WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Revolutionizing Drug Development Through Regulatory Expertise

Swapnil S. Mirajgave[1], Shubham N. Girge[2], Pavan Dhanapune[3], Shubham Deokar[4], Vinayak Nanagare[5]

B Pharmacy, Pravara Rural College Of Pharmacy, Loni, Ahmednagar 413736, Mahrashtra, India

* Corresponding Author:
Pravara Rural College Of Pharmacy,
Loni, Ahmednagar 413736,
Savitribai Phule University Pune,
Mahrashtra, India.
E-mail Address: swapnilmirajgave563@gmail.com
Tel:+91 9028980198.

ABSTRACT:

The field of drug development and regulation is changing quickly as a result of improvements in scientific methodology, data use, and technology. Accelerated drug approval processes, collaborative regulatory reviews, and the incorporation of real-world data are important themes. Traditional processes are being transformed by innovations like structured content management, population pharmacokinetics, pharmacogenomics, and artificial intelligence. These changes necessitate a workforce of regulatory professionals that are knowledgeable, flexible, and able to navigate a complicated, digitalized world. This study looks at the most recent approaches in clinical pharmacology, linked health, and regulatory harmonization to show how these developments improve the effectiveness, patient safety, and accessibility of novel medications.

Key Words Drug development,Regulatory affairs,Population pharmacokinetics (PK),Clinicalpharmacology,Harmonization,FDA accelerated approval, Manufacturing, and Controls (CMC).

Introduction :

Digital changes are affecting every part of drug development, including how medicines are regulated. Advances in science have led to more cell and gene therapies being introduced, which are providing greater benefits for patients. The increase in involvement of patients in drug development, including in regulatory reviews, is also influencing how medicines are regulated. The use of real-world data is growing, which helps speed up clinical trials and allows medicines to be approved sooner. This also means regulators are focusing more on monitoring medicines after they are on the market.

In clinical trials, there is more use of modeling, new statistics, and artificial intelligence to make the process more efficient. Regulatory agencies are working together more and sharing their responsibilities to help review these innovative products faster.

The workforce today needs to be flexible, tech-savvy, and ready to adapt quickly to new ways of working. This article explores the trends shaping how new treatments for diseases are developed and how these changes impact the role of regulatory affairs professionals.

Harmonization

is about aligning national and international standards to make drug development and regulation smoother. For instance, many countries now follow the ICH guidelines. In the field of medical devices, this process began with the Global Harmonisation Task Force (GHTF), which has since been replaced by the IMDRF.

Regulatory professionals must build the right skills, knowledge, and mindset to advance in their careers. Today's work environment is often described as VUCA, meaning it's volatile, uncertain, complex, and ambiguous. The global pandemic has made these challenges even harder.

With digital transformation playing a bigger role, regulatory professionals need to boost their digital skills. This includes learning to use dashboards and cloud tools for data visualization, understanding how data is collected and processed, and using it to make predictions. They should also develop skills in statistical analysis and data mining.

Beyond technical skills, professionals should focus on critical thinking, solving complex problems, adapting to change, communicating effectively, working well in teams, and showing leadership. These skills are essential for success in today's workplace[1.]

Clinical Pharmacology in Drug Development: Phase 1 Studies

Developing a new medicine is a long, complicated process with ethical, scientific, and financial challenges. Only about 10% of new drugs make it through clinical trials successfully (Scannell et al., 2012). Phase 1 trials are a important first step in this process. They help researchers decide whether to continue developing a new treatment or stop if it's not promising.

Phase 1 trials called Humans studies, test new drugs or new ways of using approved drugs. The goal is to learn how the drug works in the body.

These studies are usually done with healthy volunteers. This is because healthy people don't have underlying health issues that might interfere with the results. Testing on healthy volunteers allows researchers to see how the drug is absorbed, distributed, and removed from the body. It also helps identify potential side effects and establish a basic understanding of the drug's safety[2.]

Drug Interactions and Bioequivalence in Drug Development

Phase 1 trials often use healthy volunteers because it speeds up the study process and avoids ethical concerns about giving low doses of a new drug to patients who might need effective treatment.

Drug-Drug Interaction Studies

Drug-drug interaction studies check how different drugs affect each other when taken together. The main goal is to see if one drug changes how the body processes (absorbs, breaks down, or removes) another drug. Researchers want to know if these changes are significant enough to affect treatment.

These studies usually start after lab tests suggest a possible interaction. They are often done as separate studies, mainly with healthy volunteers, and not tied to a specific trial phase.

Population Pharmacokinetics (PK) and Pharmacodynamics (PD)

Population PK/PD plays an important role in drug development, especially as drugs move from Phase I to Phases II and III. It has become a common approach, with most new drug applications including it (Lee et al., 2011). Its growing importance led the U.S. FDA to issue official guidelines on population PK in 1999.

