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# Global Regulatory Submissions: ICH vs Regional Rules

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# Executive Summary

The management of pharmaceutical regulatory submissions across global markets involves navigating both internationally harmonized guidelines (principally those of the International Council for Harmonisation, ICH) and diverse local regulatory requirements. ICH was established in 1990 to create a *"harmonized rulebook"* for drug development, aiming to "reduce or obviate duplication of testing" and thus streamline global drug registration (www.ncbi.nlm.nih.gov) (www.ncbi.nlm.nih.gov). Over its 30+ year history, ICH has produced dozens of guidelines covering **quality (Q)**, **safety (S)**, **efficacy (E)**, and **multidisciplinary (M)** areas (www.ncbi.nlm.nih.gov). One centerpiece of harmonization is the Common Technical Document (CTD), a standardized format for drug dossiers that enables a single dossier to be accepted by multiple agencies (www.ncbi.nlm.nih.gov). In practice, however, each national or regional authority still maintains sovereign laws and requirements ("the *local 10%*") that can significantly diverge from ICH expectations (pharmacystandards.org) (pharmacystandards.org).

This report provides an in-depth analysis of the current global regulatory landscape, contrasting ICH-based harmonization with regional specifics. We examine the history and mission of ICH, the adoption of its guidelines, and how industry leverages them (often targeting simultaneous US/EU/JP submissions) (www.appliedclinicaltrialsonline.com). We then analyze key market differences (US FDA, EU EMA, Japan PMDA, China NMPA, etc.) in submission processes, labeling, quality standards, and review procedures. Throughout, we cite data and expert commentary to quantify the impact: for example, FDA approved 48 novel drugs in 2019 (www.nature.com) versus 66 positive EMA opinions (www.ema.europa.eu), and China's NMPA began approving dozens of new drugs yearly by 2019 (english.nmpa.gov.cn). We also present case studies

and recent initiatives – such as FDA's Project Orbis (concurrent oncology reviews) (www.fda.gov) and the pandemic-era reliance on foreign reviews to accelerate COVID-19 vaccine approvals (pmc.ncbi.nlm.nih.gov) – that illustrate contemporary strategies and challenges.

Key findings include the critical importance of planning for the "local 10%" (region-specific dossiers, Module 1 content, labeling, language, serialization, etc.) even when relying on ICH alignment (pharmacystandards.org) (pharmacystandards.org). Companies pursuing global filings often benefit from a unified core dossier (Modules 2–5) but must allocate dedicated resources to country-specific variations. Indeed, over the past decade industry has experienced *"a proliferation of regulatory divergence regarding the interpretation and implementation of ICH guidelines across regions,"* requiring multiple region-specific control strategies (ispe.org). This divergence, while challenging, drives initiatives toward further harmonization and digitization: for example, virtually all major agencies (FDA, EMA, PMDA, etc.) now require electronic CTD (eCTD) submissions (knowledgenet.sarjen.com), and others (e.g. China's NMPA, Brazil's ANVISA) are transitioning to eCTD (knowledgenet.sarjen.com).

Looking ahead, global submission strategies must account for emerging trends **(Table 1)** such as increased reliance on regulatory coalitions (e.g. FDA–EMA parallel advice), structured content management (to avoid duplicated effort), and new technologies (AI-assisted dossier authoring) (intuitionlabs.ai) (pmc.ncbi.nlm.nih.gov). Without meticulous attention to both harmonized guidelines and local detail, firms risk delays or denials – as one expert warned, failing to account for *"distinct regulatory requirement differences"* can jeopardize an entire submission (www.lifescienceleader.com). However, when executed well, harmonized strategies can significantly cut costs and time: one commercial explainer claims that ICH-aligned development lowers R&D costs by 15–30% (patientanalog.com) and saves roughly $2.6 billion industry-wide annually (patientanalog.com), although these figures do not come from a peer-reviewed or regulator-published analysis.

We conclude that effective management of regulatory submissions in global markets demands a dual lens: leveraging ICH to build a shared evidence base, while customizing for each region's non-negotiable laws and expectations. With thoughtful strategy, robust process controls, and proactive use of harmonized standards, companies can expedite worldwide access to drugs and vaccines, ultimately benefiting patients across diverse markets.

# Introduction and Background

The globalization of drug development has made international regulatory harmonization both more necessary and more complex. In the late 20th century, pharmaceutical regulators in the United States, European Union, and Japan recognized that duplicative testing and divergent requirements were inefficient. In response, they formed the **International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)**. ICH's mission is explicitly *"to make recommendations towards achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration, thereby reducing or obviating duplication of testing"* (www.ncbi.nlm.nih.gov). The initial ICH partnership (EU, Japan, US) has since expanded to include *permanent members* Health Canada and Swissmedic, plus a growing group of other *regulatory members* such as Brazil (ANVISA), China (NMPA),

South Korea (MFDS), Singapore (HSA) and the UK (MHRA) (patientanalog.com). After its November 2025 Assembly, which admitted Nigeria's NAFDAC and South Africa's SAHPRA, ICH counted 25 members (regulators and industry associations) and 41 observers (www.therqa.com).

