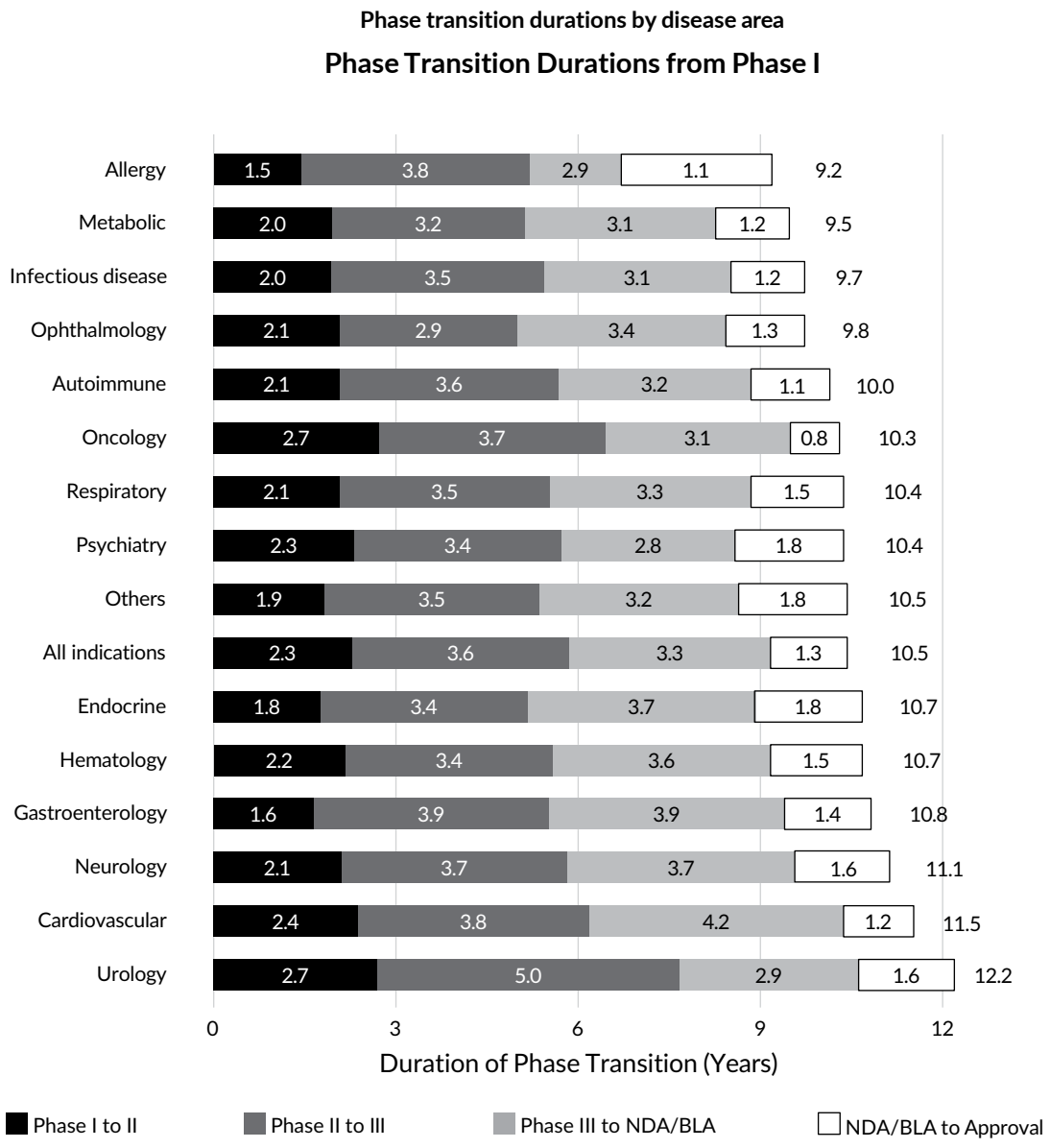
Regardless of which approach is taken to develop a medicinal product, the steps in the development process are a continuum. Depending on the target, indication, drug novelty, etc., the development process may be at Step 1 for target discovery, Step 2 preclinical research, or Step 3 clinical research. Once beyond Step 2, the drug development success rate often depends on clinical development and progression from Phase 1.

According to one analysis, it takes an average of 10.5 years for a medicinal product to successfully progress from Phase 1 to regulatory authorization. That period includes 2.3 years at Phase 1, 3.6 years at Phase 2, 3.3 years at Phase 3, and 1.3 years at the regulatory review and authorization stage.[17] Of course, phase duration can vary greatly depending on numerous factors, including disease area and indication, clinical trial design best practices, and patient eligibility and availability. **Figure 1-3** shows the phase transition duration from Phase 1 to authorization in 14 major disease areas.

There are noteworthy differences in duration within individual phases based on disease area. For example, oncology and urology

Purchased from RAPS Library (library.raps.org) for the exclusive use of unknown.
© 2026 RAPS Library. Please report unauthorized use to raps@raps.org

Figure 1-3. Phase Transition Duration From Phase 1 Through NDA/BLA Authorization



Source: Biomedtracker® and Pharmapremia® 2020.

share the longest Phase 1 transition, at 2.7 years. Oncology is the only therapeutic area with an average regulatory review of less than 1 year; the 0.8-year duration is almost half as short as the cumulative total for all non-oncology indications (1.4 years). Urology drug candidates see the longest Phase 2 duration (5.0 years). Excluding urology, the remaining therapeutic areas lie close to the average duration of 3.6 years. Ophthalmology is the fastest disease area for Phase 2 research (2.9 years). When looking at Phase 3 timelines, cardiovascular has the longest Phase 3 duration (4.2 years). The large patient populations in cardiovascular trials and the long-term evaluation of cardiovascular outcomes contribute to longer timelines than seen in other prevalent disease areas, such as psychiatry (2.8 years), which typically assesses short-term symptomatic improvement using rating-scale questionnaires.

The medicinal product development continuum is a lengthy and costly proposition with no guarantee of success. However, understanding the steps and developing a clear product development plan, including CMC, will help minimize delays and risks and increase the probability of success. To that end, a high-level summary of each step in the development continuum is provided below, with more specific details for each step provided later in this book.

Purchased from RAPS Library (library.raps.org) for the exclusive use of unknown.
© 2026 RAPS Library. Please report unauthorized use to raps@raps.org

Step 1: Discovery

Discovery research is the first step in the development continuum. Historically, discovery involved identifying active ingredients in traditional medicines or simply by chance. An example is the discovery of penicillin by Alexander Fleming in 1928. Fleming was investigating staphylococcus bacteria, and a speck of dust contaminated one of his petri dishes. Around the resulting patch of mold, a clear, bacteria-free zone formed, which Fleming later identified as containing the world-changing antibiotic penicillin.

Later, large libraries of small molecules or herbal products were screened against established drug targets to identify those binding with high affinity, indicating a potential therapeutic effect.

With the completion of the sequencing of the human genome, reverse pharmacology has become the preferred way of identifying new compounds. Here, the first step is the development of a hypothesis that the modulation of the activity of a specific target in the human body has a disease-modifying effect. Then, based on this hypothesis, the selected target is characterized in depth, and compounds are tailor-made in the lab to fit the target. Finally, screening processes test large libraries of compounds for their affinity, potential efficacy, and safety.[18]

Traditionally, the discovery has included the following five steps:

1. Target Identification and Validation

The first step in the discovery phase is identifying a therapeutic target that plays a significant role in the disease process. A good target involves a crucial biological pathway, distinct from any previously known target, extensive functional and structural characterization, and druggability. Druggability is characterized by having a well-accessible binding site and being capable of binding standard therapeutic molecules (e.g., small molecules, biologics). Therapeutic drug targets can be identified via publicly available libraries, such as the Sanger Whole Genome CRISPR Library or the HEAL Targets and Compounds Library. Most known drug targets are proteins; however, many other biomolecules have been validated as targets. An example is ribonucleic acid (RNA), a key target for antisense oligonucleotides.