Traditional vs. Population PK Approaches

Feature	Traditional Approach	Population Approach
Study Population	Healthy volunteers	Target patient population
Sampling	Intensive (12–15 samples per person)	Sparse (1–3 samples) with some intensive sampling
Study Design	Balanced design required	Mixed designs from different studies, populations, or sites
Complexity	Moderate	Highly complex and time-consuming
Analysis Method	Two-step process: regression + summary stats	Single-step nonlinear mixed-effects modeling
Variability	Minimized using strict criteria	Reflects real-world variability
PK-PD Analysis	Not possible	Possible with population approach

Advantages of Population PK Studies

- **Real-World Application**: Studies are done with the target patient population, not just healthy volunteers.
- **Less Sampling Needed**: Instead of taking 12–15 blood samples per person, only 1–3 samples are needed.
- **Understanding Variability**: Researchers can see how PK varies across different people.
- **Covariate Analysis**: It allows for the study of how factors like age, weight, or genetics affect drug behavior.
- **Predictive Simulations**: Using PK data, researchers can simulate "what-if" scenarios, like how the drug might behave in different patient groups.

Population PK/PD helps researchers understand how a drug works in real-world patient groups, not just in controlled trial conditions. It also reduces the burden of frequent sampling and enables better prediction of drug behavior in different populations[2.]

Clinical Pharmacology in Patient Care

Clinical pharmacology helps ensure medications are used safely and effectively in healthcare. This is done by:

- **Evaluating New Drugs**: Reviewing new medications for use in hospitals and healthcare facilities.
- **Therapeutic Drug Monitoring (TDM)**: Tracking drug levels in patients to make sure they are within a safe and effective range.
- **Personalized Dosing**: Adjusting doses for specific groups, like children, elderly, or people with certain genetic traits.
- **Model-Informed Precision Dosing (MIPD)**: A newer method that uses data about a patient's age, genetics, disease, and environment to choose the best dose. This approach helps improve drug effectiveness and reduce side effects .

Pharmacogenomics in Drug Development :

Pharmacogenomics looks at how a person's genes influence their reaction to medications. It is used throughout the entire drug development process, from early research to monitoring drugs after they are approved. The table below shows its role in each stage:

Phase	Applications	Examples
Pre-Clinical	- Identify and validate drug targets. - Remove unsuitable targets. - Use genetic methods like Mendelian Randomization to link drug targets to health outcomes.	**Example**: Using genetics to confirm if a drug target affects disease.
Phase 0	-Learn how genes influence how the body absorbs, processes, and gets rid of drugs. - Identify biomarkers for drug effects.	**Example**: Finding genetic reasons why some people process drugs faster or slower.
Phase I	- Identify active drug forms in the body. - Study drug toxicity and efficacy. - Identify drug-drug interactions. - Choose trial volunteers based on genetic traits.	**Example**: Including/excluding volunteers with specific genetic traits to avoid bad reactions.
Phase II	- Study drug effectiveness. - Test the clinical usefulness of genetic testing.	**Example**: Excluding patients who lack the specific gene required for a cancer drug to work.
Phase III	- Look for new genetic markers linked to drug response. - Measure drug effects on patients with different genetic profiles. - Assess drug-drug interactions in people with different genes.	**Example**: Identifying genetic markers that predict which patients will have side effects.
Phase IV	- Monitor for rare side effects after the drug is on the market. - Study possibilities for repurposing the drug for other uses. - Create tools to predict how patients will react to treatment.	**Example**: Finding ways to use an existing drug to treat a different disease in people with specific genes.

Pharmacogenomics makes drug development safer, faster, and more personalized. By understanding how genes affect drug responses, healthcare providers can offer more tailored treatments to patients[2.]

Therapeutic Drug Monitoring (TDM)

TDM is a method used to adjust a patient's medication dose to make sure it works well and stays safe. It is especially helpful for drugs that have a small range between a safe and harmful dose or drugs that people process differently.

For TDM to be effective, a few key factors are important:

- **Availability of drug tests**: Quick and affordable drug tests must be available.
- **Understanding drug response**: Knowing how the drug concentration in the body relates to its effects.

TDM is commonly used for drugs like:

- **Antibiotics**: Vancomycin, aminoglycosides
- **Immunosuppressants**: Tacrolimus, cyclosporine
- **Anti-seizure medications**: Phenytoin, valproic acid

There is growing interest in using TDM for more drugs, especially **antimicrobials** and **anti-cancer drugs**, such as:

- HIV medications
- Antifungal drugs
- Beta-lactam antibiotics
- Anti-tuberculosis drugs
- Busulfan (used for cancer treatment)
- Tyrosine kinase inhibitors (cancer drugs)

These drugs are often used to treat **life-threatening diseases** where it's difficult to measure a patient's response using clear clinical signs. Even though many of these drugs meet the criteria for TDM, it is not always done because of limited access to the necessary testing tools[2.]

Trends in Drug Approvals Over the Last 18 Years

The pattern of drug approvals has changed significantly from 2000 to 2017. Here's a breakdown of the key trends:

2000–2008

- **Total Drugs Approved**: 209
- **Key Categories**:
  - **Cardiovascular Drugs**: 9.09% (e.g., fondaparinux, ranolazine)
  - **Neurological Drugs**: 12.91% (e.g., rivastigmine, aripiprazole)
  - **Antibiotics**: 5.26%
  - **Antivirals**: 5.74%
  - **Anti-Cancer Drugs**: 11.96%
  - **Biologics**: 7.17%

During this period, approvals for antibiotics and antivirals were relatively low. This may be because pharmaceutical companies focused more on other types of drugs or faced challenges in developing new antibiotics due to failed New Chemical Entities (NCEs).

