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From IVDD to IVDR: The interplay between notified bodies and EURLs

Jennifer Rosendahl ▪ Marta Carnielli ▪ ▪ Panna Vass ▪ Karin Agrenius ▪ Alex Laan ▪ Tom Patten ▪ Olga Tkachenko ▪ Aisha V. Sauer

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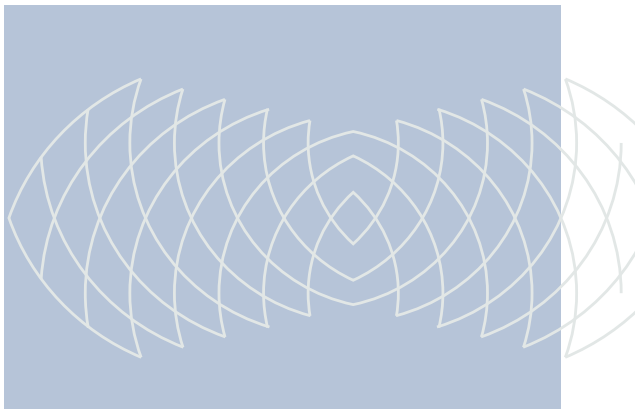

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Introduction: Journal of Regulatory Affairs, May-June 2026

Renée Matthews

Welcome to the Journal of Regulatory Affairs, featuring articles on in vitro diagnostic (IVD) medical devices and the associated workflow between notified bodies and reference laboratories in the EU, the Eurasian Economic Union (EAEU) regulatory pathway, comparability protocols, commercial investigational new drug (IND) applications in the academic setting, and regulatory intelligence on cell and gene therapies.

We thank the authors for sharing their real-world knowledge and expertise with their global regulatory peers. Their commitment, both in time and effort, to writing the articles and seeing them through to final publication is greatly appreciated. We acknowledge their contributions to the existing regulatory literature and hope others will also consider contributing in this way.

Notified bodies, reference labs, and the EAEU

In **From IVDD to IVDR: The interplay between notified bodies and EURLs** (p. 4), **Jennifer Rosendahl** and colleagues, **Marta Carnielli, Panna Vass, Karin Agrenius, Alex Laan, Tom Patten, Olga Tkachenko,** and **Aisha V. Sauer,** track the transition from the former EU In Vitro Diagnostic Directive, under which notified bodies (NBs) verified devices, to the EU In Vitro Diagnostic Medical Device Regulation and its associated EU reference laboratory (EURL) legal framework for confirming the performance of high-risk, Class D IVDs through laboratory testing. The authors present the EURL designation and technical areas and discuss the development of harmonized agreements and workflows between NBs and EURLs. The harmonization efforts have streamlined processes and standardized testing templates, ensuring improved consistency and efficiency during testing and delivery of a safe and effective final product. Rosendahl and colleagues also present key operational steps, manufacturer obligations, and batch testing criteria.

The transition to unified EAEU registration rules was completed on 31 December 2025, resulting in a new regulatory environment for pharmaceutical manufacturers in the member countries of Armenia, Belarus, Kazakhstan, Kyrgyzstan, and Russia. In **The EAEU regulatory pathway: A practical guide for global applicants** (p. 14), **Natalia Tsygankova** provides a practical guide to the key regulatory institutions, the hierarchy of normative documents, registration procedures, and electronic common technical document dossier requirements and preparation. The author highlights common applicant mistakes and offers strategies for optimizing the regulatory process, noting that the focus of regulatory work in 2026 will be on registering new products and the lifecycle management of medicines that have already been authorized. Longer-term, the union will address further digitalization of document flow, continued harmonization with international standards, pharmacovigilance, and oversight of postmarketing obligations.

Comparability protocols and academic drug development

Comparability protocols rooted in strong scientific reasoning, proper analytical comparability, and clear acceptance criteria can provide structured, pre-approved plans for managing postapproval chemistry, manufacturing, and controls (CMC) changes, resulting in lower reporting categories and faster implementation while ensuring product quality. In **Comparability protocols as a strategic tool for postapproval CMC changes** (p. 27), **Piyush Modi, Jigneshkumar Modasiya,** and **Dhaval Desai** highlight the protocols' usefulness when they are incorporated into the pharmaceutical quality system through risk assessment, ongoing process monitoring, and management review to maintain consistency in quality control. The authors note that the protocols should be used for quality changes only and not for changes that might affect clinical outcomes. They also detail how to create and implement a protocol and address the benefits and limitations of using a protocol, suitable and unsuitable chemistry CMC changes, lifecycle management, and the differences between the US Food and Drug Administration and the European Medicines Agency's approaches in regulating and guiding these valuable tools.