The therapeutic target is then further validated. Target validation involves establishing a clear link between the target and the disease, which confirms the functional role of the chosen target in the disease phenotype and confirms that its modification has a therapeutic effect. An example of an established disease target is the Human Epidermal Growth Factor Receptor 2 (HER2), an epidermal tyrosine kinase that plays a pivotal role in the etiology of certain types of breast, ovarian, and gastric cancers. This receptor is targeted by a broad range of marketed monoclonal antibodies and small molecules (e.g., Herceptin, Tykerb). By interaction with the HER2 receptor, these compounds prevent the activation of signaling pathways that further enhance the proliferation of malignant growth.

A typical technique to validate targets is by elucidation of their function. One such approach is the use of mRNA modulation to suppress gene expression of the chosen target. A drug sponsor can confirm whether the target merits further development by observing the phenotypic effect that results from a decrease in the expressed target.[18]

2. Assay Development and Screening

Following target validation, compound screening assays are developed. These screening assays are tests that evaluate the effects of the new drug candidate at the cellular, molecular, and biochemical levels. One example is the enzyme-linked immunosorbent assay (ELISA), which in its simplest form applies a matching antibody to the targeted antigen so that it can bind to it. The antibody is linked to an enzyme, and in a following step, the enzyme's substrate is added. If the antibody shows a high affinity to the antigen and binding occurs, a subsequent reaction produces a detectable signal (usually a color change), which can also be assessed quantitatively.

Assay development can be a very long and time-consuming process – from several weeks to 6 months – because standard assays often need to be adapted to the smaller volumes used in high throughput screening (HTS), where processes are conducted in microtiter plates of high density.[18]

3. High Throughput Screening

HTS uses robotics, data processing/control software, and sophisticated detection mechanisms to rapidly conduct thousands of pharmacological, chemical, and genetic tests, such as ELISA, flow cytometry, fluorescence polarization, and clustered regularly interspaced palindromic repeats (CRISPR)-based tests for gene-based therapies. HTS assesses large libraries of compounds for their affinity to the chosen target.

HTS data are then analyzed to determine and refine further structure-activity relationships. In addition, these screens also provide preliminary information about which compounds are nonselective, cytotoxic, and potentially genotoxic and should be eliminated from further screening.[18]

4. Hit to Lead

In the hit to lead process, compounds that gave a hit (i.e., were found to have a high affinity against the investigated target) are evaluated and structurally pre-optimized into lead compounds.[18]

5. Lead Optimization

In the lead optimization process, the lead compounds discovered in the hit to lead process are resynthesized and further modified to improve affinity and reduce side effects. Potential properties such as potency (strength), efficacy, selectivity, or bioavailability are improved during the lead optimization process. In addition, lead optimization includes experimental testing using animal efficacy models and in silico tools to predict the absorption, distribution,

Purchased from RAPS Library (library.raps.org) for the exclusive use of unknown.
© 2026 RAPS Library. Please report unauthorized use to raps@raps.org

Table 1-1. Pharmacology Studies – Overview

Area	Study Type
Pharmacodynamics	Primary pharmacodynamics
	Secondary pharmacodynamics
	Safety pharmacology
	Pharmacodynamic drug interactions
Pharmacokinetics	Absorption
	Distribution
	Metabolism
	Excretion
	Pharmacokinetic drug interactions

Table 1-2. Toxicology Studies – Overview

Area	Study Type
General toxicity and toxicokinetics	Single-dose toxicity
	Repeat-dose toxicity
Genotoxicity	In vitro
	In vivo
Carcinogenicity	Short-term
	Long-term
Reproductive and developmental toxicity	Fertility and early embryonic development
	Embryofetal development
	Prenatal and postnatal development
Local tolerance	In vitro
	In vivo

metabolism, excretion, and toxicity (ADMET) of the lead compound, leading to the ultimate drug candidate.

During the discovery process, a basic level of quality control needs to be established to ensure adequate structural characterization and reproducibility of the chosen lead drug candidate. However, no formal quality system is required; all drug candidates are manufactured and tested under non–good practice (GxP) conditions. Formulation development activities at this stage are minimal and mainly focused on preparing a formulation that allows the compound to be screened without interfering with the selected assays. However, additional formulation and manufacturing feasibility studies may have been undertaken at this early stage to gauge the developability of the short-listed candidates. An effective candidate may be worthless if it cannot be formulated or manufactured in a commercially viable manner. Thus, formulation feasibility may serve as an additional tool for choosing a viable candidate. Analytical assays used at this stage do not need to be fully validated. Still, it should be demonstrated that they are fit for purpose, that is, they should undergo a basic qualification that demonstrates measurements will be specific, precise, and accurate with a high degree of certainty.

Once a compound is identified as the lead candidate (often supported by a second compound as a backup candidate), it moves into Step 2, preclinical research.[18]

Step 2: Preclinical Research

Before initiating Phase 1 clinical trials in human subjects, the chosen lead candidate undergoes extensive characterization in relevant animals, such as rodents, dogs, and primates, as well as in vitro models, such as cell cultures using patient-derived tissues or safety pharmacology screens testing inhibition of the human ether-à-go-go-related gene (hERG) cardiac potassium channel, which is predictive of potential cardiovascular off-target effects. Studies in animal and in vitro models are usually referred to as nonclinical studies. These studies must be conducted in compliance with Good Laboratory Practice (GLP) principles and regulations (21CFR Part 58, EU directive 2010/63EU and ICH S6R1) to ensure data integrity and regulatory acceptance.

The main objective of the preclinical research phase is the determination of a safe starting dose for the first-in-human (FIH) study. First, the pharmacologic properties of the chosen lead candidate are further investigated.

These tests reconfirm the mode of action and allow the development of a detailed understanding of how the molecule interacts with the body at the desired and non-desired on-target and off-target effect.[18]

The pharmacology evaluation investigates the pharmacodynamics (PD) and pharmacokinetics (PK) of the chosen lead candidate. Generally speaking, PD studies the effects of a drug on biological systems, and PK studies the effects of biological systems on a drug. Pharmacodynamics investigates the interaction with biological receptors, and PK discusses the absorption, distribution, metabolism, and excretion (ADME) of the drug from the biological system. Drug PK determines the onset, duration, and intensity of a drug's effect and its metabolic profile, and it is vital to developing an efficacious drug formulation (see **Table 1-1**).

These pharmacology studies are discussed in more detail in **Chapters 4** and **5**.

Next, the lead candidate undergoes an extensive toxicology characterization, which helps to establish a preliminary safety profile and a safe starting dose in humans. A standard battery of toxicology and genotoxicity studies form the basis for initiating clinical trials. These studies must be conducted under strict GLP principles and submitted in the original IND or clinical trial application (CTA), and they form the basis of the regulatory agency authorization to proceed with the FIH study. These nonclinical studies are sometimes referred to as IND/CTA enabling studies. Data on carcinogenicity and reproductive developmental toxicity are needed for MA and are typically conducted in parallel with Phase 3 clinical trials (see **Table 1-2**). Not all of the evaluations described above are required for all therapeutic modalities – especially for biological products where an abbreviated nonclinical program may be adequate.

Purchased from RAPS Library (library.raps.org) for the exclusive use of unknown.
© 2026 RAPS Library. Please report unauthorized use to raps@raps.org

It should be highlighted that the investigational product (test article) used in Phase 1-enabling preclinical studies needs to be representative of the investigational product used in Phase 1 clinical trials to provide a pharmacokinetic and toxicokinetic profile representative for the product to be used in the clinic. Thus, while the use of quality material manufactured under Good Manufacturing Practice (GMP) is not required in the preclinical Phase 1–enabling trials, a quality system should be in place for the manufacture and testing of the investigational medicine to ensure adequate traceability and records. The investigational product used in the preclinical studies is typically referred to as non-GMP material or tox batches. The formulation used at this stage should be as close as possible to the proposed clinical formulation or at least demonstrate an exposure scenario (i.e., level and duration of exposure, route of administration) comparable to the proposed clinical GMP material.