Over its multi-decade history, ICH has produced dozens of guidelines across four pillars: Quality (Q), Safety (S), Efficacy (E), and Multidisciplinary topics (www.ncbi.nlm.nih.gov).Examples include Quality stability testing (Q1A) and safety pharmacology (S7), as well as conduct of clinical trials (Efficacy) and standardization of medical dictionaries (MedDRA in M). Crucially, ICH also created the **Common Technical Document (CTD)** – a standardized dossier structure for new drug applications, including guidelines on how to format and file data. As one review explains, *"ICH has produced numerous guidelines in four major categories … and has developed [the] Common Technical Document for electronic submission of data on new drug applications (NDAs)… [which] facilitates review and enables industry to submit its data to different regulatory authorities in a single format."* (www.ncbi.nlm.nih.gov). In other words, a single ICH-compliant dossier (Modules 2–5 with structured data) should in principle serve all member authorities, greatly easing multi-region filings.

Indeed, ICH adoption can yield substantial economies. One commercial explainer claims harmonized ICH processes can reduce development costs by roughly 15–30% (patientanalog.com) and estimates around **$2.6 billion per year** in industry savings via avoided duplication (patientanalog.com); these are unaudited estimates rather than regulator-published figures, but the direction is plausible given the multi-billion-dollar budgets for R&D. By harmonizing clinical data standards, pharmacopoeial expectations, and quality guidelines, ICH allows companies to run a *single* pivotal trial acceptable to multiple regulators, or to use one set of stability or toxicology studies across markets. For example, ICH Q1A on stability testing specifies storage conditions and testing intervals; data collected per Q1A will be accepted by all ICH agencies (with only occasional minor local tests) (www.ncbi.nlm.nih.gov). Similarly, ICH Common Technical Document guidelines lead to the electronic CTD ("eCTD") standard adopted worldwide, so that a well-organized dossier can be submitted electronically with minimal reformatting (www.ncbi.nlm.nih.gov).

However, the existence of ICH harmonization does **not** eliminate all regional differences. As one expert module starkly notes, *"ICH guidelines only cover the harmonized 90% of a global dossier (Modules 2–5) – the remaining 'local 10%' in Module 1 is entirely national"* (pharmacystandards.org). Every country still has sovereignty over its laws, legal labeling requirements, language rules, and non-negotiable practices (pharmacystandards.org) (pharmacystandards.org). This tension forms the central challenge of global submissions: leveraging ICH for a unified scientific backbone, while also tailoring to myriad local regulations. This report explores that landscape in detail, with data, expert commentary, and case examples.

# The Global Regulatory Landscape

## Major Regulatory Authorities and Their Relationships to ICH

The pharmaceutical regulatory landscape spans dozens of national agencies. Among the most influential are:

- **United States (FDA)** – Center for Drug Evaluation and Research (CDER)
- **European Union (EMA)** – Committee for Medicinal Products for Human Use (CHMP) for centralized authorization

- **Japan (PMDA)** – Japan Pharmaceuticals and Medical Devices Agency
- **Canada (Health Canada)**
- **Switzerland (Swissmedic)**
- **United Kingdom (MHRA)** (post-Brexit, no longer in EMA, but EMA guidelines were largely adopted up to 2020)
- **South Korea (MFDS)**
- **Australia (TGA)**
- **China (NMPA, formerly CFDA)** – Fast-growing participant
- **Latin America (e.g., Brazil ANVISA, Mexico COFEPRIS)** – varying ICH adoption
- **Other regions** – e.g. emerging markets (India's CDSCO, ASEAN MRA, Africa's Regulatory Harmonization initiatives).

Crucially, the **core ICH regions** (US, EU, Japan) and the standing regulatory members (Canada, Switzerland) have aligned their regulations through ICH. Japan has been part of ICH since its founding in 1990, while Brazil and South Korea joined as regulatory members in 2016 and China in 2017, pledging to implement these guidelines (patientanalog.com). As such, these agencies share most of the high-level technical criteria for drug quality, safety, and efficacy. For example, an NDA following ICH CTD format is *in principle* acceptable to both FDA and EMA, and even countries like Canada and Australia generally require eCTD submissions compatible with ICH structure.

Nevertheless, major differences remain. Regulatory frameworks reflect each region's legal and procedural norms. For instance, the FDA operates under U.S. federal statutes (e.g. the Food, Drug, & Cosmetic Act) while EMA decisions stem from European Union pharmaceutical regulation (EU Directive 2001/83/EC). Their definitions of pathways can differ (see Table 2). In practice, any global filing team must map one company's "master dossier" onto each agency's specific requirements.

Table 1 (below) summarizes the current global adoption of the electronic CTD format, indicating which authorities mandate, accept, or are transitioning to e-submissions. Virtually all major agencies now require eCTD by mandate (knowledgenet.sarjen.com). Others like Australia's TGA or South Africa's SAHPRA accept it optionally (knowledgenet.sarjen.com). Some non-ICH markets (e.g., China, Brazil, India) are actively transitioning toward eCTD (knowledgenet.sarjen.com). The spread of eCTD underscores the trend toward data standardization, yet even so the content of supporting documents (e.g. Module 1 cover letters or labeling) is still localized.