In **Regulatory roadmap for NCE commercial IND submissions in academia: A case study** (p. 37), **Sebastian Biglione** and **Chad Bennett** draw on their experience as academic drug developers to document the regulatory pathway from academic discovery to IND submission and the unique challenges in development in that setting. Their brief introductory discussion about the differences in drug development between industry and academia provides a helpful context for their case study, which includes valuable takeaways for other academic institutions pursuing similar ventures. The authors emphasize the importance thorough preparation, regulatory strategy, interdisciplinary collaboration, regulatory expertise, and the ability to swiftly respond to feedback.

Regulatory intelligence and CGTs

Two articles by **Padma Priya Togarrati,** focusing on cell and gene therapies (CGTs), highlight the importance of incorporating regulatory intelligence into strategic decision making throughout the CGT product lifecycle while remaining responsive to regulatory fluctuations and scientific and technological advances. In the first article, **Strategic regulatory intelligence on cell and gene therapies** (p. 51), Togarrati notes the prevailing gaps between product approvals and patient access despite significant advances. She contends that integrated strategies addressing CMC robustness, the generation of real-world evidence, collaboration among stakeholders, and region-specific market access could help address these gaps and underscore commercial viability. The second article, **Strategic regulatory intelligence on pricing and reimbursement models for CGTs** (p. 65), Togarrati examines regulatory intelligence across China, the EU, Japan, South Korea, and the US, specifically, health technology assessments, payer expectations, and reimbursement scenarios defining commercial access for approved CGT products.

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From IVDD to IVDR: The interplay between notified bodies and EU reference laboratories

Jennifer Rosendahl, MSc, PhD

Marta Carnielli, PharmD

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The EU In Vitro Diagnostic Medical Devices Regulation (EU IVDR) introduced a new layer of oversight for high-risk Class D in vitro diagnostic (IVD) medical devices by requiring performance verification and batch testing by designated EU reference laboratories (EURLs). This article outlines the transition from the former EU In Vitro Diagnostic Directive (IVDD), under which notified bodies (NBs) conducted device verification using various alternative methods, to the EURL legal framework established under EU IVDR, Article 100. It summarizes EURL designation and technical areas, the development of harmonized agreements and workflows between NBs and EURLs, and the phased implementation of performance verification and batch testing. It also outlines key operational steps, manufacturer obligations, and batch testing criteria.

Keywords – batch testing, EU IVDR, EU reference laboratory, notified body, performance verification

Introduction

Regulation (EU) 2017/746, also known as the EU IVDR, introduced performance verification and batch testing by designated EURLs to strengthen the oversight of high-risk Class D IVDs.[1] The primary goals are to ensure device quality, safety, reliability, and batch consistency both prior to certification and throughout the product lifecycle. Testing of Class D IVDs is performed by designated EURLs, while the notified body remains responsible for the device's conformity assessment. This article reviews the workflow developed between the notified bodies and EURLs and the implementation of testing activities of Class D IVDs at these laboratories, as set forth in Regulation (EU) 2022/944.[2]

Notified bodies are entities designated by EU member states and notified in a dedicated electronic system. They are responsible for conducting conformity assessments for IVDs when required by the EU IVDR. For Class D IVDs, NBs examine the manufacturer's quality management system and technical documentation and issue corresponding certificates to the manufacturer. After receiving the necessary certificates, the manufacturer may affix the CE mark and place their device on the EU market.

Since the publication of the EU IVDR in 2017, the number of IVDR NBs has grown to 19, most of which are designated for Class D IVDs. Although NBs are separate and independent entities, they collaborate closely through the Notified Body Coordination Group, established under Article 45 of the IVDR, as well as the European Association of Medical Devices Notified Bodies, known as Team-NB.

EU reference laboratories are designated by the European Commission for different scopes of class D IVDs. Where an EURL is

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designated for the scope that covers a given device, the NB must involve the EURL to verify the device's performance before issuing the technical documentation certificate and to conduct batch testing post-certification. In the absence of a designated EURL, NBs may verify the conformity data provided by the manufacturer during conformity assessment through *alternative means*, such as witness testing during audits and batch documentation review.

Regulatory background: From IVDD to IVDR

The concept of verifying or testing batches is not new. Under the IVDD, which was adopted in 1998, NBs were required to perform "verification of manufactured products" for high-risk IVDs listed in Annex II, List A.[3] However, the IVDD did not specify detailed procedures for conducting such verification. Guidance provided by the former NB-MED,[4] an informal coordination group of NBs, outlined the following options:

- Independent batch testing: NBs could directly test samples from product batches, typically through contracted independent laboratories;
- Manufacturer-performed testing with NB materials: NBs could provide reference materials to manufacturers, who would test batch samples according to agreed procedures; and
- On-site witnessed testing: NBs could witness the manufacturers performing batch testing at their facilities in accordance with agreed procedures.

The IVDR was introduced as a more robust and harmonized regulatory framework. Among other changes, it strengthened requirements for clinical evidence for devices, significantly expanded the role of NBs, and strengthened coordination between member state competent authorities. The IVDR also established the legal basis for the designation of EURLs and set forth their roles in independently verifying the performance of high-risk IVDs.