In addition, an analytical characterization capturing critical properties of the investigational medicine must be performed. The extent of the analytical characterization depends on the therapeutic modality and is usually far more extensive for biological products than small-molecule drugs. As with the discovery stage, analytical methods do not need to be fully validated; but they do need to be fit-for-purpose or qualified, as described above, and align with GMP principles. Any bioanalytical methods used in Phase 1–enabling preclinical studies require full analytical validation.[19]

Once Phase 1–enabling preclinical studies are completed, the program moves into clinical research.

Step 3: Clinical Research

Every treatment on the market takes years of research, including clinical research. In its simplest terms, clinical research is the study of human health and disease. Clinical research is an essential part of the medicinal product development continuum and is the longest and most expensive step. Clinical research involves human participants in some way, essentially translating preclinical research into finding ways to help patients – finding the right drug at the right dose for the right patient.

Clinical research conducted on human participants (i.e., patients, subjects, and volunteers) is called a clinical trial or clinical study. These terms usually are interchangeable. The US National Institutes of Health (NIH) in 2014 revised the definition of a clinical trial to "a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes."[20] Clinical trials in human subjects are conducted to investigate whether a new medicinal product is safe and effective to treat, prevent, or diagnose a disease in a particular patient population. Clinical trials may have different objectives depending on the phase of development; trials may investigate the clinical safety and efficacy of a proposed treatment regimen and the pharmacodynamic/pharmacokinetic characteristics of an investigational medicine. Clinical trials ultimately establish the essential safety and efficacy data for MA by global regulatory agencies.

Clinical trials investigating a new medicinal product are called interventional trials because they are prospective and specifically tailored to evaluate a direct impact of a treatment or preventive measure on disease. Each trial design has specific outcome measures. In contrast, observational trial designs are often retrospective and are used to assess potential causation in exposure-outcome relationships. In rare cases, observational studies may be registration-enabling, because they may allow the building of an external control group predicting the course of disease in a non-treated patient population in lieu of exposing patients to placebo.[21]

Good clinical practice (GCP) is a scientific and ethical quality standard for the design, conduct, performance, auditing, recordkeeping, analysis, and reporting of clinical trials involving human subjects. GCP ensures that the integrity of a clinical trial and the safety and well-being of trial subjects (participants) is protected. ICH adopted the Guideline for Good Clinical Practice E6 (Revision 3) on 6 January 2025.[22] In addition, ICH issued several clinical guidelines covering topics such as trials in specific patient populations and indications and biostatistical evaluation to standardize clinical practice globally.

Apart from the ICH guidelines, national agencies have issued numerous other guidelines and reflection papers defining minimum quality standards and principles of clinical trial conduct.

Clinical Trial Overview

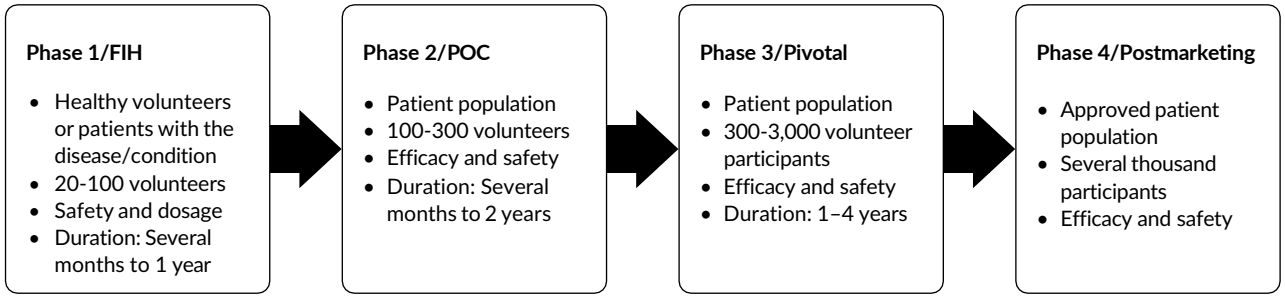
Clinical trials in human subjects are conducted in phases (see **Figure 1-4).**[23] Each phase is designed to answer a separate research question and to collect specific information about a new treatment, such as its delivery mechanism (e.g., pill, solution, injection), administration regimen and schedule, safety profile, and efficacy outcome(s). The clinical trial process is covered in depth in **Chapter 18**.

The clinical research pathway is typically a linear progression, but some clinical programs may include more than one phase, especially for rare diseases and significant unmet medical needs. Information from each phase is used to inform the next phase and to decide whether to continue clinical research, to return to a previous phase to gather additional information (e.g., PK or bioavailability), or to stop development of the investigational medicine.

Phase 0. A Phase 0 trial (Pre-Phase 1 or exploratory trial) is designed to speed up the development of promising medicines by generating preliminary data in healthy human volunteers to see if the agent performs as expected based on the preclinical research. A Phase 0 trial is not required. The Phase 0 trial provides no safety or efficacy data, because the dose is too low to produce a therapeutic effect (microdosing studies). Phase 0 trials are very small, with fewer than 15 participants, and the drug is administered for a short time. These trials are typically conducted to rank drug candidates to decide which candidate has the best PK parameters to move forward into further development. Recent progress extends Phase 0 benefits beyond assessment of PK to include understanding of mechanism of action and pharmacodynamics (PD) and enable more informed

Purchased from RAPS Library (library.raps.org) for the exclusive use of unknown.
© 2026 RAPS Library. Please report unauthorized use to raps@raps.org

Figure 1-4. Phases of Clinical Research



FIH, first-in-human; **POC**, proof of concept.

Source: World Health Organization, Clinical trials overview.

developmental decisions.[24] Additional preclinical research may be conducted if the medicinal product acts differently than expected.

Phase 1. Typically, Phase 1 or FIH trials represent the initial human exposure to an investigational medicine. The FIH trial of a new treatment, which has been determined to be safe (nontoxic) for use in animals, is usually conducted in a small group of healthy human volunteers (i.e., 20-100 subjects). In some cases, Phase 1 trials may also be conducted in patients with the disease, for example, for rare diseases, oncology products, or highly toxic treatments for fatal, unmet medical needs.[23]

The main objective of Phase 1 is to establish a preliminary safety profile of the investigational medicinal product, to determine the highest dose that can be administered without causing harm, a maximum tolerated dose (MTD) in humans, and to show that participants can tolerate the investigational medicine. In addition, Phase 1 trials typically assess the pharmacodynamic or "what the drug does to the body" and pharmacokinetic (PK) profile or "what the body does to a drug" of the investigational medicine. Phase 1 trials may also include specialized studies, such as radio-labeled studies to establish drug metabolism and other PK parameters, cardiovascular safety studies, hepatic and renal impairment studies, and drug-drug interaction studies. Phase 1 trials are used to determine the most appropriate delivery mechanism (e.g., pill, solution, injection), adequate dose, and administration schedule. Preliminary signs of efficacy are often observed in Phase 1 trials, although not the primary end point. Generally, Phase 1 trials are shorter than Phase 2 trials and typically last several months to a year.

Phase 2. Building on the results from Phase 1, in Phase 2 trials the investigational medicine is administered to patients with the disease or condition for which the medicine is being developed. Phase 2 trials typically involve several hundred participants (100-300) at multiple sites and are designed to evaluate PD end points, determine preliminary evidence of efficacy, and identify an appropriate dose and administration schedule for evaluation and confirmation in Phase 3. Phase 2 typically lasts approximately 2 years. Phase 2 trials are typically referred to as nonpivotal or pilot trials.[23]

Sometimes, Phase 2 trials are separated into Phase 2a and 2b trials. Phase 2a focuses on dosing requirements. Phase 2b specifically focuses on efficacy – treating, preventing, or diagnosing the disease. In Phase 2a, a small number of participants is administered the investigational medicine in increasing quantities after safety is confirmed at that dose to determine a dose-response relationship. That is, to determine whether there is an increase in response that is correlated to the dose. Additionally, the frequency of dosing for the best response also is determined. This step is referred to as proof of concept (POC) or proof of principle (POP), linking Phase 1 and dose-finding studies. A POC study is an important clinical development success criterion, because it demonstrates a measurable biological effect related to the target of interest. This effect may reasonably translate to a clinically meaningful effect in later-phase clinical trials.