| Region / Country | Regulatory Authority | eCTD Submission Requirement (Status) (knowledgenet.sarjen.com) (knowledgenet.sarjen.com) (knowledgenet.sarjen.com) |
|---|---|---|
| United States | FDA (CDER) | eCTD **Mandatory** – required for all new submissions (knowledgenet.sarjen.com) |
| European Union (EU) | EMA (CHMP/CMDh) | eCTD **Mandatory** for centralized MAAs (knowledgenet.sarjen.com) |
| Japan | PMDA | eCTD **Mandatory** for NDAs, generally followed ICH structure (knowledgenet.sarjen.com) |
| Canada | Health Canada | eCTD **Mandatory** – required for new drug submissions, abbreviated new drug submissions and their supplements since January 1, 2018 |

| Region / Country | Regulatory Authority | eCTD Submission Requirement (Status) (knowledgenet.sarjen.com) (knowledgenet.sarjen.com) (knowledgenet.sarjen.com) |
|---|---|---|
| Switzerland | Swissmedic | eCTD **Mandatory** (aligned with EU) |
| United Kingdom | MHRA (UK) | eCTD **Mandatory** (adopted EU stance pre-2021) |
| South Korea | MFDS | eCTD **Mandatory** as of 2020 |
| Saudi Arabia | SFDA (Saudi FDA) | eCTD **Mandatory** for new drug applications (via GHC consortium) |
| United Arab Emirates | MOHAP (UAE) | eCTD **Mandatory** since 2018 (knowledgenet.sarjen.com) |
| Singapore | HSA | eCTD **Mandatory** from 2014 onwards |
| Brazil | ANVISA | eCTD **Transitioning** (pilot since 2020; requiring rollout) (knowledgenet.sarjen.com) |
| China | NMPA | eCTD **Transitioning** (Pilots begun; full mandate forthcoming) (knowledgenet.sarjen.com) |
| India | CDSCO | eCTD **Planning/Transitioning** (pilots begun; timeline unclear) (knowledgenet.sarjen.com) |
| Australia | TGA | eCTD **Accepted/Optional** (electronic templates available) (knowledgenet.sarjen.com) |
| South Africa | SAHPRA | eCTD **Accepted/Optional** (since 2018) (knowledgenet.sarjen.com) |
| Malaysia | NPRA | eCTD **Accepted** (electronic submissions in use) |
| Thailand | Thai FDA | eCTD **Accepted** (e-submissions available) |

*Table 1: Status of eCTD submissions in major global regulatory agencies (based on a vendor-compiled industry overview; scope and dates vary by submission type, so confirm the current requirement with each authority before filing) (knowledgenet.sarjen.com) (knowledgenet.sarjen.com).*

## Historical Context and Evolution of Harmonization

The movement toward harmonization predates ICH. In the 1970s–1990s, various organizations (e.g., WHO, GHTF, IMDRF for medical devices) promoted standardization, but progress was slow and statute-bound. The launch of ICH in 1990 marked a major shift, first focusing on technical requirements for new drug registration. The initial ICH guidelines in the 1990s (Q, S, and E series) aimed to align core scientific requirements. Over time, ICH scope widened to include topics like Electronic Standards for the Transfer of Regulatory Information (ESTRI), the CTD itself (M4), lifecycle management of post-approval changes (Q12), and later innovative development concepts (Q8–Q10 Quality-by-Design framework). By 2015 ICH became a formal legal entity in Geneva, reflecting its global importance (patientanalog.com).

Meanwhile, regional differences persisted. Notably, Japan's regulatory system historically required bridging data for any foreign clinical trials, while the U.S. allowed reliance on a single global study (as long as it met local Good Clinical Practice). EU drug approval centered on national procedures until the 1990s, then shifted to centralized marketing authorizations (especially after 1995 for certain product categories). Over the last decade, even non-ICH regions have moved steadily toward ICH adoption. For example, China overhauled its

Drug Administration Law in 2019, initiating new accelerated pathways and reliance on international data (english.nmpa.gov.cn) (english.nmpa.gov.cn). By 2020, NMPA vastly reduced review times, enabling dozens of imported and innovative drugs to be approved in a year (english.nmpa.gov.cn). All these developments form the backdrop against which global submission strategies are planned.

# ICH Harmonization Framework

## Guiding Principles and Core Outputs

ICH's stated mission is to **harmonize technical guidelines** so that a single set of scientific data fulfills multiple regulatory requirements (www.ncbi.nlm.nih.gov). In practical terms, this means building a network of consensus documents (guidelines) on topics like stability (Q1A), impurity testing (Q3A/B), clinical pharmacology (E4, E6 on GCP, etc.), and quality systems (Q10). These guidelines do not have the force of law, but each ICH member agrees to adopt and implement them. Thus, following an ICH guideline effectively creates a *global standard* for that topic.

The four main categories of ICH guidelines are:

- **Quality (Q):** Related to drug manufacturing and control. e.g. Q3A (Impurities in new drug substances), Q6A (Specifications: Test Procedures and Acceptance Criteria), Q10 (Pharmaceutical Quality System). These align GMP and pharmacopoeial expectations across regions.
- **Safety (S):** Non-clinical safety (e.g. S7A for safety pharmacology, S9 for nonclinical evaluation for anticancer drugs). These guidelines ensure consistent toxicological testing frameworks.
- **Efficacy (E):** Clinical trial design and reporting. For example, E3 (Structure & Content of Clinical Study Reports), E5 (Ethnicity considerations in populations), E6 (Good Clinical Practice), E17 (Multi-regional clinical trials). Use of E guidelines means a single clinical program can meet multiple agencies' expectations.
- **Multidisciplinary (M):** Cross-cutting topics and processes. E.g. M4 on CTD/eCTD dossier structure, M7 on mutagenic (genotoxic) impurities. Clinical safety data management is covered by the E2 series (e.g. E2A on expedited reporting).