The regulation gives the European Commission discretion as to when and which EURLs are designated. Prior to their designation, in the absence of EURLs, NBs have continued to apply an oversight mechanism (also known as an alternative means) like the one used under the IVDD for batch testing of Class D IVDs.[5]

EURL designation under IVDR

To be designated as an EURL, a candidate laboratory must meet the criteria set out in Article 100(4) of the IVDR, as further detailed in Regulation (EU) 2022/944 on tasks and criteria.[2] These include qualified staff, adequate equipment and reference materials, and an appropriate administrative structure. EURLs must operate independently, maintain confidentiality, and avoid any conflicts of interest, such as financial ties to the medical device/IVD industry, to ensure their impartiality and ability to act in the public interest.

Tasks and criteria

Under Article 100 of the IVDR, EURLs perform the following main tasks regarding IVD Class D devices both before and after market placement:

- Article 100(2)(a): Verify that the manufacturer's claimed performance complies with the applicable common specifications, if such exist, or with other solutions chosen by the manufacturer that ensure a level of safety and performance that is at least equivalent; and
- Article 100(2)(b): Carry out appropriate tests on samples of manufactured Class D devices or on batches of Class D devices, in accordance with Section 4.12 of Annex IX and Section 5.1 of Annex XI of the IVDR.

EURLs also perform advisory tasks under Article 100(2), including:

- Providing scientific and technical assistance, as well as advice regarding the state of the art;
- Contributing to the development of appropriate testing and analysis methods for conformity assessment and market surveillance, as well as contributing to the development of best practices for the performance of conformity assessment procedures;
- Recommending suitable reference materials and reference measurement procedures of higher metrological order; and
- Contributing to the development of common specifications and of international standards.

Article 100(5) specifies additional activities that the EURLs must carry out as a network, including coordinating methods, procedures, and processes, establishing and maintaining a peer review system, and conducting regular proficiency tests.

Calls for designation

In 2022, the European Commission launched a first call for the designation of EURLs for Class D IVDs. These EURLs could be designated in eight different scopes: hepatitis or retrovirus infection, herpesvirus infection, infection with bacterial agents, arbovirus infection, respiratory virus infection, infection with hemorrhagic fever viruses or other biosafety level 4 viruses, parasite infection, and blood grouping markers.

The call outlined a selection process in line with Article 100(1) of the IVDR. The selection had two stages: an assessment of the candidate laboratories' applications by a relevant authority in their EU member state, followed by an assessment by the European Commission. On 5 December 2023, the Commission designated four single laboratory organizations and one consortium as EURLs through Regulation (EU) 2023/2713.[6] These entities became the first to be operational within the EURL network, each with a defined scope(s) relating to specific categories of infectious agents.

A second call for further applications was launched in 2024. Following a similar assessment, the scopes of designation was expanded in December 2025 through Regulation (EU) 2025/2526,[7] amending Regulation (EU) 2023/2713 to include parasite infection markers and blood grouping tests. As of early 2026, five EURLs cover six of the eight scopes for Class D IVDs (**Table 1**). Another call for designation to

Table 1. Designated EU reference laboratories by country and markers

Designated reference laboratory	Country	Markers
Paul Ehrlich Institut	Germany	Hepatitis or retrovirus infection Respiratory virus infection Blood grouping
Consulting Químico Sanitario	Spain	Herpesvirus infection Infection with bacterial agents Parasite infection Blood grouping
Instituto de Salud Carlos III	Spain	Hepatitis Herpesvirus infection Infection with bacterial agents Parasite infection
Consortium coordinated by Servicio Madrileño de Salud[a]	Spain	Herpesvirus infection Infection with bacterial agents
Research Institutes of Sweden	Sweden	Respiratory virus infection Blood grouping

[a]The consortium is comprised of three hospitals: Hospital General Universitario Gregorio Marañón, Hospital Universitario La Paz, and Hospital Universitario Ramón y Cajal.

expand the current EURL pool is expected to be completed by the second half of 2026.

If more than one EURL is designated for a category of devices, those EURLs will form a subnetwork. The subnetworks produce and maintain up-to-date common procedures for performance verification and batch testing for the devices within the category. The designated EURL subnetworks are:

- **Hepatitis or retrovirus infection –** Paul-Ehrlich Institut, Germany; Instituto de Salud Carlos III
- **Herpesvirus infection –** Consulting Químico Sanitario; Instituto de Salud Carlos III; and Servicio Madrileño de Saluda, which is comprised of three hospitals: Hospital General Universitario Gregorio Marañón, Hospital Universitario La Paz, and Hospital, Universitario Ramón y Cajal
- **Infection with bacterial agents –** Consulting Químico Sanitario; Servicio Madrileño de Saluda; Instituto de Salud Carlos III
- **Arbovirus infection –** No designated EURLs
- **Respiratory virus infection –** Paul Ehrlich Institut, Germany; Research Institutes of Sweden
- **Infection with hemorrhagic fever viruses or other biosafety level 4 viruses –** No designated EURLs
- **Parasite infection –** Consulting Químico Sanitario; Instituto de Salud Carlos III
- **Blood grouping markers –** Research Institutes of Sweden; Paul Ehrlich Institut, Germany; Consulting Químico Sanitario

While the EURLs are located in specific EU member states, they serve the entire EU. This means that any NB can request an EURL to carry out performance verification or batch testing for any device and manufacturer, regardless of the country in which they are located, provided that the device is within the EURL's designation scope.