The primary purpose of Phase 2b, in a larger number of participants than 2a, is to find the optimal dose with minimal side effects (dose-response studies) while keeping the therapeutic benefit (efficacy), a critical step in the drug development continuum. It is referred to as the definitive dose range-finding trial. Proper dosing is critical to the effectiveness of the medicine. Phase 2b clinical trials evaluate dose escalation as single ascending dose (SAD) and multiple ascending dose (MAD) trials to identify the optimal dosage and dosing schedule for confirmation in Phase 3 clinical trials.

Phase 3. During Phase 3 trials, the investigational medicine is given to a much larger group of participants (300-3,000), depending on the condition being studied, to confirm its effectiveness, to monitor side effects, to compare it to the current standard of care, and to collect information to allow the product to be used safely. Phase 3 trials typically last approximately 1-4 years.[23]

Phase 3 trials are often randomized, multicenter trials and typically have the longest duration, sometimes lasting years (1-4). Randomized trials randomly assign participants to receive either the investigational agent or an approved medicine (often the standard of care) or placebo if no treatment exists for the investigational medicine. Phase 3 trials are typically double-blind; neither participants nor investigators know which treatment is assigned. Randomization helps eliminate bias in interpreting results. Phase 3

Purchased from RAPS Library (library.raps.org) for the exclusive use of unknown.
© 2026 RAPS Library. Please report unauthorized use to raps@raps.org

trials are the pivotal safety and efficacy trials supporting the commercial marketing authorization and labeling, defining the commercial dose and actual conditions of use. Because Phase 3 trials are more extensive and longer, the results are more likely to detect long-term or rare side effects. Phase 3 trials often are referred to as pivotal or registrational trials, and they form the substantial evidence for approval of the drug. Data from trials conducted in Phase 1 and 2 are also submitted as supportive evidence for regulatory review.

Phase 4. After authorization, postauthorization trials usually are carried out under the scope of postmarketing safety assessment or surveillance, or as a result of a condition of authorization. Phase 4 trials also are conducted to gather more information on the drug's desired and undesired effects, to check performance in real life and a larger user population, to identify long-term benefits and risks, and to identify any rare side effects. The trials may involve specific or varied patient populations (e.g., pregnant or nursing women) generally excluded from clinical trials or confirm side effects associated with its long-term use in the approved patient population. Where previous clinical trials were limited in thoroughly evaluating factors that could influence the drug's performance, Phase 4 trials can be used to evaluate the factors more thoroughly. For example, clinical trial participants may be instructed to follow a strict diet and drug regimen. In contrast, Phase 4 trials are conducted on regular populations where various foods and other drugs may be taken.

Phase 4 trials also may be used to find new applications for approved medicines (repurposing or reworking). Once identified, clinical trials to support new indications with approved drugs enter the drug development continuum at Phase 2 or Phase 3, depending on the indication and available supportive information.

Because Phase 3 trials are conducted in well-controlled trials with a smaller population, previously unseen harmful effects can be seen in postauthorization trials. Medicines have been removed from the market based on new safety data not reported at the time of the original authorization and in the supportive Phase 3 trials. For example, the pain reliever rofecoxib (Vioxx) showed an increased relative risk for serious cardiovascular events, including heart attack and stroke, during long-term treatment (18 months) for a new indication during a Phase 3 trial. Merck and Co. subsequently announced a voluntary, worldwide withdrawal of Vioxx from the market.[25]

The results of Phase 3 confirmatory trials are key to moving to Step 4, agency review and marketing authorization. Clinical research and the clinical trial phases of the development continuum, including conduct and objectives, are discussed in more detail in Section 4.

Step 4: Agency Review and Marketing Authorization

If all the data and evidence from discovery and development, preclinical research, clinical research, and CMC (quality) development demonstrate that the medicine is safe and effective for its intended purpose, and the product developer has fully characterized the medicine, including the quality, strength, purity, potency, and stability attributes, and the medicine can be reproducibly made, tested, and supplied, the product development continuum moves to step 4, agency review and marketing authorization.

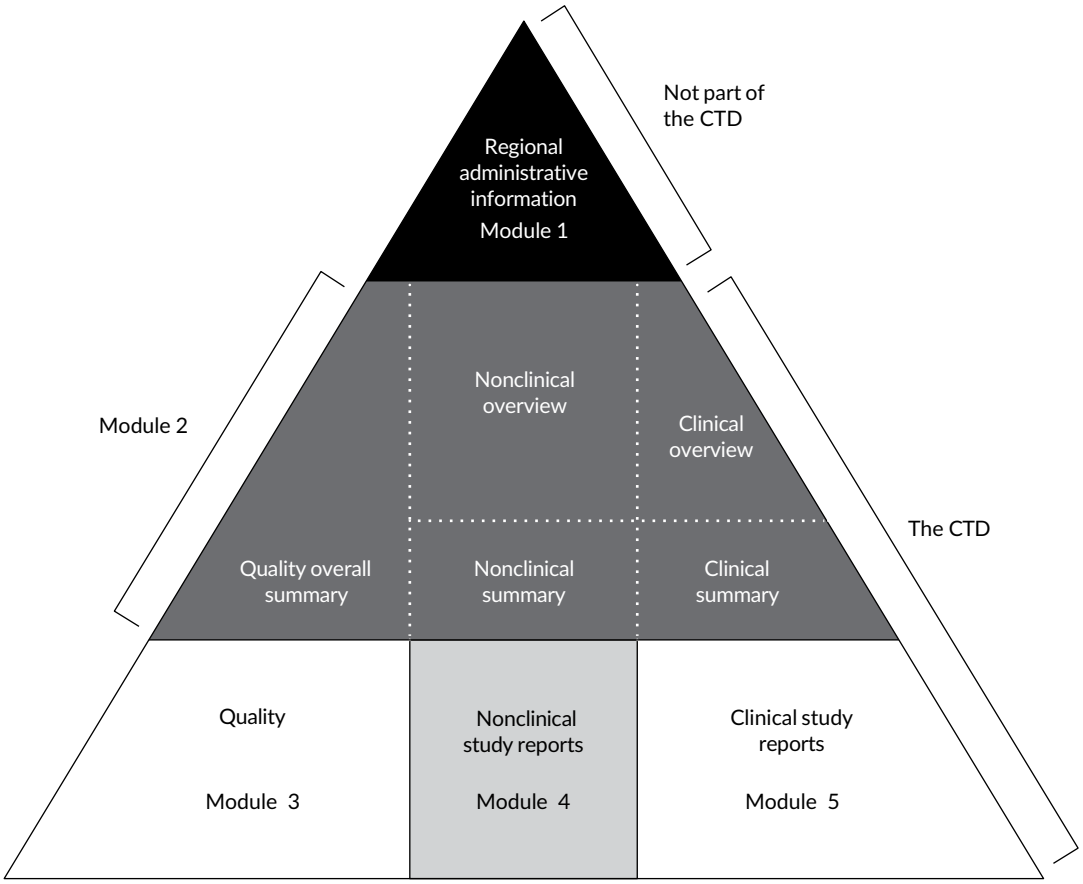
In step 4, the sponsor compiles all the relevant information demonstrating that the medicinal product is safe, effective, and of appropriate quality and submits a marketing authorization application (MAA, also called a regulatory dossier) to a regulatory agency (e.g., US FDA, EMA, Brazilian Health Regulatory Agency (ANVISA)) requesting authorization to market the product. The MAA must include data and reports from preclinical research through Phase 3 confirmatory clinical trials and CMC information about the medicine following the rules and regulations of that region. There are more than 150 regulatory agencies worldwide regulating healthcare products in individual regions.[26] Each region has regulatory requirements to which the medicinal product must conform to gain authorization. This means developers and sponsors must understand each region's requirements and create multiple documents for submission to the different regulatory agencies, adding to the complexity of product development.