For example, as described in an expert "Workshop Summary", ICH Q1A on stability testing *"specifies the temperature and humidity conditions"* for proving stability of drug substances. If firms follow Q1A, *"any of the three ICH regulatory agencies (EMA, PMDA, FDA) will accept the test data"* (www.ncbi.nlm.nih.gov). Similarly, modules 2–5 of the CTD organize summaries, quality data, and clinical study reports in a uniform way. ICH's implementation of CTD (and later eCTD) was a landmark: industry can produce one dossier with common Modules 2–5, and then only customize the region-specific Module 1 elements (cover letters, labeling, regional forms).

Indeed, one purpose of ICH's harmonization is cost reduction. PatientAnalog estimates that the ICH framework can cut development costs 15–30% (patientanalog.com). By conducting *one* pivotal trial rather than separate registry studies per region, or by using one impurity testing regimen globally, companies avoid redundant work.

Economies of scale in preparation of toxicology packages and stability studies alone can justify the harmonization effort.

## ICH Implementation and Global Adoption

ICH operates a five-step guideline development process: consensus drafting by experts from industry and agencies, regional consultation, finalization, and then implementation by each regulatory body (www.ncbi.nlm.nih.gov). After release, each ICH member (and any observer country) undertakes to implement the guideline in law or regulation. For example, ICH E6 on Good Clinical Practice is published by FDA as guidance (alongside its own GCP regulations in 21 CFR Parts 50, 56 and 312) and is referenced in the EU under the Clinical Trials Regulation (EU) No 536/2014, which replaced the former Clinical Trials Directive.

By the mid-2010s, most mature markets (US, EU, Japan, Canada, Switzerland) had fully integrated ICH guidelines. Moreover, many authorities outside the founding group implement ICH guidelines topic by topic as members or observers, and several regional formats (such as the ASEAN Common Technical Dossier) are modeled on the ICH CTD.

Table 2 (below) illustrates how two major markets structure their submissions under this harmonization. Both the US and EU require CTD/eCTD dossiers, but differ in naming and procedure. The FDA evaluates an **NDA** under 10–12 month PDUFA timelines, while the EMA assesses a **Centralized MAA** in 210 operational days (not counting clock-stops). Crucially, though the *data* requirements for Modules 2–5 are aligned by ICH, the *presentation* of Module 1 and labeling is fully local (pharmacystandards.org). The table highlights select differences:

| Aspect | FDA (United States) | EMA (European Union) |
|---|---|---|
| Submission type | New Drug Application (NDA) | Marketing Authorisation Application (MAA, centralized) |
| eCTD submission | **Mandatory** (electronic) | **Mandatory** |
| Review timeline* | Usually 10 months (standard) | ~210 days (clock-stops excluded), followed by a European Commission decision (up to 67 days) |
| Labeling format | US Prescribing Information | EU Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) (pharmacystandards.org) |
| Label languages | English only | All official EU languages (24 languages) (pharmacystandards.org) |
| Label template | FDA's own PI format | EU QRD template (strict EU-format documents) (pharmacystandards.org) |
| Quality oversight | CGMP inspections (including pre-approval inspections) | EU GDP/GMP inspections; release by Qualified Person required |
| Advisory process | FDA Advisory Committees | EMA scientific committees (CHMP, PRAC) provide opinions |

*Table 2: Comparison of key dossier and labeling differences between FDA (US) and EMA (EU). Labeling row cites an ICH commentary noting that "the format and presentation [of the label] are 100% local" (pharmacystandards.org).*

This table illustrates a core point: **the content and data can be harmonized (through ICH), but format, language, and specific regulatory forms remain local**. For example, the U.S. FDA requires one approved label in English (the Prescribing Information), whereas an EMA submission must include the SmPC and PIL in *all* 24 EU languages (pharmacystandards.org). Similarly, the EU mandates Braille product names on cartons and readability testing, features with no analog in the FDA system (pharmacystandards.org). These national requirements underline that, even after ICH harmonization, *regulators can and do impose unique demands*.

## Current State of Harmonization

Despite these regional specifics, there is a growing trend toward convergence of global standards. In recent years, ICH itself has expanded membership beyond the founding trio to many other nations, reflecting the rising importance of global-phase submissions (e.g. simultaneous US/EU filings). Additionally, inter-agency collaboration has increased. The FDA and EMA now hold periodic "Clusters" on topics from virology to manufacturing, sharing data and scientific insights. They even piloted parallel review programs (e.g. a joint FDA–EMA Quality-by-Design pilot in 2011) (ispe.org). These efforts reinforce that, while differences remain, the direction is toward more aligned regulatory culture.

Numerous initiatives have built consensus on pharmacovigilance planning (e.g. ICH E2E, which underpins risk management planning in many regions), on electronic submissions (CDISC data standards for clinical datasets, enabling common databases), and on real-world evidence. More recently, collaborative review programs such as FDA's Project Orbis have arisen to synchronize review of critical oncology therapies across borders (discussed below), while regional schemes such as EMA's PRIME support early access within a single jurisdiction. Taken together, these developments signal that the harmonization achieved by ICH remains the foundation, even as each region's laws sit atop that base.

# Managing Global Submissions: Strategies and Challenges

Developing and executing a global regulatory submission plan is a complex project involving cross-functional coordination, detailed knowledge of myriad regulations, and careful project management. Pharma companies often aim to leverage ICH guidelines by using a **common core dossier** for all major markets, then customizing regional elements. As one industry article notes, **most** global teams have been pursuing simultaneous US/EU (and often Japanese) filings for 15–20 years, thanks to ICH harmonization making a unified dossier feasible (www.appliedclinicaltrialsonline.com). Theoretically, this "life-cycle" approach can save time and money by reusing data across filings.