EURLs and NBs in cooperation

Operationalizing EURLs

Together, these five EURLs form a network intended to ensure scientific robustness, regulatory harmonization, and increased confidence in IVD performance across the EU. Their designation is followed by a transition period during which designated laboratories establish networks and harmonized procedures, and manufacturers and NBs adapt their processes to include EURL testing. The EURLs assume their conformity assessment tasks in Article 100(2) of the IVDR at the end of the transition period, specified in the corresponding designation acts.

Prior to the first EURLs becoming operational in October 2024, NBs continued to utilize the previously established approach for batch testing (i.e., verification by alternative means). As of 1 October 2024, NBs are required to engage designated EURLs for devices within the scopes of hepatitis or retroviruses, herpesviruses, bacterial agents, and respiratory viruses for both performance verification and batch testing. EURLs designated for parasites and blood grouping assume their conformity assessment tasks from 1 May 2026. In line with Regulation (EU) 2023/2713, performance verification requirements are implemented in phases depending on whether the manufacturer submitted the device's conformity assessment application to the notified body before or after 1 October 2024 or 1 May 2026, respectively.

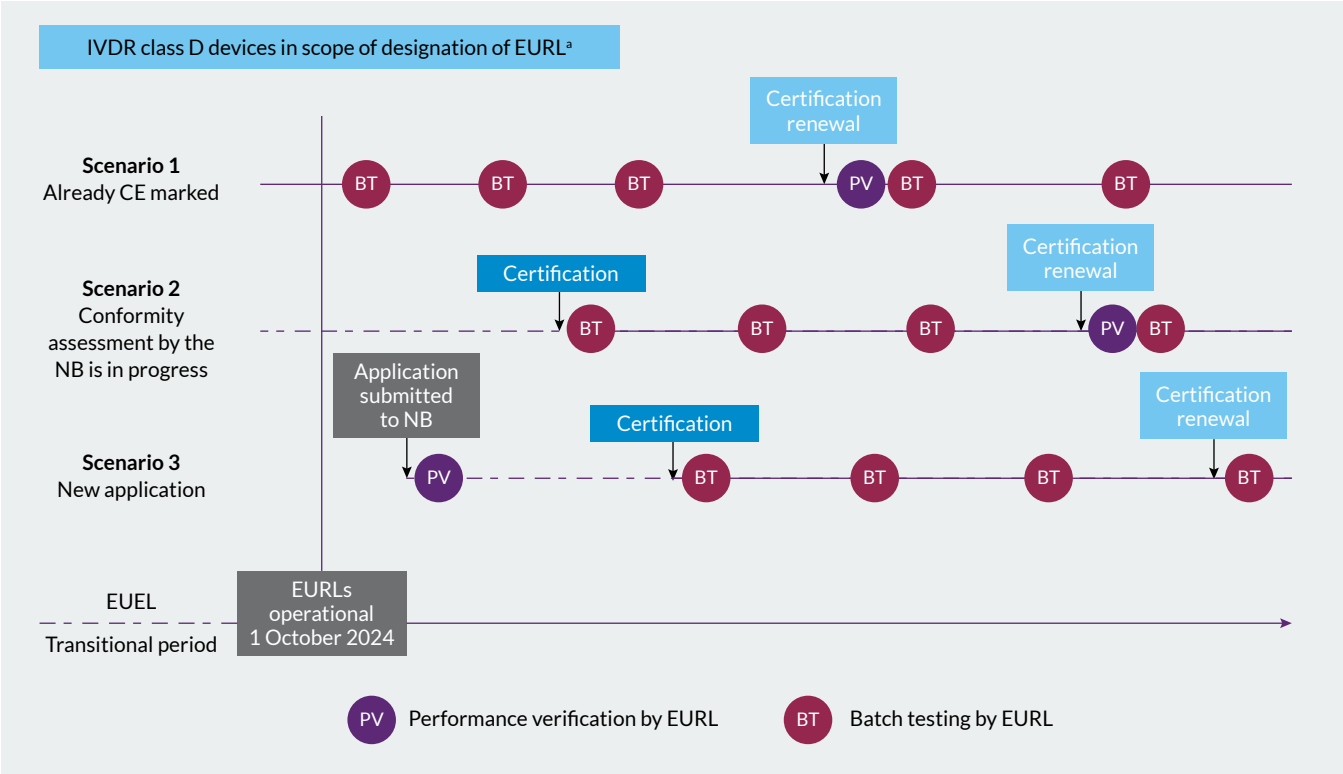
Testing sequence

The sequencing of EURL performance verification depends on when the manufacturer submits the application for conformity assessment to the NB (**Figure 1,** p. 8):

- For devices that were CE-marked before 1 October 2024, performance verification must occur prior to certificate renewal. Performance verification is also required for changes to an approved device (Annex IX, Section 4.11);
- For applications submitted before 1 October 2024, performance verification must occur prior to certificate renewal (Annex IX) and as part of type examination (Annex X, Section 3); and
- For applications submitted after 1 October 2024, performance verification must occur as part of the initial technical documentation assessment (Annex IX, Section 4.9).