2009–2017

- **Total Drugs Approved**: 302 (a significant increase from the previous period)
- **Key Categories**:
    - **Cardiovascular Drugs**: 5.29% (e.g., prasugrel, rivaroxaban) — a 4% decrease from the previous period
    - **Neurological Drugs**: 9.93% (e.g., perampanel, pimavanserine) — a 3% decrease from the previous period
    - **Antibiotics**: 5.29%
    - **Antivirals**: 5.96%
    - **Anti-Cancer Drugs**: 17.54% — a sharp increase from the previous period
    - **Biologics**: 15.56% — a significant rise compared to the previous period

Compared to 2000–2008, there was a noticeable increase in the approval of anti-cancer drugs and biologics, while approvals for cardiovascular, neurological, antibiotics, and antiviral drugs remained low.

Key Observations

- More anti-cancer drugs and biologics were approved than drugs for lifestyle diseases like diabetes, obesity, heart problems, and respiratory conditions.
- This shift raises the question of whether drug development is driven by discovery (finding new treatments for diseases) or market demand (focusing on profitable markets).

What's Driving the Increase in Drug Approvals?

Several factors may explain the rise in drug approvals, especially for anti-cancer drugs and biologics:

1. **Growing Disease Burden**:
    - **Cancer**: The number of cancer cases is expected to rise to **23.6 million by 2030**. In the U.S. alone, **1.73 million new cancer cases** were diagnosed in 2018, and over **609,000 deaths** occurred.
    - **Diabetes**: By 2030, diabetes cases in the U.S. are expected to rise by **54%**, with related deaths increasing by **38%**. The annual cost of diabetes could reach **$622 billion** by 2030.
2. **More New Drug Applications (NDAs) and Biologic License Applications (BLAs)**:
    - The number of new drug approvals per year has steadily increased:
        - **2000–2010**: Average of **23 approvals per year**
        - **2011**: **35 approvals**
        - **2012**: **39 approvals**
        - **2015**: **45 approvals**
        - **2017**: **46 approvals**

The increase in drug approvals can be linked to a combination of growing health needs (like cancer and diabetes), more investment in drug development, and a rise in (NDAs) andBiologic License Applications (BLAs) submitted to regulatory agencies[3].

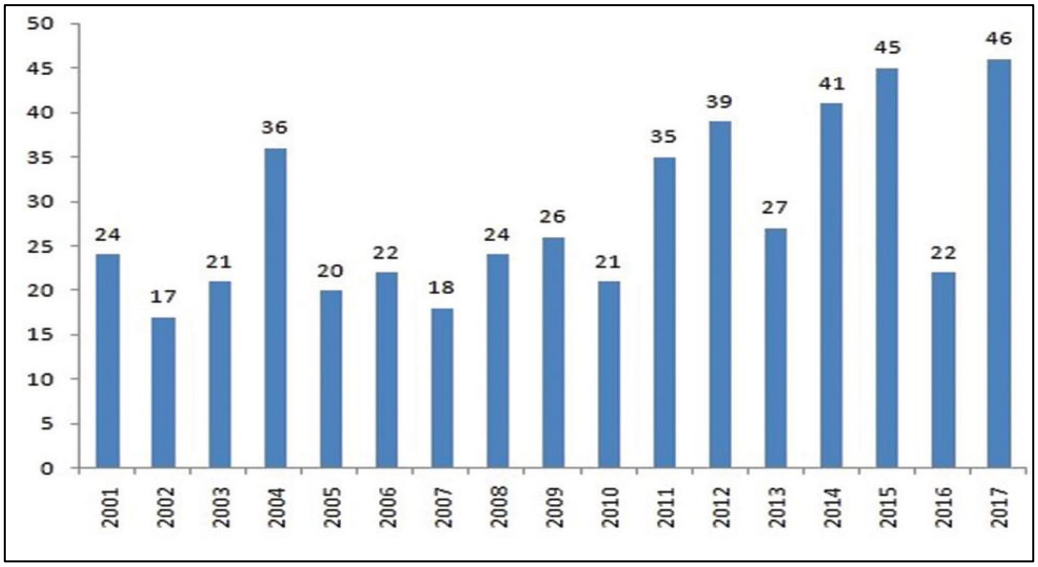

Figure 1 : Year-wise new drug approvals.

Faster Drug Approvals Help Patients Get New Medicines Sooner

Health authorities offer special pathways to speed up the approval of new medicines, especially when early clinical trials show promising results. To use these pathways, companies must work closely with regulatory agencies early in the drug development process. This includes discussions about drug manufacturing, testing, and filing requirements.

For new or complex therapies, health agencies may require extra collaboration between experts in different fields like clinical research, quality control, and safety testing.