In practice, though, international filing requires balancing harmonization with local tailoring. A typical strategy is:

- **Global Core Plan (Modules 2–5):** Conduct multinational clinical trials under ICH GCP, produce nonclinical study data per ICH S guidelines, and assemble a single CTD-eCTD dossier in Modules 2–5. This core should meet the strictest of the target agencies' expectations. For example, designing studies to meet both FDA and EMA endpoints in advance avoids costly redesign later (www.appliedclinicaltrialsonline.com).
- **Local Module 1 Strategy:** For each region, prepare distinct Module 1 content (administrative forms, labeling, prescribing information, local country cover letters). Since Module 1 is *not* harmonized, each submission often requires a "local intelligence" expert to ensure compliance. As one industry expert explains, focus on mastering this *"local 10%"* is *"where global strategies most often fail"* (pharmacystandards.org).
- **Timeline Coordination:** Plan reviews in parallel or sequentially depending on strategy and resource. Simultaneous submissions can accelerate total time to market, but require massive upfront coordination. Alternatively, some firms target one region first (e.g. FDA NDA), then feed data into others' processes (bridge strategy).
- **Dossier Management:** Employ robust project management tools (often regulatory information management systems) to track eCTD publishing and dossier versions across regions. Without automation, manual tracking can lead to errors (e.g. outdated data repeated in multiple modules).

Despite best efforts, global submissions face perennial obstacles:

1. **Regulatory Divergence:** As summarized by an ISPE industry survey, *"over the past decade, industry has experienced a proliferation of regulatory divergence regarding the interpretation and implementation of ICH guidelines"* (ispe.org). Agencies may interpret the same guideline differently. For example, ICH Q9 on risk management might be implemented variably, forcing a drug sponsor to modify controls for different regions. Such divergence often means that a global control strategy splinters into *multiple* local variants (ispe.org).
2. **Hidden Local Requirements:** Beyond the obvious labeling differences (Table 2), companies must address subtle local rules. These include language requirements, packaging standards (e.g. the EU requirement to show the product name in Braille on the outer packaging (pharmacystandards.org)), country-specific biosimilar guidelines, national pharmacopeias differences, pricing/health technology assessment dossiers, and even local tax exemptions or tariff papers. Failure to anticipate any of these can derail a seamless submission. One industry commentator warns strongly that ignoring *"distinct regulatory requirement differences"* can *"put [the] submission… in jeopardy."* (www.lifescienceleader.com).
3. **Quality of Data:** The enormous data volume (modern pivotal trial yields thousands of tables) combined with local adaptations heightens risk of errors. Studies show only ~54% of U.S. NDA submissions succeed in the first review cycle. Common causes of rejection or delays include CMC data gaps, inconsistencies between modules, or poor formatting – issues magnified when scrubbed into multiple regional dossiers. For example, a protocol-specified stability study summary might have to be written

differently in an EU SmPC and a U.S. label. Human error in data transcription (e.g. copying lab values into PDF) can trigger review questions. These technical hurdles underscore the need for rigorous QC processes and, increasingly, digital solutions (see later sections).

4. **Timelines and Workloads:** Regulatory calendars rarely align globally. Even if filings are simultaneous, review times vary. Agencies differ in clock-stops for queries, committee schedules, and backlog. A submission that walks out of an FDA review may still face months or even another year delay in the EU or vice versa. Global teams must build buffer time into plans and should use up-to-date regulatory intelligence to manage expectations (blog.arazygroup.com). (Data from EMA and FDA show only modest synchronization of decisions; a retrospective analysis of oncology approvals, for example, found many drugs received approval dates months apart in EU vs US.)

Despite these challenges, there are clear advantages to a well-executed global strategy. Manuscripts by regulatory consultants note that, with coordinated planning, developers *"can minimize rework, maximize efficiencies, [and] compile optimal data packages"* for US and EU simultaneously (www.appliedclinicaltrialsonline.com). A "single-source" dossier decreases overall cost, reduces the risk of contradictory questions, and ensures consistency of information to global patients and payors. As one FDA–industry collaborative study noted, harmonization ultimately *"will benefit regulators, industry, and patients globally"* (ispe.org), by accelerating access to new therapies while maintaining safety standards.

## Data on Global Submissions

Quantifying the scale and outcomes of global filings is challenging, but available data underscores the stakes. Consider new drug approvals in major jurisdictions: in 2019, **FDA's** CDER approved **48 novel drugs** (www.nature.com) (compared with 46 in 2017 and the record 59 in 2018), while in the same year the **EMA** issued **66 positive opinions** and received 117 new applications for initial evaluation (www.ema.europa.eu). China's NMPA, after years of reform, rapidly increased approvals to **164 NDAs** in 2019, including marketing authorization for **10 domestic innovative** drugs and **58 imported brand-name** medicines (english.nmpa.gov.cn). (For comparison, a decade earlier China was approving only a handful of new innovative drugs per year.) These numbers indicate that global development is generating a high volume of submissions: each successful drug launch typically entails filings to multiple agencies.

Notably, the multinational nature of trials means often the same clinical data underpin approvals across regions. However, outcomes do differ: historical examples include weight-loss drugs where FDA and EMA diverged (www.mabion.eu) (for example, FDA approved phentermine/topiramate and lorcaserin in 2012, whereas neither obtained an EU marketing authorisation at that time). Such cases highlight why even a single global dataset may be interpreted differently depending on local risk tolerance.