Recognizing the diversity in technical requirements from country to country and the challenges of making new medicines available internationally, ICH in 1990 brought together the regulatory authorities from the US, EU, and Japan, along with pharmaceutical industry representatives, to discuss scientific and technical aspects of pharmaceuticals with the objective to develop harmonized regulatory requirements and guidelines in these regions. Since then, ICH has developed numerous guidelines on safety, quality, and efficacy topics. The guidelines have been adopted by an increasing number of regulatory agencies worldwide. Now in its fourth decade, ICH is working to extend harmonization beyond the founding regions.[27]

The Common Technical Document (CTD), finalized in 2003, fostered considerable harmonization in the technical requirements for the authorization of medicinal products. The agreement to organize all safety, efficacy, and quality information in a common format to generate well-structured regulatory dossiers negated the need to reformat the information submitted to the different regulatory authorities. It is important to note that the CTD does not address the content of information to regulatory authorities. The CTD fundamentally changed the regulatory review process and practices. The CTD is the mandatory submission format for MAAs in major markets, including Canada, Japan, EU, US, and Australia. Other regions, including the Middle East and North Africa (MENA), are implementing CTD, including the successful implementation of the electronic CTD (eCTD) specification. For example, since 2015, Saudi Arabia, Jordan, and Qatar have implemented the eCTD format.[28] At the time of writing, a major update to version 4.0 is planned to be rolled out in September 2025 with the FDA as first adopting agency, enabling major feature updates (e.g., bidirectional communication, document reuse, and a more granular data structure).[29]

Purchased from RAPS Library (library.raps.org) for the exclusive use of unknown.
© 2026 RAPS Library. Please report unauthorized use to raps@raps.org

Figure 1-5. CTD Triangle[30]



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region-specific, and modules 2, 3, 4, and 5 are intended to be common for all regions.

Source: International Council for Harmonisation.[30]

The CTD is organized into five modules (see **Figure 1-5**).[30] Module 1 is region-specific, providing information that cannot be harmonized. It includes administrative information such as application forms and labeling, including prescribing information and proposed labels for use in the region. Modules 2-5 are intended to be harmonized for all regions and make up the main body of the CTD. Module 2 contains the CTD summaries, which are basically overviews and summaries of Modules 3-5. Module 3 contains information on quality and CMC that describes how the medicinal product was developed, manufactured, controlled, and released in compliance with GMP and quality regulations. Module 4 contains nonclinical information, including study reports. Module 5 contains clinical research information, including study reports and the data from clinical trials that demonstrate safety and efficacy for its intended use. ICH has finalized guidelines for each discipline, assigning codes to each category: Q (quality), S (safety), and E (efficacy).

Also in 2003, the EMA began accepting eCTD,[31] which became mandatory for centralized procedure applications in 2010.[32] On 1 July 2015, the EMA announced it would no longer accept paper application forms for products applying to the centralized procedure.[33] Other countries followed suit. In 2017, the US announced that all new drug submissions are required to be made in eCTD format.[34] In Japan, the Pharmaceuticals and Medical Devices Agency (PMDA) issued an eCTD implantation guide in December 2017.[35] Health Canada announced eCTD as mandatory as of 1 January 2018.[36] The eCTD is increasingly becoming mandatory in different countries for various submission types. As of early 2025, the eCTD is accepted and often a mandatory format of submission in the following countries: Canada, China, EU, Japan, Jordan, Saudi Arabia, Singapore, South Korea, Switzerland, United Kingdom (UK), and the US.[37]

After the MAA is authored, formatted, compiled, and published following country-specific requirements, the eCTD allows

Purchased from RAPS Library (library.raps.org) for the exclusive use of unknown.
© 2026 RAPS Library. Please report unauthorized use to raps@raps.org

for the seamless and automatic electronic submission of the CTD to the regulatory agency. The eCTD provides a harmonized technical solution to implementing the CTD electronically. Submission of the regulatory dossier is through a method "gateway" of securely providing regulatory dossiers for review (e.g., the EU eSubmissions Gateway, the US Electronic Submission Gateway [ESG], and Health Canada's Common Electronic Submission Gateway [CESG]).

After acknowledgment of receipt and validation by the regulatory agency that the regulatory dossier is complete for formal review, the dossier is accepted, and a holistic, rigorous review begins. An agency review team that may include scientists, chemists, biologists, pharmacologists, toxicologists, statisticians, and physicians, among other experts, begins to review the evidence generated by the application holder that demonstrates the quality, safety, and effectiveness of the medicine's intended use and following proposed labeling. In addition to making key decisions regarding the medicine's safety and effectiveness profile when used as intended, the CMC used to ensure and maintain product quality are assessed to demonstrate that the processes are adequate to preserve the identity, purity, strength, potency, and microbial control throughout product use and expiry. Key to authorization is also demonstrating a favorable benefit-risk profile. Prior to final authorization of new molecular entities, the regulatory agency may require an inspection of the manufacturing facility to verify the quality information and to ensure the facility is compliant with cGMPs and is capable of manufacturing and supplying a safe medicine.

Although global regulatory authorities share the same goal – protecting public health by regulating medicinal products – the processes and timelines for reviewing MAAs vary. The US and EU are considered to have the most advanced and defined regulatory systems in the world. In the US, review fees and times are defined and driven by the Prescription Drug and User Fee Act (PDUFA) for new molecular entities, the Biosimilar User Fee Amendments (BSUFA) for biosimilars, and the Generic Drug User Fee Amendments (GDUFA) for generics.[38] NDAs and BLAs under standard FDA review have an action date of 10 months; those under priority review have an action date of 6 months. The action date may be a decision to approve the drug, not approve it, or issuance of a complete response letter when more information and adequate review time are needed.

In the EU, EMA has four registration pathways to MA, depending on the type of product and the number of countries targeted: centralized, decentralized, national, and mutual recognition procedures.[39] Evaluation of the MAA under the centralized procedure when used for authorization in the EU (27 member states) can typically take up to 210 days, not including pauses in the review cycle (clock stops) when applicants are asked to provide additional information from the Committee for Medicinal Products for Human Use (CHMP). CHMP is EMA's scientific committee responsible for human medicines and prepares scientific opinions on whether the medicine may be authorized after a thorough evaluation of the MAA. Ultimately, the scientific opinion issued by CHMP is sent to the EMA.[40] The EMA then sends the opinion to the European Commission (EC), which makes a decision to issue the MA if approved. Other regulatory agencies are improving and enhancing their regulatory systems, and the process of harmonization continues.

One significant enhancement to the regulatory review process is the result of regulatory agencies recognizing that patients with serious or rare conditions can derive clinical benefit by gaining access to potential therapies more quickly than standard review times. Accordingly, regulatory authorities across the globe have developed expedited development and nonstandard review and authorization pathways to facilitate the development of new medicines (e.g., futibatinib, pembrolizumab) for such conditions. An applicant may pursue more than one of the expedited pathways in parallel. These pathways also encourage early and continued interactions between the medicinal product developer and the regulatory agencies.

In the US, the FDA has developed four programs to facilitate and expedite the development and review of new drugs to address an unmet medical need in the treatment of a serious or life-threatening condition. The four programs are fast-track designation, breakthrough therapy designation, accelerated authorization, and priority review designation.[41]

Similarly, EMA instituted PRIME (PRIority MEdicines) to support the development of medicines that target an unmet medical need. Through PRIME, the agency offers early and proactive support to medicine developers to optimize the generation of robust data about a medicine's benefits and risks and to enable accelerated assessment of medicines applications.[42]

PMDA Japan developed the SAKIGAKE Designation System to promote research and development and early clinical research/trials in Japan aimed at early practical application for innovative medical products with significant prospective efficacy. The SAKIGAKE strategy includes priority consultations, prior assessments, and priority reviews, as well as the Scheme for Rapid Authorization of Unapproved Drugs.[43] More detail is provided in **Chapter 26**.