Global Challenges in Fast-Tracking Drugs

One major challenge is that different countries have different rules for speeding up drug approvals. Just because a drug gets fast-track approval in one country doesn't mean it will be approved quickly in another.

How It All Started

The U.S. Food and Drug Administration (FDA) started faster drug approval processes in 1988. These were designed to speed up the development and review of drugs for serious or life-threatening conditions, especially when no other effective treatments exist[4.]

CMC Challenges in Regulatory Submissions for Accelerated Drug Development

When drugs are developed under fast-track procedures, companies face challenges related to Chemistry, Manufacturing, and Controls (CMC). Since development timelines are shorter, companies often have to provide critical CMC data much earlier than usual.

Early Clinical Data and Compressed Timelines

Regulatory agencies sometimes allow companies to submit phase 2 clinical trial data if it clearly shows that the drug works. Companies can start phase 3 trials after submitting their application, but this compressed schedule creates challenges. For example, at the start of important trials, the final dose of the drug may not be confirmed. This uncertainty forces companies to prepare multiple versions of the drug in case changes are needed, adding cost and complexity.

Manufacturing Challenges

Companies may need to change the production site or increase the production scale to meet demand. These changes require new data on process validation (proof that the manufacturing process works consistently) and product stability (proof that the drug stays effective over time). This data is often essential for marketing approval, creating a "critical path" where everything depends on CMC data being ready on time.

Limited Product Supply at Launch

Since much of the manufacturing and validation happens close to the submission deadline, there is often limited supply of the product at launch. This can increase complexity and require regulatory filings to make updates after the product is approved. Managing these updates globally can be difficult since different countries have different requirements.

Data Tracking and Submission Complexity

The CMC process requires companies to track large amounts of data and respond to regulatory questions. This process is time-consuming, especially because current filing systems rely on traditional, document-based submissions. Each document must be written, checked for accuracy, formatted, and published, all of which require significant resources.

The Role of Digital Tools

One possible solution is to use smarter data management tools, like Structured Content and Data Management (SCDM) systems. Unlike traditional document-based systems, these tools work directly with data, making it easier to track, update, and manage information. This can reduce the time and effort required to prepare CMC data for submission, helping companies meet the tight timelines of accelerated drug development[4.]

Current Uses of SCDM in the Pharmaceutical Industry

In the pharmaceutical industry, companies are using modern Information Technology (IT) systems to handle the growing demands of regulatory filings and interactions with global health authorities. One key approach is the use of **Structured Content and Data Management (SCDM)**, which plays an important role in managing regulatory data more efficiently.

What is SCDM?

SCDM is a smart way to organize and manage information. Instead of dealing with large, hard-to-manage documents, SCDM breaks down information into smaller, reusable parts or "components." This makes it easier to track, update, and share important data for regulatory submissions.

Types of Data in SCDM

- **Structured Data**: This data is neatly organized, like a table with rows and columns. It follows a specific format and uses a list of pre-approved terms (like drop-down menu options) to maintain consistency.
- **Semi-Structured Data**: This data has some structure, but it also allows for flexibility. For example, it may follow a loose format but also allow the use of free text for additional details.
- **Unstructured Data**: This is free text, like paragraphs in a document, that does not follow a specific format. It often contains key details but is harder to organize and track.

Why is SCDM Important?

SCDM helps pharmaceutical companies modernize their regulatory processes. By managing data instead of full documents, companies can save time and resources. This system also supports the goals of "Pharma 4.0," which focuses on using technologies like (AI) and Machine Learning (ML) to make drug development smarter and faster.

In summary, SCDM helps pharmaceutical companies organize and manage regulatory data in a more efficient way. It allows for better tracking, faster updates, and easier sharing of information, supporting the faster approval of new drugs[4.]

New Regulatory Changes Supporting SCDM

Adopting **Structured Content and Data Management (SCDM)** can help pharmaceutical companies work more efficiently, especially when filing for fast-track drug approvals. However, there is currently no formal requirement for drug companies to use SCDM. Companies can still prepare regulatory documents manually using traditional methods.

But as the industry moves toward **Pharma 4.0** — a shift toward more digital, automated, and data-driven operations — the push for structured data systems like SCDM is growing. Regulatory authorities are starting to promote the idea of managing drug information in a more organized, digital format.

New Submission Requirements for CMC and Quality Data

One big change on the horizon is the requirement for drug companies to submit **structured, standardized data** for Chemistry, Manufacturing, and Controls (CMC) and quality-related information.

Here's why this matters:

- **Data Consistency**: Standardizing how data is presented will make it easier to compare and analyze across different health authorities and companies.
- **Interoperability**: With a consistent format, different regulatory agencies can review the same data more easily, speeding up drug approvals.

Currently, drug companies must follow local laws, **ICH (International Council for Harmonization)** guidelines, and country-specific rules when preparing regulatory submissions. However, there is **no standard format** for how CMC data should be presented. This lack of standardization creates extra work for companies, as they have to reformat their data for different regulatory authorities.

What's Next?