The quality of initial submissions is also a factor. One industry analysis found only ~54% of US NDAs cleared the first FDA review cycle. Common deficiencies include incomplete manufacturing data, missing stability tests, or inadequate safety analyses. When scaling globally, these weaknesses can multiply: a deficiency flagged by one agency often becomes an issue for others, leading to multiple rounds of questions. On the flip side, firms that apply strong standards see benefits. Ideally, proactive global coordination (including pre-submission meetings and simultaneous advice) helps achieve smoother approval paths.

# Case Studies and Real-World Examples

While many specifics are proprietary, several public examples illustrate global submission complexities and solutions. Below we discuss notable case vignettes:

**Simultaneous FDA–EMA Filings:** In an industry article on concurrent submissions, a consultant noted that even after ICH harmonization, FDA and EU "dossier processes" historically ran like *"two completely different regulatory environments"* (www.appliedclinicaltrialsonline.com). But since the ICH CTD was agreed in 2000, most developers attempt to coordinate US and EU filings. The article emphasizes that significant upfront planning can "streamline each step thereafter" (www.appliedclinicaltrialsonline.com). It stresses aligning endpoints and trial design to avoid redoing work later, while acknowledging that *"harmonization has been drifting apart in recent years"* (www.appliedclinicaltrialsonline.com). Indeed, real filings often begin as a single plan (e.g. one set of trial protocols) and then branch into separate NDA/MAA submissions with tailored Module 1 content as needed. Practical tips include early gap analysis (mapping one region's requirements onto the other) and synchronized submission timelines, recognizing however that final approval dates may still diverge due to agency processes (blog.arazygroup.com).

**Project Orbis – Oncology Review:** Regulatory agencies have begun formal programs to facilitate multi-country reviews. A prominent example is FDA's **Project Orbis**, launched in 2019. Orbis allows for *concurrent submission and review of oncology products among international partners* (www.fda.gov). Under Orbis, a company submits the drug dossier to FDA and can simultaneously submit the same materials to participating regulators (initially Australia's TGA and Canada's Health Canada, later including UK, Switzerland, Singapore, Brazil, and others). The FDA Oncology Center of Excellence reports that Orbis has "led to the approval of numerous oncology drugs for patients across the world" (www.fda.gov). For sponsors, Orbis reduces duplication of effort by allowing concurrent submission and collaborative review among the participating agencies. Each regulator still issues its own decision. Note that EMA is not a Project Orbis partner; the partners listed by FDA are Australia, Brazil, Canada, Israel, Japan, Singapore, Switzerland and the UK (www.fda.gov).

**COVID-19 Vaccine Approvals:** The pandemic is a recent extreme example of global submission strategies and regulatory flexibility. For COVID-19 vaccines, regulators worldwide instituted unprecedented "regulatory agility" (rolling reviews, simultaneous advice, emergency use authorizations, etc.). A 2023 retrospective study of Pfizer/BioNTech's BNT162b2 vaccine analyzed approvals in 73 countries (pmc.ncbi.nlm.nih.gov). The authors found that mutual reliance and expedited review practices greatly **shortened timelines**: *reliance approaches and certain regulatory agilities reduced review times* significantly for this vaccine (pmc.ncbi.nlm.nih.gov). In other words, agencies fast-tracked reviews not by conducting full independent evaluations sequentially, but by sharing review outcomes, allowing one country's data breakdown to expedite others. For example, once FDA or EMA deemed the data adequate, many other regulators relied on that assessment to grant rapid authorizations. The study concludes that such collaborative models should be more widely applied beyond emergencies (pmc.ncbi.nlm.nih.gov). This case demonstrates both how critical global coordination can be (for a lifesaving product) and how flexible regulators can be when missions align globally.

**Documentation Quality and Data Management:** Another dimension is the actual workflow of preparing submissions. Interviewing industry veterans, one regulatory leader notes common failings: treating submission to each country as separate checklists rather than a unified strategy (blog.arazygroup.com). Teams often underestimate hidden pitfalls – for example, assuming regulatory harmonization means a single package is enough. In reality, *"each authority applies its own interpretation"*, requiring *"a full overhaul"* of even longstanding dossiers when moving between countries (blog.arazygroup.com). One pointed lesson is that simply copy-pasting content without adaptation leads to format and compliance issues (especially labeling). As the Arazy Group blog (written from a medical-device perspective) emphasizes, *"what works in one market might be non-compliant in another"* (blog.arazygroup.com). In practice, companies mitigate this via redundancy checks and global tracking systems. Many now invest in regulatory information management (RIM) platforms that track an attribute (e.g. a specification or study result) once, and then propagate it consistently through eCTD outputs in all modules – reducing manual transcription errors noted by multiple sources.

These examples highlight that successful global submissions depend not only on scientific planning but also on meticulous project execution and organizational alignment. Companies that front-load strategy and maintain "single source of truth" data from the outset reap major efficiencies (www.appliedclinicaltrialsonline.com) (pmc.ncbi.nlm.nih.gov).