As of 1 October 2024, batch testing by an EURL is compulsory for devices falling within its designated scope. Therefore, contractual and logistical arrangements among EURLs, NBs, and manufacturers needed to be established. Until these arrangements were fully in place, NBs could temporarily continue to use alternative means established in the absence of the EURL contract. NBs may still also use alternative means for device scopes that are not yet covered, per the Medical Device Coordination Group (MDCG) guidance.[9] For parasites and blood grouping devices, the same principles apply from 1 May 2026, in line with the phased implementation.

Figure 1. EURL performance verification sequencing for high-risk IVDs[8]



EURL, EU reference laboratory; **IVD,** vitro diagnostic [medical device]; **IVDR,** [EU] In Vitro Diagnostic Medical Devices Regulation; **NB,** notified body.

[a]**NB** legacy devices are not subject to **EURL** testing

Adapted from **MDCG** in vitro diagnostic working group meeting[8]

Contractual arrangements

As per Regulation (EU) 2022/944, NBs and EURLs must establish contractual and logistical arrangements that allow testing activities to be established and implemented. To ensure consistent implementation of their respective responsibilities and roles, NBs and EURLs have jointly developed a general framework agreement template comprising a master service agreement and a statement of work template. These two documents together will form the contractual agreement between an EURL and an NB.

Following agreement and approval of these templates, each NB must execute contracts with the EURLs whose designated device categories fall within its scope. Using standardized templates will also support smoother future collaborations between newly designated NBs and the EURLs. Additionally, to further harmonize the testing workflow, NBs and EURLs have agreed to use and develop common templates for performance verification and batch testing activities, promoting a unified approach to these critical processes. This joint effort contributes directly to the development of a harmonized workflow, as described below.

Harmonized workflow

Creating a common and harmonized workflow between EURLs and NB working groups was a particularly ambitious challenge. The work had to be completed under a tight deadline, and the teams were tasked with developing a new process in an area with no prior process. This joint work took place during the first transition period, which ended on 1 October 2024. The initial contact between the NB and the EURLs took place in April 2024, followed by intensive work to establish both the workflow and the necessary procedural documents (e.g., general framework agreement).

After several iterations and reviews, a unified workflow was agreed upon, outlining the key steps for performance

verification and batch testing. In **Figure 2**, rectangles indicate a process, ovals indicate a document, and the cylinder indicates a batch of Class D devices. The criteria-setting step will only apply if the IVDR certification was initiated before 1 October 2024 and performance verification had not occurred. Batch criteria setting will occur before performance verification is conducted, as per MDCG 2021-4 Rev. 1.