In the near future, it's expected that health authorities will start requiring drug companies to use **standardized, structured data** in regulatory filings. This will likely speed up the review process, reduce errors, and make it easier for companies to submit the same data to multiple regulatory bodies around the world.

In summary, while using SCDM is not yet a requirement, changes are coming as part of the industry's move toward Pharma 4.0. The shift to structured, standardized data for CMC submissions will increase efficiency and improve the drug approval process globally[4.]

Innovations in Cloud-Based Technology

Cloud-based technology uses a network of connected servers to offer a range of computing services. These services include data analysis tools, software applications, remote data storage, and access to large amounts of information via the internet or a company's internal network.

Key Benefits of Cloud Technology

1. **Flexibility**: Companies can easily adjust the services they need, scaling up or down as required.
2. **Scalability**: As business needs grow, cloud services can expand to handle more data or users.
3. **Interoperability**: Different systems within the cloud can connect and share information, making it easier to combine data from various sources.

For **pharmaceutical companies and regulators**, cloud-based technology makes it easier to use **Structured Content and Data Management (SCDM)**. By connecting different data sources into one unified system, users can access and work with data more efficiently. This **seamless access to information** helps companies streamline regulatory filings, improve collaboration, and speed up drug approvals[4.]

Use of Expedited Pathways Among ICH Members

The Centre for Innovation and Regulatory Science (CIRS) studied how expedited regulatory pathways affect drug approval times. The analysis looked at new drug approvals by six major agencies: the EMA (Europe), FDA (U.S.), PMDA (Japan), Health Canada, SwissMedic, and TGA (Australia).

Use of Expedited Pathways

CIRS data shows that different countries use expedited review pathways at different rates. In 2020, the U.S. used these pathways the most, with 71% of new drugs approved through Priority Review. Japan followed with 45%, while Canada and Australia used them for 26% and 14% of approvals, respectively.

Impact on Review Time

The use of expedited review pathways significantly reduces the time required for drug approval. Across ICH members, the average reduction in review time for expedited reviews, compared to standard reviews, is around 40%. This time savings is a key advantage of expedited pathways, as it allows for faster access to new treatments.

Industry Perception of Expedited Pathways

A 2019 survey by CIRS found that the FDA's Breakthrough Therapy Designation (BTD) and Japan's Sakigake designation had a positive impact on companies, patients, doctors, regulators, and investors. However, the FDA's Fast Track designation and EMA's PRIME scheme were less well-received.

Issues with PRIME included a short application window and limited eligibility for new uses of existing drugs. The European Medicines Agency (EMA) acknowledged these problems in a five-year review of the PRIME scheme.

Impact of Faster Development Tools on Drug Timelines.It's difficult to measure exactly how much faster drug development becomes when using special "expedited" pathways. This is because many different factors affect the overall development process. Some researchers have tried to study this, but the results are not always clear.

Impact on Review and Approval Times :

Research on how Priority Review affects the time it takes to review drug applications has found that it significantly speeds up the process. Studies from the U.S. and Canada show that using Priority Review or other expedited pathways can cut review times by more than half.

The fastest approval times were seen when multiple expedited pathways were combined. For example:

- Accelerated Approval + Priority Review + BTD: Median approval time of 166 days.
- Using Fast Track, Accelerated Approval, Priority Review, and Breakthrough Therapy Designation (BTD) leads to a median approval time of 145 days.

For comparison:

- Drugs with only Priority Review took about **242 days**.
- Drugs with standard review took about **365 days**.

On average, using any of these pathways shortened review time by around **four months** (median of **243 days** compared to **365 days** for standard review).

It's worth noting that from 2011 to 2020, only **14 out of 410 new drugs** approved by the FDA received all four expedited designations, and **12 of these were cancer drugs**[5.]

Approvals Based on Early Evidence

When drugs are approved using early evidence (like results from small patient groups or data from surrogate measures), there is more uncertainty at the time of approval. This approach is often justified by the potential benefits for patients, but it comes with the condition that more evidence must be collected after approval.

A major challenge is that these follow-up studies might show that the drug's benefits do not outweigh its risks for all patients. In some cases, the benefits may only apply to a specific group of patients.

If this happens, regulators have to decide what to do. Their options include:

- **Revoking the approval** and removing the drug from the market.
- **Extending the time** allowed for further data collection.
- **Limiting the use** of the drug to a smaller group of patients where the benefit is clear[5.]

Potential Impact on Submission Strategy :

The growing availability of expedited approval pathways worldwide is likely to influence the order in which drug developers submit their applications and plan product launches.

In the future, companies may no longer prioritize the **U.S. and EU** as the first markets for submission. Instead, they might take advantage of collaborative review programs like **Project Orbis** or **Access Consortium** as part of their initial strategy[5.]

The **Common Technical Document (CTD)**, introduced in the ICH M4Q(R1) guideline, created a standard format for submitting quality information for drug approvals. While it has made the registration process easier for human-use drugs, some regions still haven't fully adopted it. The guideline is now being updated (ICH M4Q(R2)) to improve drug registration and lifecycle management, use digital tools, and speed up patient access to medicines.