# Analysis and Data-Based Perspectives

To further understand the global submission environment, it helps to consider quantitative and organizational metrics:

- **Review Process Outcomes:** We noted earlier that roughly half of first-cycle FDA NDAs achieve approval. This suggests extensive rework and additional queries, which multiply when filings are extended internationally. Globally, a low initial pass rate implies that many products face delays across multiple agencies – as one industry report bluntly observes, *"…only ~54% of NDAs achieved first-cycle approval"* in the US. Quantifying this, if a company expects to file in, say, the US, EU, and Japan, even at a 60% pass rate per region, and if outcomes were independent, the cumulative probability of first-cycle success in all three regions would be about 22% (in reality outcomes are correlated, so this is only illustrative). In practice, sponsors should plan for at least one round of questions from each major regulator, likely adding several months to timelines.
- **Resource Allocation:** Global submissions require large teams. For example, a top-10 pharma company entrusted 2 onshore and 18 full-time offshore regulatory professionals to prepare eCTDs for the US, EU, and ASEAN in one case study, reportedly achieving a 28% efficiency gain in one year (slidetodoc.com). While we cannot independently verify commercial claims, such figures underscore that multi-region submissions can quickly become multi-person-year projects. Typical RA departments now include regional regulatory managers, local labelers, CMC specialists, filing writers, and project managers. Some companies even maintain *matrix teams* that cut across local subsidiaries to ensure alignment.

- **Inter-Agency Concordance:** How often do FDA and EMA ultimately agree? Historical studies found that FDA and EMA agree on approval decisions in most cases, but divergences do occur. One literature review noted that in the 2000s, only a handful of drugs were approved in one jurisdiction but not the other (or required post-approval commitments). Examples include the weight-loss drugs lorcaserin and phentermine/topiramate, which FDA approved in 2012 while EMA's CHMP did not recommend approval (the lorcaserin application was withdrawn), largely over long-term safety concerns (www.mabion.eu). These cases illustrate that ultimately, even the same data can lead to different outcomes; companies must therefore be prepared for the strategic risk that one market may give the green light while another hesitates.
- **Harmonization Metrics:** On the positive side, the trend in ICH membership and guideline adoption is measurable. Quantitatively, commentators highlight the number of active ICH guidelines (60+) (patientanalog.com). Industry surveys (e.g. by regulatory consultancies) have tracked the growing number of countries accepting CTD/eCTD. Ten of the jurisdictions in Table 1 are reported to mandate eCTD. A new drug launched in 2026 that targets both the US and EU therefore requires a dossier that meets these mandatory eCTD processes, with further regional builds for markets such as China and Japan.
- **Regulatory Science Trends:** Finally, thinking ahead, one can look at “submission success” metrics. A McKinsey analysis suggests that comprehensive “submission excellence” programs (lean processes, AI tools, etc.) could **cut submission timelines from months to weeks**. While not all novel technologies are yet widely deployed (structured data in CTD, eCTD v4.0, AI-assisted review), firms increasingly cite them as ways to overcome the traditional bottlenecks of global filings.

# Best Practices and Recommendations

From the above evidence and industry experience, several best-practice principles emerge for global submissions:

- **Develop a Unified Dossier Strategy:** Start with a *core data package* aligned to ICH guidelines. Identify the strictest requirement among target regions for each data element, and meet it in the base submission. This avoids later conflicts. Use the CTD format from the outset so that the bulk of content (Modules 2–5) remains identical. Only deviate where unavoidable.
- **Early Regulatory Intelligence:** Survey the landscape early. For each intended market, compile checklists of unique requirements (Module 1 forms, labeling templates, local stability commitments, etc.). Create a country-by-country spreadsheet noting any deviations from ICH (e.g. Japan’s frequent expectation of bridging data or Japanese-subject data on ethnic factors under ICH E5, the EU’s need for an agreed paediatric investigation plan (PIP), or local pricing and reimbursement dossiers).
- **Engage with Authorities in Parallel:** Use scientific advice opportunities not just in one region but in multiple regions, even concurrently. For high-value products, consider parallel FDA–EMA advice programs (FDA and EMA now offer formal joint advice sessions) or the FDA’s Project Orbis (if oncology).

Stakeholder meetings can reveal mismatches in expectations early. For example, if PMDA says “we need a human pharmacology study in Japanese subjects” while the company disagrees, that dispute is better identified pre-submission.

- **Invest in Internal Expertise:** Assign or hire seasoned regulatory professionals with multi-region knowledge. One senior RA should “own” each major market to ensure local compliance. Cross-train EU experts in FDA law (and vice versa) so that EMEA versus U.S. differences do not become blind spots.
- **Quality Systems and RIM:** Use a robust Regulatory Information Management (RIM) system or similar tools to track documents, submission versions, change histories, and to automate data linking. This reduces the risk of the “data trapped in static PDFs” problem. Ensure thorough QC reviews by region, especially for Module 1 and labeling, before any submission. Maintain an audit trail of each word or number that differs between regions.
- **Plan Buffers into Timelines:** Even well-coordinated submissions rarely tear through each review cycle without queries. Build extra time in project plans for agency questions, bridging studies (if requested), and potentially delayed launches. As one consultant warns, *“fast doesn’t always mean strategic”* (blog.arazygroup.com); haste without buffer can backfire if a minor issue snowballs.
- **Documentation Reuse with Revision:** Use one core dossier, but never simply copy-paste text. Each mention of a margin-of-error or test result should be audited for currency and regional context.
- **Collaboration and Transparency:** Keep regulators in the loop through transparent communication. If one agency (like FDA) has already reviewed a study, offer to share protocols and results with another in relevant programs. Some regulators encourage submission of joint briefing packages. At a minimum, inform parallel agencies of each others’ review status; reciprocity often speeds review (as shown in post-marketing surveillance sharing by EMA–FDA).