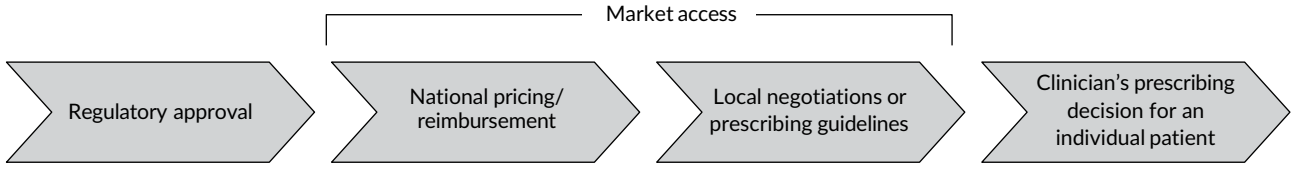
Receiving marketing authorization from any global regulatory authority is a significant milestone in a medicine developer's product development continuum to provide therapeutics to treat large population segments affected by a given disease and develop pharmaceutical innovations targeting unmet medical needs (e.g., rare diseases) for patients around the world. This step leads to Step 5 in the product development continuum, Market Access, making the medicinal product available to the right patient at the right time and at the right price.

Step 5: Market Access

The ultimate goal and focus of the medicinal product development continuum is gaining authorization and commercialization so that patients have access to a new, alternative treatment or one to meet an unmet medical need. For global pharmaceutical and biotechnology companies, this is market access, generally described as getting the right treatment to the right patient at the right time for the right

Purchased from RAPS Library (library.raps.org) for the exclusive use of unknown.
© 2026 RAPS Library. Please report unauthorized use to raps@raps.org

Figure 1-6. Communicating Value to Healthcare Stakeholders



price. Prescribers and patients need immediate, consistent, and continued access to medicines once approved and available.

Often, market access and activities are planned closer to marketing application, submission, authorization, and launch. To be successful, however, market access planning should be part of the process from early development through post-launch. That planning should provide input into the target product profile and other key development input, such as patient preferences, quality-of-life metrics, health behaviors, symptoms, and health status.

The important role of market access is illustrated in **Figure 1-6**. The simplified model shows the key considerations to market access between regulatory authorization and having the medicine prescribed.[44] Although this model shows a sequential approach to market access after authorization, the reality is that, for a successful market access strategy, the considerations need to be incorporated much earlier.

Before the patient can access the medicine, regulatory authorization must be received from the health authority in a particular country or countries. Even when authorized, the medicine may not be available to patients immediately, if ever. In many countries, national pricing and reimbursement need to be determined first. Within the EU, for example, a marketing authorization is typically followed by health technology assessments (HTAs) at the national level, which are used to guide pricing and reimbursement recommendations.

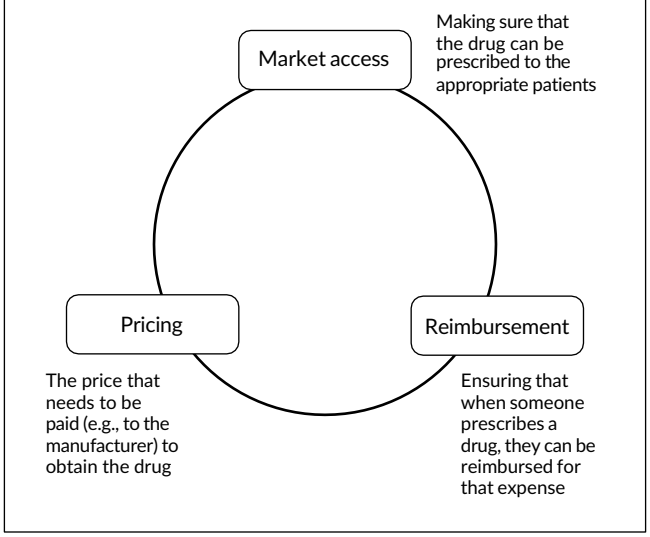
Reimbursement is not always guaranteed. For example, in January 2020, the UK National Institute for Health and Care Excellence (NICE) recommended against reimbursement for Spravato (esketamine) for treatment-resistant depression because of uncertainties about its clinical cost and effectiveness.[45] A few years later, in July 2024, NICE recommended against reimbursement for Enhertu (trastuzumab deruxtecan) for advanced breast cancer because of the sponsor companies "having been unwilling to offer a price that would enable NICE to recommend Enhertu as cost-effective for the NHS."[46] Likewise, in May 2022, the Canadian Agency for Drugs and Technologies in Health (CADTH) recommended against reimbursement for Spinraza (nusinersen) for adults with spinal muscular atrophy based on the lack of clinical trials in SMA patients age 18 years and older.[47] In October 2024, CADTH also recommended against reimbursement for Ebglyss (lebrikizumab) for treatment of atopic dermatitis. The agency cited uncertainties regarding longer-term safety and efficacy because of study design and analysis limitations, as well as a lack of appropriate comparators.[48]

Access to medicines is also affected by a variety of decision makers at the local, regional, or hospital levels. For example, a country may have 30 reimbursable licensed drugs available for a condition. However, if the local prescribing guidelines state that the patient cannot be prescribed one of the medicines, it is unlikely to be prescribed.

Once these key elements are in place, then physicians or other prescribers play a critical role in deciding which drug to prescribe to patients based on several factors, including clinical guidelines, local formularies, how a previous patient responded to a drug (including treatment-related symptoms and side effects), and other available treatments. These factors may also include health-related quality of life (QoL), which can reflect patients' perceptions of their physical, psychological, social, and overall general well-being. In Italy and Spain, QoL data are important at the regional and local levels for inclusion in formularies and guidelines.[49]

The relationship that pricing and reimbursement have with market success is shown in **Figure 1-7**. Pricing is the list price or the national price of the drug, the published price paid to the manufacturer. The price can be adjusted to include charges from wholesalers, negotiated discounts, incentives, and other agreements. In the US, the MAA holder sets the price without regulation. In many other countries, the price is set based on prices in other countries. For example, pricing in France, Germany, and the UK are commonly referenced and influence the price set in other countries.[44] In the UK, reimbursement of medicines through the National Health Service (NHS) is influenced by the NICE, the

Figure 1-7. Relationship Between Pricing, Reimbursement, and Market Access



Purchased from RAPS Library (library.raps.org) for the exclusive use of unknown.
© 2026 RAPS Library. Please report unauthorized use to raps@raps.org

Scottish Medicines Consortium (SMC), and the All Wales Medicines Strategy Group (AWMSG). In France, the Haute Autorité de Santé (HAS) uses an HTA to determine the percentage of the price to be reimbursed by the government and paid by the patient. In China, a drug needs to be included in the National Reimbursement Drug List (NRDL) to be eligible for reimbursement.[50] Eligibility for inclusion in the NRDL is decided by the central government in Beijing and the provincial governments. The process for negotiation and inclusion into the NRDL was simplified in 2016, and a significantly larger number of drugs has since become eligible for reimbursement.[44]

Reimbursement is also country-specific. In many European countries, an HTA that measures the relative effectiveness assessment (REA) of a new drug compared with the standard of care is a requirement for reimbursement. The health-related QoL is a recognized REA end point. However, there is a lack of consensus on which QoL data to use, for example, quality-adjusted life years or equal value of life years gained.[51]

While it is important to target the broadest market access possible with the most favorable pricing, it is also important to define the value of the medicine to each stakeholder. Medicinal product development companies are now including real-world evidence (RWE) tools in the product lifecycle to help achieve launch success and optimal market access, positioning the right drug to the right patient.

In simplest terms, RWE is informing and supporting decision making across the product lifecycle using analytics that provide real-world knowledge on patients, different clinical phenotypes, and the burden of disease, which was not possible in the past.[52] RWE can facilitate comparative effectiveness, help determine new product insights, and differentiate products concerning broad-based outcomes such as medication adherence, patient satisfaction, resource utilization, and associated costs.[52] These data are then used to inform the target product profile, define product specific-attributes, inform clinical trial design (right disease and patient population), and target specific markets. Clinicians and patients are also using RWE to understand advancement in care, efficiency, and health outcomes. Moving forward, RWE is a tool that is increasing in use across the drug development continuum to maximize value and increase the probability of market success.