The updated CTD will use a structured format, like the electronic CTD (eCTD), to simplify communication with the FDA, make information clearer for FDA reviewers, and improve global regulatory processes throughout a product's lifecycle. The new format will align with modern quality guidelines (ICH Q8-Q14), use digital tools like KASA, and provide clear regulatory requirements. This will help the industry present manufacturing and quality information consistently and support global harmonization in how applications are submitted and reviewed.

The **ICH M4Q(R2)** guideline organizes information about a drug's chemistry, manufacturing, and controls (CMC) to support quality assessments based on science and risk. However, it doesn't set standards for structuring and sharing this data, making it harder to assess risks and analyze data consistently across applications.

The **FDA** is working to identify which pharmaceutical quality/chemistry, manufacturing, and controls (PQ/CMC) information should be submitted in a structured format. This effort aligns with laws that allow the FDA to require electronic submissions. PQ/CMC will include standard data formats to ensure future submissions provide structured quality data that digital systems like KASA and QSD can easily process.

Benefits of structured data include:

- Ensuring the FDA and industry work with the same information.
- Reducing manual data handling.
- Supporting advanced analytical tools.

By enabling KASA and improving ICH M4Q, PQ/CMC accelerates digitization and enhances management of a drug's information throughout its lifecycle, including when changes are made[6.]

When applying for drug approval in multiple countries that don't use harmonized rules like the ICH Common Technical Document (CTD), companies often need to create separate dossiers for each country.

Each dossier includes two types of content:

1. Standard content: Parts taken directly from the original CTD submission (e.g., to the FDA or EU regulators).
2. Customized content: Parts modified to meet specific requirements of each country.

This process is time-consuming and requires a lot of effort because of the customizations needed for each country and the updates required over the drug's lifecycle. Usually, the Clinical (Module 5) and Nonclinical (Module 4) parts of the CTD stay unchanged across submissions.

Comparing Submissions With and Without a Core Dossier

To see how using a core dossier helps, two drug submissions were compared:

- NME1, which used a core dossier.
- NME2, which didn't use a core dossier.

Both drugs were similar in type and dosage form and were submitted to the same countries around the same time. NME1 had three dosage strengths, while NME2 had two. Regulatory authorities (NRAs) didn't know which submission used a core dossier.

For both drugs, NRAs sent review letters for each dosage strength. However, NME2 received extra questions in Guatemala and Uruguay. In Ecuador and the Dominican Republic, there were no questions about chemistry, manufacturing, and controls (CMC) for NME2. Most questions for NME2 were of low to medium complexity, but high-complexity questions came from Peru and Uruguay[7.]

Definition of Generic Drugs by Regulatory Authorities (RAs)

Regulatory Authorities (RAs) generally define a **"generic medicine"** with these common rules:

- The active ingredient must be the same in both type and amount as the original drug.
- The dosage form and method of administration must be the same or very similar.
- The generic must show it works the same as the original drug (bioequivalence).

However, different RAs have different views on how they treat salts or esters of the active ingredient. For example:

1. In the USA, EU, Australia, and Singapore, different salts of the same drug are considered the same if they have the same main component as the original drug.
2. Japan does not treat different salts as the same ingredient.

Generic Drug Dossier Formats

Out of the ten RAs studied, most use one of two common formats for drug dossiers:

- **ICH CTD format**: Used by Australia, Canada, the EU, India, Japan, the USA, and South Korea.
- **ASEAN CTD (ACTD) format**: Used by Malaysia.
- **Singapore** accepts both formats.

For generic drugs:

- In the **ICH CTD format**, Modules 4 and 5 (which include animal and clinical study data for the original drug) are replaced with bioequivalence data.
- In the **ACTD format**, Parts III and IV also replace innovator study data with bioequivalence data.

Electronic Submissions

- All RAs except Sri Lanka accept electronic drug dossiers, such as eCTD, South Korea's e-Drug Service, or other electronic systems.
- India uses both electronic submissions and paper copies.

Time Taken for Generic Drug Registration

Here's a summary of approval times for generic drugs from various RAs:

- **USA**: In 2010, the target was to approve 90% of drug submissions within 10 months.
- **Canada**: Similar to the USA, the goal was to review 90% of submissions in 10 months.
- **Australia**: The Therapeutic Goods Administration (TGA) has a legal timeline of 40 working days to accept or reject a submission. The total approval time is up to 300 calendar days (about 10 months).
- **Japan**: The approval timeline is 12 months, including 1.5 months for applicant responses and 2 months for Good Manufacturing Practices (GMP) inspections. In practice, the review process takes about 9 months.
- **Singapore and Malaysia**: Both countries use a faster review process for drug dossiers[8.]
- Connected health technology is becoming more important in healthcare. In this paper, we define connected health as using tools like information technology, digital networks, artificial intelligence (AI), and machine learning (ML) to collect, share, and analyze health data. This technology helps patients, healthcare providers, and health authorities make better decisions and improve health outcomes. Connected health aims to create systems where devices, services, or treatments are designed to fit the needs of individual patients.

While it includes digital health, connected health is broader, with digital health being just one part of it[9.]