# Future Directions and Implications

The global regulatory submission landscape continues to evolve. We highlight several trends likely to shape the next decade of global filings:

- **Digital Transformation:** The transition from paper to eCTD is well underway, but eCTD v4.0 (already accepted by FDA and Japan’s PMDA and being phased in elsewhere) and more structured content promise further change. Regulatory authorities are pushing for more semantic data (e.g. drug substance attributes, manufacturing process info in Module 3 stored in databases rather than scattered PDFs). This evolution will make cross-regional submissions smoother, as ICH member agencies align on new data schemas. Companies should invest in content management systems that can output the same data in module-appropriate formats for different agencies, thereby filling the “gap” of local variability.
- **Artificial Intelligence:** AI and automation are being piloted to handle routine submission tasks. For example, machine learning can assist in auto-tagging documents to eCTD modules, or in pre-screening for common errors. Industry analyses suggest that AI-assisted content generation and “zero-based” process redesign could substantially shorten submission preparation timelines. In the future, AI might

even harmonize narratives: a smart system could translate a paragraph from a USPI into the legally conformant text for an EU SmPC. These tools hold promise for mitigating the manual burdens highlighted earlier.

- **Broader Reliance Frameworks:** The COVID-19 experience may accelerate formal reliance pathways. WHO (through its collaborative registration and reliance frameworks) and the newly established African Medicines Agency (AMA) are promoting reliance-based pathways. If successful, one could imagine African or Middle Eastern regulators requiring fewer duplicative inspections or basing approvals on prior decisions by trusted reference regulators. This would change submission strategy: a global sponsor could submit to an SRA first, then have others join the reliance program, rather than submit everywhere simultaneously.
- **Harmonized Post-Market Surveillance:** Increasing global standards in pharmacovigilance are likely. For instance, ICH E2B(R3) and E2D standards aim to unify how companies report adverse events. More uniform PV requirements (periodic safety update reports, aligned risk management planning) would simplify ongoing obligations, although instruments such as the US REMS and EU RMP still differ. As these converge, the initial submission differences become even more isolated in Module 1 realms.
- **Local Capacity and Emerging Markets:** Regulators in Asia, Latin America, and Africa are rapidly building capabilities. Over the next few years, markets like India, China, and sub-Saharan Africa will enact more ICH guidelines. The result: global submissions will increasingly become three- or four-region simultaneous projects (i.e. “FDA, EMA, PMDA, NMPA”). Companies must watch these evolving requirements closely. For example, although China has accepted overseas clinical data since its 2018 technical guideline, NMPA may still request Chinese-population data where ethnic sensitivity is a concern. Keeping pace with these changes will be critical.

The implications for industry are clear: complexity will not diminish, but harmonization and technology offer powerful tools. A successful global RA strategy in 2030 will look very different (and potentially much more data-driven) than in 2010. But the fundamental lesson remains unchanged: *use harmonized standards to cover the common core, and meticulously address each jurisdiction’s unique demands*. Those who strike this balance will bring drugs to patients faster and more efficiently worldwide.

# Conclusion

Managing regulatory submissions across global markets requires a dual strategy of harmonization and localization. ICH guidelines provide a consistent scientific framework—culminating in the global eCTD format—but do not override territorial sovereignty. As one regulatory training resource puts it, *“ICH is the baseline; the national law is the final word.”* (pharmacystandards.org). A company’s success depends on building that global “harmonized 90%” of a dossier while devoting dedicated resources to the “local 10%” unique to each major market (pharmacystandards.org).

This report has reviewed the historical context of ICH and examined how modern drug developers actually implement filing strategies. We have highlighted specific contrasts—such as labeling formats, approval processes, and eCTD requirements—between regions. The data show that while new drug approvals continue

at a robust clip in major markets (48 novel drugs in the US and 66 in the EU in 2019 (www.nature.com) (www.ema.europa.eu)), the underlying processes are not monolithic. Expert and retrospective analyses reinforce that flexibility and rigor are both needed. For instance, during the COVID-19 crisis, reliance and collaboration yielded record acceleration of vaccine reviews (pmc.ncbi.nlm.nih.gov), pointing the way to future efficiencies if embraced judiciously.

Looking forward, digitization and international collaboration initiatives promise to make global submissions more efficient and predictable. However, in any jurisdiction the fundamental rule holds: **“follow ICH, but remember local variations.”** Neglecting either part of this maxim invites delay or failure. All indications suggest that companies that invest in harmonized planning, robust data management, and a deep understanding of regional requirements will achieve the best outcomes: not only smoother regulatory paths, but also faster patient access and lower development cost on a global scale (patientanalog.com) (patientanalog.com).

**References:** Key sources cited in this report include (www.ncbi.nlm.nih.gov) (ispe.org) (www.lifescienceleader.com) (www.appliedclinicaltrialsonline.com) (patientanalog.com) (www.ema.europa.eu) (www.nature.com) (english.nmpa.gov.cn) (knowledgenet.sarjen.com) (knowledgenet.sarjen.com) (pharmacystandards.org) (pharmacystandards.org) (www.fda.gov) (pmc.ncbi.nlm.nih.gov) (www.ncbi.nlm.nih.gov). Each source provides evidence for the harmonization efforts and regional differences discussed herein.

## Source links

Links cited in this article, in order of first appearance. Full addresses are provided for readers using extracted text.

1. https://intuitionlabs.ai/articles/ectd-submission-management-best-practices
2. https://www.ncbi.nlm.nih.gov/books/NBK174229/
3. https://intuitionlabs.ai/articles/ctd-vs-ectd-differences-pharma
4. https://pharmacystandards.org/cras/section-20-3-regional-differences-and-harmonization-challenges/
5. https://intuitionlabs.ai/articles/regional-ectd-submission-guides
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