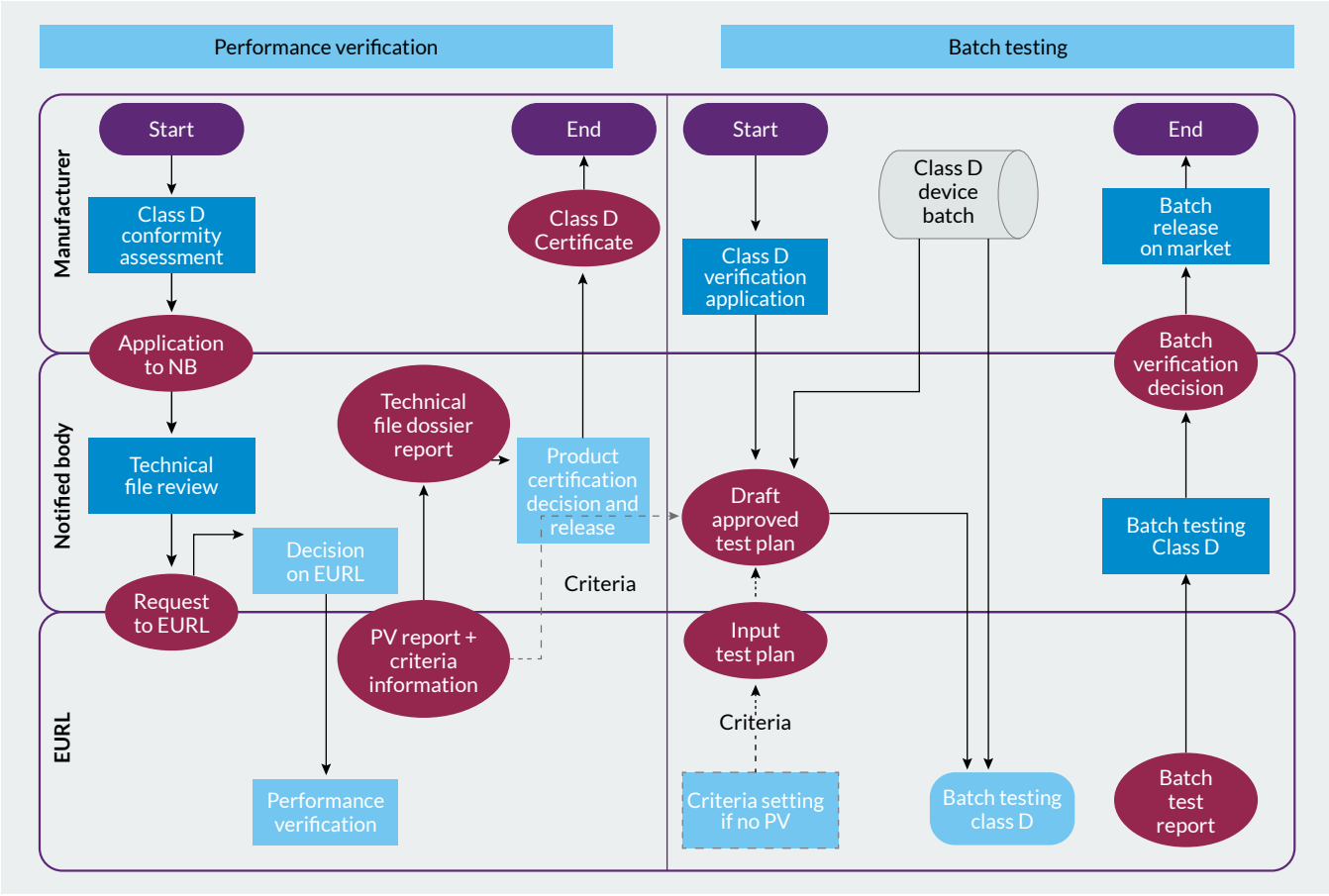
Performance verification

As illustrated in Figure 2, performance verification begins with the manufacturer's submission of a Class D conformity assessment application to the NB during contract review. Once the NB accepts the application, it collaborates with the relevant EURL during the technical documentation assessment to organize and initiate the performance verification process. An application is considered accepted by the NB once the NB has completed its contract review and confirmed that the submission is complete, eligible, and ready to enter the conformity assessment process.

The NB provides the EURL with all documentation related to the device and other relevant information in its possession that is necessary to fulfill the task (i.e., the performance verification). The NB ensures that the manufacturer provides the EURL with the necessary equipment and reference materials for testing the device. This includes the necessary device samples for testing. Within 60 days of receiving the required documentation and device samples, the EURL issues a written scientific opinion (i.e., a written testing report) to the NB.

The EURL's scientific opinion is based on the testing results

Figure 2. Harmonized workflow between manufacturer, notified body, and EURL



BT, batch testing; **EURL,** EU reference laboratory; **PV,** performance verification.
Created by Carnielli et al

and plays a crucial role in determining the certification outcome. When the scientific opinion is negative, the NB will halt the device's certification process. On the other hand, if the scientific opinion is positive and all related conformity assessment review activities are successfully completed, the NB can proceed with a positive decision on the device's certification.

The results of the performance verification testing activity are used to establish the batch testing criteria that will be applied to verify the performance of individual batches post-certification.

Batch testing

Batch testing is initiated post-certification when the manufacturer informs the NB when the batches will be produced. The NB provides the necessary documentation to the EURL and ensures that the manufacturer provides equipment, reference materials, and device samples. The NB prepares the testing plan based on the criteria resulting from performance verification.

IVD manufacturers should contact their NB in a timely manner to clarify which IVDR requirements apply to their device and to determine the appropriate timing for installing instrumentation at the EURL.

The frequency of batch testing is based on MDCG 2022-3 Rev. 1.[10] For Class D IVDs, where performance verification is conducted only at certificate renewal, the EURL must establish the batch testing criteria for the device. To establish the criteria for future batches, the EURL tests three batches of the device. These criteria must be in place before the first batch is tested, irrespective of the performance verification. MDCG 2022-3 also provides additional guidance on the detailed arrangements that must be put in place for performance and batch testing to take place. The requirement to provide all necessary materials to the EURL can be formalized in the contract between the manufacturer and the NB and, where applicable, through separate loan agreements between the manufacturer and the EURL for equipment provision.

During routine batch testing, the EURL tests the IVD against the predetermined batch testing criteria and provides a summary of the results to the NB within 30 days of receipt of the device. When the scientific opinion resulting from the batch testing is positive, the NB releases the device batch. NBs must ensure that all equipment and materials required to perform the testing are provided to the EURLs free of charge. The costs of the actual EURL testing are included in the NB's quotation to the manufacturer, usually during the preapplication phase.