Market access, including pricing and reimbursement, advertising, and other factors that influence market success, are discussed in more detail in **Chapters 35** and **36**.

In parallel with market access, the MAA holder is responsible for postmarketing regulations and lifecycle management of the approved medicine. The MAA holder must ensure product quality, safety, and efficacy and mitigate any potential identified postmarket impact on patient health and safety through ongoing compliance with cGMP regulations and guidance related to quality systems, including product complaints. In addition, the MAA holder must keep the application up to date regarding labeling, CMC changes (e.g., manufacturing or formulation), and pharmacovigilance (safety), including adverse event reporting. These activities are typically categorized as postauthorization activities, discussed in more detail in Section 6: Postmarketing Authorization.

Conclusion

Medicinal product development is a continuum with specific steps that are globally recognized. The process is long, complex, costly, and made more challenging by the different country-specific requirements. ICH continues to work on harmonization of regulatory requirements and guidelines beyond the founding ICH regions, and emerging markets are adopting and implementing standards such as the CTD and eCTD submission formats, ICH E8(R1) on General Considerations for Clinical Studies and ICH E6(R3) Good Clinical Practice, ICH S6 (R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals – Scientific Guideline. CMC development is an integral part of the development continuum that ensures the quality, consistency, safety, and availability of the medicinal product.

Regulatory agencies recognize the need to expedite the authorization and availability of medicinal products – especially for serious, life-threatening, rare, and orphan indications – while maintaining safety and effectiveness. Agencies such as the FDA, EMA, and PMDA have worked to create and publish guidelines and approaches to expedite development programs and nonstandard review and authorization pathways to facilitate the availability of new medicines. Agencies are encouraging early and frequent interactions for novel medicines and new indications.

Marketing authorization is key to allowing medicines to be sold in the regions authorized. In many countries, however, national pricing and reimbursement need to be determined and agreed upon before the medicine is prescribed and patients can access the medicine. Often, decisions also are made at the local, regional, or hospital levels. Market success needs to take into account pricing, reimbursement, and stakeholder (payer, physician, and patient) needs. Health technology assessments, health-related quality of life metrics, and real-world evidence are playing important roles in the product development continuum and provide input to clinical trial design, target product profile, and more, helping to ensure the right drug is developed for the right patient at the right price.

References

All references verified 12 February 2025.

1. Food and Drug Administration. The drug development process. Last updated 4 January 2018. https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process

2. European Medicines Agency. From lab to patient: Journey of a medicine. Last updated 10 February 2020. https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines#from-lab-to-patient

Purchased from RAPS Library (library.raps.org) for the exclusive use of unknown.
© 2026 RAPS Library. Please report unauthorized use to raps@raps.org

References (continued)

3. Food and Drug Administration. Exclusivity and generic drugs – What does it mean? Date of last update unknown. https://www.fda.gov/files/drugs/published/Exclusivity-and-Generic-Drugs--What-Does-It-Mean-.pdf
4. Food and Drug Administration. Determining whether to submit an ANDA or 505(b)(2) application [Guidance document]. Issued May 2019. Last updated 3 March 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/determining-whether-submit-anda-or-505b2-application
5. Official Journal of the EU. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001. Last Updated 1 January 2025. https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX%3A32001L0083
6. Food and Drug Administration. Generic drugs: Questions and answers. Updated 16 March 2021. https://www.fda.gov/drugs/frequently-asked-questions-popular-topics/generic-drugs-questions-answers
7. European Medicines Agency. Generic and hybrid medicines. https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/generic-hybrid-medicines
8. European Medicines Agency. Biosimilar medicines: Overview. https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview
9. Food and Drug Administration. Biosimilars and interchangeable biologics: More treatment choices. Current as of 17 August 2023. https://www.fda.gov/consumers/consumer-updates/biosimilar-and-interchangeable-biologics-more-treatment-choices
10. European Medicines Agency. Omnitrope. Last updated 20 September 2023. https://www.ema.europa.eu/en/medicines/human/EPAR/omnitrope#authorisation-details-section
11. Drugs@FDA. BLA 125553 Approval Letter, 6 March 2015. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/125553Orig1s000ltr.pdf
12. Quartz. Viagra's famously surprising origin story is actually a pretty common way to find new drugs. Last updated 20 July 2022. https://qz.com/1070732/viagras-famously-surprising-origin-story-is-actually-a-pretty-common-way-to-find-new-drugs
13. Kim JH, Scialli AR. Thalidomide: The tragedy of birth defects and the effective treatment of disease. Toxicol Sci. 2011 Jul;122(1):1-6. 19 April 2011. Erratum in: Toxicol Sci. 2012 Feb;125(2):613. https://doi.org/10.1093/toxsci/kfr088
14. Huang R, Southall N, Wang Y, Yasgar A, Shinn P, Jadhav A, Nguyen DT, Austin CP. The NCGC pharmaceutical collection: A comprehensive resource of clinically approved drugs enabling repurposing and chemical genomics. Science Translational Medicine. 2011;3(80):80ps16. https://doi.org/10.1126/scitranslmed.3001862
15. Drugs@FDA. BLA 125514. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=125514
16. Rudrapa M et al. Drug repurposing (DR): An emerging approach in drug discovery. In Badria AF, ed. Drug Repurposing – Hypothesis, Molecular Aspects and Therapeutic Applications. https://www.intechopen.com/chapters/72744
17. BIO/QLS Advisors/Informa UK Ltd. Clinical development success rates and contributing factors 2011-2020. https://www.bio.org/clinical-development-success-rates-and-contributing-factors-2011-2020
18. Hughes JP, Rees S, Kalindjian SB, Philpott KL. Principles of early drug discovery. Br J Pharmacol. 2011 Mar;126(6):1239-49. https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/j.1476-5381.2010.01127.x
19. Food and Drug Administration. Content and format of investigational new drug applications (INDs) for Phase 1 studies of drugs, including well-characterized, therapeutic, biotechnology-derived products [Guidance document]. Current as of 6 May 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/content-and-format-investigational-new-drug-applications-inds-phase-1-studies-drugs-including-well
20. National Institutes of Health. NIH's definition of a clinical trial. Last updated 18 September 2024. https://grants.nih.gov/policy/clinical-trials/definition.htm
21. International Council for Harmonisation. General considerations for clinical studies E8(R1) [guideline]. Adopted 6 October 2021. https://database.ich.org/sites/default/files/ICH_E8-R1_Guideline_Step4_2021_1006.pdf
22. International Council for Harmonisation (ICH). Guideline on good clinical practice E6(R3). Adopted 6 January 2025. https://database.ich.org/sites/default/files/ICH_E6%28R3%29_Step4_FinalGuideline_2025_0106.pdf
23. National Institutes of Health. NIH clinical research trials and you: The basics. Last reviewed 24 April 2025. https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics
24. Burt T, et al. Phase 0/microdosing approaches: Time for mainstream application in drug development? Nat Rev Drug Discov. 2020;19(11):801-818. https://doi.org/10.1038/s41573-020-0080-x
25. Food and Drug Administration. Vioxx (rofecoxib) Questions and answers. Current as of 6 April 2016. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/vioxx-rofecoxib-questions-and-answers
26. Pharmaguideline. International health regulatory bodies. https://www.pharmaguideline.com/2011/02/international-regulatory-bodies.html
27. International Council for Harmonisation. History. https://www.ich.org/page/history
28. Biomapas. eCTD implementation across MENA region: What is the current status? https://www.biomapas.com/ectd-implementation-across-mena-region-what-is-the-current-status/
29. Food and Drug Administration. Electronic common technical document (eCTD) v4.0. Last updated 19 September 2024. https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd-v40
30. International Council for Harmonisation. CTD. https://www.ich.org/page/ctd
31. European Agency for the Evaluation of Medicinal Products. Work programme 2023. Adopted 19 December 2002. https://www.ema.europa.eu/en/documents/work-programme/work-programme-european-agency-evaluation-medicinal-products-2003_en.pdf
32. European Medicines Agency. EMEA implementation of electronic-only submissions and eCTD submissions: Practical guidelines relating to non-eCTD electronic submissions. December 2008 EMEA/6339/2008 V1. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/emea-implementation-electronic-only-submission-ectd-submission-practical-guidelines-relating-non_en.pdf
33. European Medicines Agency. Regulatory information – Transitioning to mandatory use of electronic application forms. 25 February 2015. https://www.ema.europa.eu/en/news/regulatory-information-transitioning-mandatory-use-electronic-application-forms
34. FDA Guidance for Industry, Providing regulatory submissions in electronic format – Certain human pharmaceutical product applications and related submissions using the eCTD specifications. September 2024. https://www.fda.gov/media/135373/download
35. Pharmaceuticals and Medical Devices Agency. ICH electronic common technical document (eCTD) v4.0 implementation guide in Japan v1.20. Provisional Translation (as of December 2017). https://www.pmda.go.jp/files/000222267.pdf
36. Government of Canada. Notice – Mandatory requirements for using the Common Electronic Submissions Gateway (CESG). https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/notice-mandatory-requirements-using-common-electronic-submissions-gateway.html
37. International Council of Harmonisation. ICH M8 electronic common technical document (eCTD) v3.2.2 Implementation Status. Date of last update unknown. https://www.ich.org/page/multidisciplinary-guidelines
38. Food and Drug Administration. FDA: User fees explained. Current as of 22 May 2024. https://www.fda.gov/industry/fda-user-fee-programs/fda-user-fees-explained