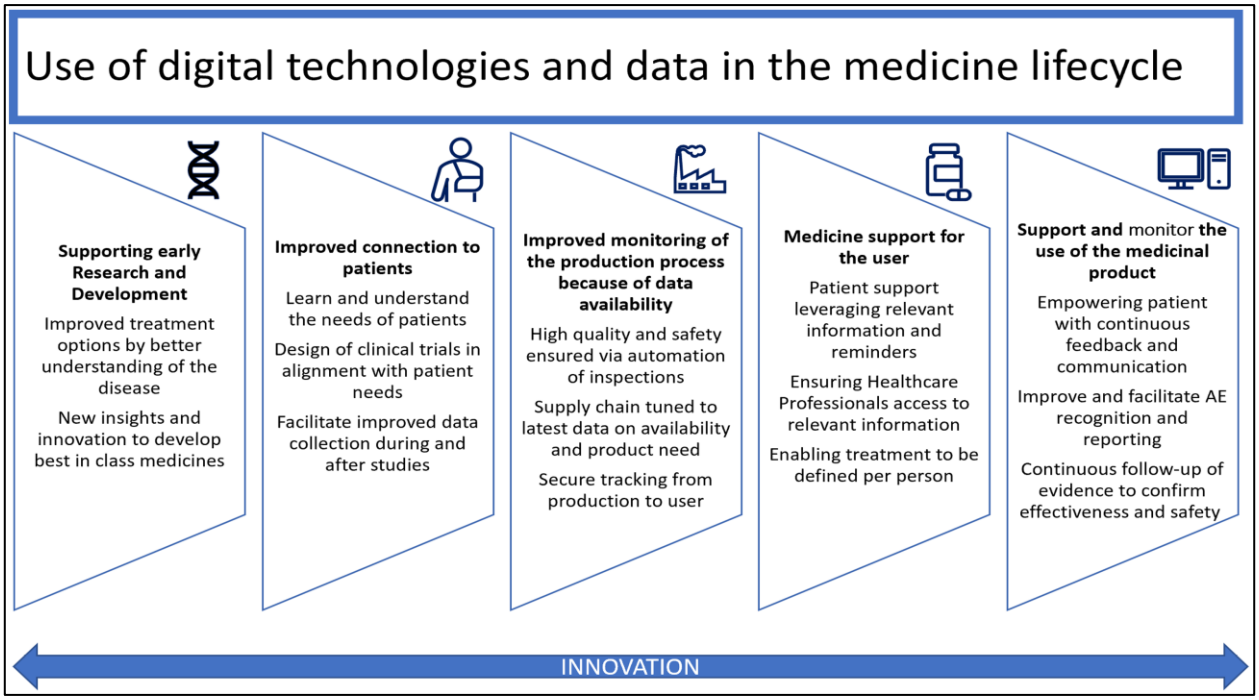

Figure 2: The use of digital technologies and data throughout the lifecycle of medical products, based on information from EFPIA [Ref: Digital Health (efpia.eu) Accessed 28 April 2023]9.

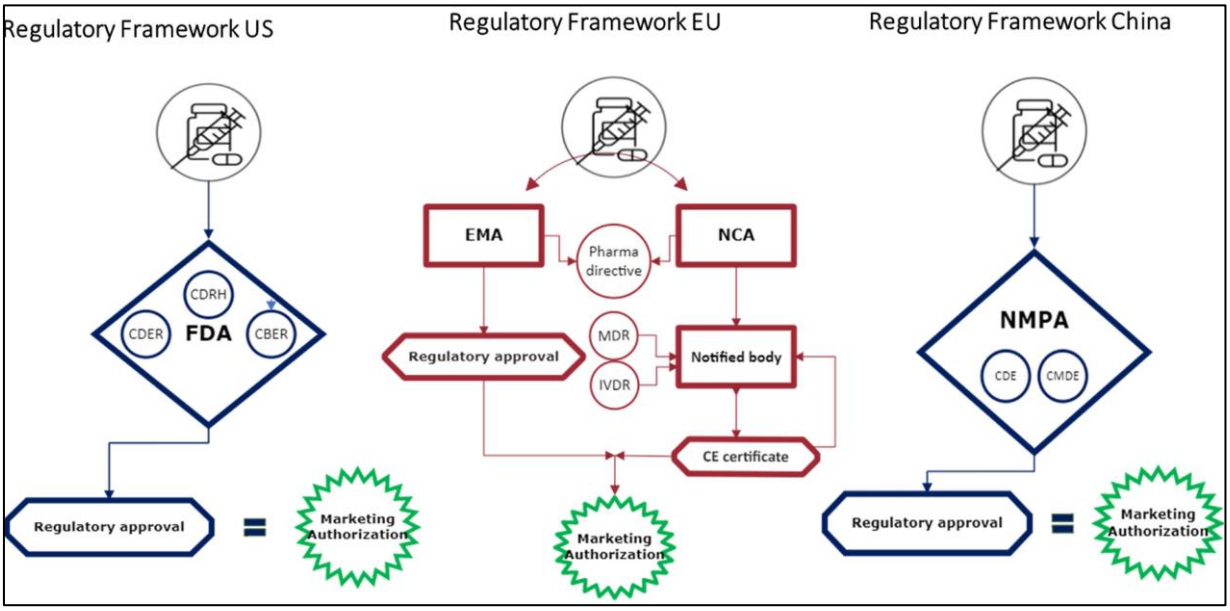

Figure 3: Regulatory frameworks9.