Considerations for IVD manufacturers

When enrolling in the conformity assessment process, it is important for IVD manufacturers to have a clear dialogue with NBs to develop a solid understanding of the entire workflow, as this helps predict the certification process. IVD manufacturers should contact their NB in a timely manner to clarify which IVDR requirements apply to their device and to determine the appropriate timing for installing instrumentation at the EURL. These discussions may take place through *structured dialogue* – a formal, preassessment exchange in which the NB and manufacturer address scope, expectations, and procedural requirements – or as part of the application process itself.

If communication is not initiated early, this can lead to delays in scheduling EURL activities and ultimately a longer overall conformity assessment timeline. For Class D IVDs falling under testing categories for which EURLs have not yet been designated, alternative batch testing methods may currently be used.

Conclusion

EURLs are a new type of scientific body established by the IVDR, tasked with confirming the performance of high-risk IVDs through laboratory testing. As of early 2026, five EURLs have been designated in the EU, and another call is expected to be completed by the second half of 2026. Since 1 October 2024, EURLs have been active in the areas of Class D devices for the detection of hepatitis and retroviruses, herpesviruses, respiratory viruses, and bacterial pathogens. As of 1 May 2026, they also cover Class D parasites and blood grouping IVDs.

NBs and EURLs have closely collaborated to establish a harmonized contract template, testing workflows, and standardized testing templates for Class D IVDs. These significant achievements streamline interactions between

EURLs and NBs, ultimately improving consistency, clarity, and efficiency throughout the testing process.

The establishment of EURL testing is a major milestone in implementing the IVDR, contributing to the availability of safe and performant IVDs in the EU. Devices subject to EURL testing are used for tissue compatibility testing and blood supply testing in Europe, as well as for the detection and monitoring of life-threatening infectious diseases. The work of EURLs is therefore highly relevant and important for public health.

Abbreviations

EU, European Union; **EURL,** EU reference laboratory; **IVD**, in vitro diagnostic [medical device]; **IVDD**, In Vitro Diagnostic Medical Devices Directive; **EU IVDR,** EU In Vitro Diagnostic Medical Devices Regulation; **MDCG,** Medical Device Coordination Group; **NB,** notified body.

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Disclaimer The information and views set out in this article by Aisha V. Sauer, Olga Tkachenko, Jennifer Rosendhal, and Panna Vass are those of those four individuals and do not necessarily reflect the official opinion of the European Commission.

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The EAEU regulatory pathway: A practical guide for global applicants

Natalia Tsygankova, MPharm

This article examines the Eurasian Economic Union (EAEU) regulatory pathway following the completion of the transition period in December 2025, after which all medicinal products on the union's market must comply with unified registration rules. It provides a practical guide to the key regulatory institutions, the hierarchy of normative documents, registration procedures, and eCTD dossier requirements. Particular attention is paid to document preparation, common applicant mistakes, and strategies to optimize the regulatory process. The recommendations are based on an analysis of the EAEU regulatory framework and the author's extensive hands-on experience.

Keywords – EAEU, eCTD, generic drugs, orphan drugs, regulatory strategy

Introduction

The Eurasian Economic Union, comprising Armenia, Belarus, Kazakhstan, Kyrgyzstan, and Russia, is an integrated market with a population of approximately 185 million and a combined GDP exceeding $2.4 trillion.[1] The union's pharmaceutical market demonstrates steady growth: by early 2026, the unified medicines register included over 11,500 marketing authorizations issued under EAEU rules.[2] For international pharmaceutical companies, the EAEU remains one of the largest integrated markets, with a regulatory model harmonized with international requirements while retaining local specificities.

Medicinal product registration in the EAEU is governed by the Rules for Registration and Examination of Medicines for Medical Use, approved by the Eurasian Economic Commission (EEC) Council in November of 2016.[3] The transition to unified regulatory standards for the union's member states was completed on 31 December 2025.[4] By this deadline, marketing authorization holders had aligned dossiers for products previously registered under national procedures with the union's requirements. In May 2025, the EEC Council adopted additional simplifying amendments, which entered into force on 21 June 2025, aimed at optimizing registration procedures.

In 2026, the main focus for applicants is expected to be registering new medicinal products and introducing variations to existing dossiers as part of lifecycle management. This article aims to describe the main stages of the registration process in the EAEU and offer practical recommendations for optimizing the regulatory pathway for international applicants. The article will also systematically examine the EAEU's organizational structure, regulatory framework, registration procedures, pre-registration strategy, requirements for dossier compilation in the common technical document format, and postmarketing obligations of the marketing authorization holder.

In the EAEU context, the term *circulation of medicines* refers to the entire regulatory lifecycle of a medicine, including

development, marketing authorization, manufacturing and quality control, distribution, and postmarket surveillance. *Expert examination* refers to the scientific assessment of a marketing authorization application.