Purchased from RAPS Library (library.raps.org) for the exclusive use of unknown.
© 2026 RAPS Library. Please report unauthorized use to raps@raps.org

References (continued)

39. European Medicines Agency. Obtaining an EU marketing authorisation, step-by-step. https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/obtaining-eu-marketing-authorisation-step-step
40. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). https://www.ema.europa.eu/en/committees/committee-medicinal-products-human-use-chmp
41. Food and Drug Administration. Guidance for industry: Expedited programs for serious conditions – Drugs and biologics [Guidance document]. May 2014. Last updated 28 November 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics
42. European Medicines Agency. PRIME: Priority medicines. Last updated 2 June 2025. https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines
43. Ministry of Health, Labour and welfare of Japan. Strategy of SAKIGAKE. https://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/140729-01.html
44. Rx Communications. An introduction to market access in the pharmaceutical industry. First Published 1 January 2024. https://www.rxcomms.com/learning/guide-to-market-access-in-the-pharmaceutical-industry
45. Drug Discovery Today. Nasal spray medicine for treatment-resistant depression not recommended by NICE. 28 January 2020. http://www.drugdiscoverytoday.com/view/47713/nasal-spray-medicine-for-treatment-resistant-depression-not-recommended-by-nice/
46. National Institute of Health and Care Excellence. NICE disappointed companies unwilling to offer fair price to make Enhertu available for advanced breast cancer. 29 July 2024. https://www.nice.org.uk/news/articles/nice-disappointed-that-companies-unwilling-to-offer-fair-price-to-the-nhs-to-make-enhertu-available
47. CADTH Reimbursement recommendation Nusinersen (Spinraza). Last updated August 2022. https://www.cda-amc.ca/sites/default/files/DRR/2022/SR0713-Spinraza-Reassessment.pdf
48. CADTH Reimbursement recommendation Ebglyss (lebrikizumab). Last updated 9 October 2024. https://www.cda-amc.ca/lebrikizumab
49. Gardiner RB, Sealey S, Edathodu A, Makku SR. The real impact of quality of life (QoL) endpoints on market access decisions across markets – A case study of oncology products. Value Health. 2014;17(3):PA94-A95. https://doi.org/10.1016/j.jval.2014.03.550
50. Xiao Y, Gani R, Chen K, Chen C, Kongnakorn T. Health economics in China: Changing pharmaceutical pricing and reimbursement. Evidence Forum. 2019. https://www.evidera.com/wp-content/uploads/2019/10/12-Health-Economics-in-China_Fall2019.pdf
51. Kleijnen S, et al. The impact of quality-of-life in relative effectiveness of new anti-cancer drugs in European countries. Qual Life Res. 2017;26(9):2479-2488. https://doi.org/10.1007/s11136-017-1574-9
52. PharmaVoice. Ask the experts: How does real world evidence ensure market access? 1 March 2020. https://www.pharmavoice.com/news/2020-03-rwe-experts/612296/

Purchased from RAPS Library (library.raps.org) for the exclusive use of unknown.
© 2026 RAPS Library. Please report unauthorized use to raps@raps.org

Purchased from RAPS Library (library.raps.org) for the exclusive use of unknown.
© 2026 RAPS Library. Please report unauthorized use to raps@raps.org

CHAPTER 2

International Harmonization via ICH, WHO, and Other Global Initiatives

Linda McBride, RPh, RAC-US

This chapter focuses on the current international environments for the regulation of medicinal products, including a comprehensive overview of the critical roles of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the World Health Organization (WHO), which is the sole United Nations (UN) agency leading the initiatives and collaborations for the global health ecosystem. The chapter also discusses international organizations focused on harmonization and continuous improvements for efficiencies in the global regulatory processes.

International Council for Harmonisation

Established in 1990, the purpose of ICH is "to make recommendations toward achieving greater harmonization in the interpretation and application of technical guidance and requirements for pharmaceutical product registration."[1]

Regulatory harmonization offers many benefits to global regulatory authorities and the pharmaceutical industry in terms of protecting public health. The key benefits of this harmonization effort include preventing the duplication of clinical trials in humans and minimizing the use of animal testing without compromising safety and effectiveness; streamlining the regulatory assessment process for marketing applications; and reducing the development times and resources for drug development.[2]

The founding members of ICH were regulatory and pharmaceutical industry representatives from developed nations, including the US, EU, and Japan.[3] Membership has expanded to other countries and organizations holding observer status (see **Table 2-1**).[4]

ICH prioritizes transparency regarding its harmonization work as one way to build and maintain public trust. The ICH Assembly and Management Committee works to ensure that the ICH process remains transparent and has recognized that all stakeholders should have current information on the important decisions and real-time progress of ICH guideline development.

ICH harmonization activities fall into four categories: formal ICH procedures, Q&A procedures, revision procedures, and maintenance procedures. For each activity, a concept paper and/or a business plan may be required (see **Figure 2-1**).[5]

The formal ICH procedure consists of five steps. It is followed for the harmonization of all new ICH topics. An expert working group (EWG) is established, which works on the following steps and procedures for implementation.

Step 1: Consensus Building

- The EWG prepares a consensus draft of the technical document based on the objectives in the concept paper.

Step 2a: Confirmation of Consensus on the Technical Document

- This step is approached when the assembly agrees, per the EWG report, that there is sufficient scientific consensus for the technical document to proceed to the next stage of regulatory consultation.

Step 2b: Adoption of the Draft Guideline

- Based on the technical document, regulatory members will take the necessary actions to develop the draft guideline.
- Regulatory members endorse the draft guideline.

Step 3: Regulatory Consultation and Discussion

- **Stage I** – applies to the regional regulatory consultation stage;
- **Stage II** – applies to the discussion of regional consultation comments after obtaining all comments from the consultation process; and
- **Stage III** – the finalization of the step 3 expert draft guideline. The step 3 expert draft guideline with regulatory EWG signatures is submitted to the regulatory members of the assembly to request adoption.

Step 4: Adoption of an ICH Harmonised Guideline

- The assembly agrees that there is sufficient consensus on the draft guideline. The ICH regulatory members adopt the step 4 final document as an ICH harmonised guideline.

Step 5: Implementation

- Implementation is carried out according to the same national/regional procedures that apply to other regional regulatory guidelines and requirements in the ICH regions.[6]

Purchased from RAPS Library (library.raps.org) for the exclusive use of unknown.
© 2026 RAPS Library. Please report unauthorized use to raps@raps.org