Spotlight on Regulatory Framework – EU

If a product is meant for medical use, it's treated as a medical device and must go through a conformity assessment to prove it's safe and effective. Combination products, which include both a drug and a device, don't have their own category. Instead, they follow two separate regulatory processes: one for the drug and one for the device.

Drugs in the EU are usually approved by the European Medicines Agency (EMA), while medical devices are reviewed by notified bodies in individual member states. These two processes have different timelines and regulators[9].

Understanding the FDA's Accelerated Approval Program

The FDA's accelerated approval program allows treatments for serious or life-threatening diseases to be conditionally approved based on early trial results. These trials use surrogate markers—indicators that are expected to predict the drug's actual benefits.

However, drug companies must do follow-up studies after approval to confirm the treatment's effectiveness. There has been criticism of the time the FDA gives companies to complete these studies, especially after the approval of aducanumab for Alzheimer's disease. In this case, the FDA allowed 9 years for the confirmatory study, raising concerns about how long unproven drugs can stay on the market.
Postapproval trials usually take longer than earlier trials because they focus on real clinical results, not just surrogate markers. It's important to assess if the time limits set by the FDA are reasonable.

Methods L

In this study, we analyzed data from the FDA's Drugs@FDA database to identify all new drugs and biologics that received accelerated approval between January 1, 2009, and December 31, 2018. Since the study used publicly available data, it didn't need approval from an institutional review board or informed consent, as no patient data were involved. The study followed the STROBE guidelines for reporting observational research.
For each drug or biologic, we used established methods to:

- Identify pivotal trials (key studies supporting approval) and postapproval trials (designed to confirm the drug's effectiveness).
- Determine whether postapproval trials were newly initiated or ongoing.
- Identify FDA deadlines for reporting postapproval trial results.
- Locate related trial records on ClinicalTrials.gov and published studies[10.]

Conclusion:

Technological and scientific developments are propelling the modernization of medication development and regulatory procedures, with a focus on patient-centric strategies and international cooperation. Drug approvals are expedited by advancements in pharmacogenomics, digital tools, and organized data management, which improve efficiency and safety. Nevertheless, issues with postapproval monitoring, regulatory heterogeneity, and harmonization continue to exist. Adaptive strategies, a trained personnel, and ongoing regulatory framework development are necessary to address issues. Adopting these modifications will maintain high safety standards while ensuring prompt access to efficient treatments.

REFERENCES:

1. *Future directions in regulatory affairs.* **Chisholm O, Critchley H.** 2023 Jan.
2. *Clinical pharmacology applications in clinical drug development and clinical care: A focus on Saudi Arabia.* **Alsultan A, Alghamdi WA, Alghamdi J, Alharbi AF, Aljutayli A, Albassam A, Almazroo O, Alqahtani S.** 2020 Oct.
3. *Trends in FDA drug approvals over last 2 decades: An observational study.* **Batta A, Kalra BS, Khirasaria R.** 2020 Jan 28.
4. *Structured content and data management-enhancing acceleration in drug development through efficiency in data exchange.* **Beierle J, Algorri M, Cortés M, Cauchon NS, Lennard A, Kirwan JP, Oghamian S, Abernathy MJ.** 2023.
5. *Regulatory Pathways Supporting Expedited Drug Development and Approval in ICH Member Countries.* **Franco P, Jain R, Rosenkrands-Lange E, Hey C, Koban MU.** 2023 May.
6. *A network of regulatory innovations to improve FDA quality assessments of human drug applications.* **Tran R, Fraser G, Fisher AC, Lee SL, Boam A, Tsinontides S, Maguire J, Yu LX, Rosencrance S, Kozlowski S, Henry D.** 2024 Mar.
7. *Establishing a core dossier for multiple regulatory submissions: a case study in the Latin America region.* **Alvarez AL, Maisonet IO, Ruiz O, Lumsden RS, Ferreira APE, Avila Flores EM.** 2023 May.
8. *Regulatory requirements for the registration of generic medicines and format of drug dossiers: procedures in Sri Lanka in comparison with selected regulatory authorities.* **Thambavita D, Galappatthy P, Jayakody RL.** 2018 Jun.
9. *Connected health in US, EU, and China: opportunities to accelerate regulation of connected health technologies to optimize their role in medicines development.* **Awad S, Aljuburi L, Lumsden RS, Mpandzou M, Marinus R.** 2023 Aug.
10. *Comparison of Duration of Postapproval vs Pivotal Trials for Therapeutic Agents Granted US Food and Drug Administration Accelerated Approval, 2009-2018.* **Wallach JD, Ramachandran R, Bruckner T, Ross JS.** 2021 Nov.