Organizational structure and regulatory framework

The regulation of medicinal products in the EAEU is carried out at two levels: supranational and national.[3] At the supranational level, regulation is ensured by the EEC. Within its structure, the specialized divisions of the Technical Regulation and Accreditation Department, as well as advisory committees with representatives from national competent authorities, are responsible for the circulation of medicines. Expert examination is conducted by the Expert Committee on Medicinal Products, which includes heads of expert organizations from all member states.

At the national level, registration is carried out by each state's ministry of health, and scientific assessments are carried out by the following authorized bodies of the member states:

- Russian Federation – Federal State Budgetary Institution Scientific Centre for Expert Evaluation of Medicinal Products;
- Republic of Belarus – Center for Examinations and Tests in Health Service;
- Republic of Kazakhstan – National Center for Expertise of Medicines and Medical Devices;
- Republic of Armenia – Scientific Center of Drug and Medical Technology Expertise; and
- Kyrgyz Republic – Department of Drug Provision and Medical Equipment.[5]

The interaction between the supranational and national levels is based on the principle of mutual recognition of expert reports issued by the member states.[3]

Hierarchy of normative documents

The regulatory framework of the EAEU for the circulation of medicines is structured according to a multilevel hierarchy, as illustrated in **Figure 1**.

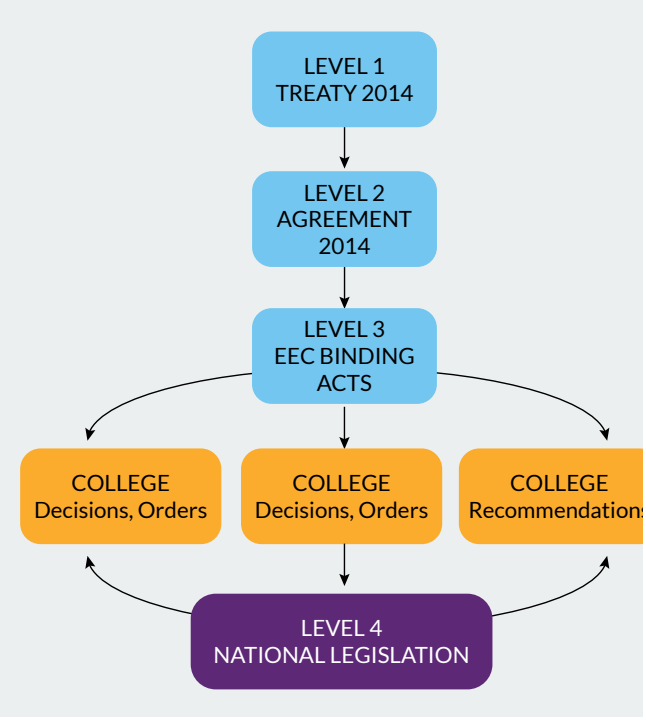
The EAEU treaty of 2014 carries the highest level of authority.[6] The EAEU's agreement on common principles and rules for drug regulation has the second-highest level of authority.[7] The EEC binding acts carry the next highest weight, and include:

- EAEU Decision No. 78, the core EAEU regulation establishing the procedures and requirements for marketing authorization;[3]
- Rules of good clinical practice,[8] good laboratory practice,[9] conduct of bioequivalence studies,[10] good pharmacovigilance practice;[11] requirements for labeling[12] and for the summary of product characteristics and package leaflet;[13]
- College of the Eurasian Economic Commission decisions and orders, which detail requirements for the electronic dossier,[14] stability testing,[15] the classifier of dosage forms,[16] and the guidelines on validation of analytical methods;[17] and
- College of the Eurasian Economic Commission recommendations about unified approaches, such as those relating to pharmaceutical development.[18]

Finally, the national legislation of each member states applies, to the extent that they do not contradict the union's law.[19]

Regulatory documents are regularly updated, so applicants should verify the current versions on the official EAEU legal portal when preparing a dossier.[20]

Figure 1. Hierarchy of Eurasian Economic Union normative documents for medicines regulation[6,7,19]



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Marketing authorization procedures

The EAEU rules for marketing authorization establish two main procedures for bringing new medicines to the EAEU market: the mutual recognition procedure and the decentralized procedure.[3] The applicant has the autonomy to select the reference state and, where necessary, the concerned states. The *reference state* is the lead country that conducts the primary scientific evaluation of the dossier, and the *concerned states* are other EAEU countries in which the applicant seeks approval. The application and dossier are submitted electronically with an electronic signature.

Mutual recognition procedure

The mutual recognition procedure involves sequential dossier submission: first to the reference state, and then to the concerned states. Marketing authorization in the reference state is granted within 140 working days. If additional materials are requested, the applicant has up to 90 working days to respond, with a possible extension (the total response period must not exceed 180 working days).[3] In the concerned states, provided there are no disagreements, marketing authorization is granted no later than 60 working days from the date of access to the expert report. In practice, the mutual recognition procedure is the more commonly used procedure, and the reference state is typically Russia (**Figure 2**).

Decentralized procedure

The decentralized procedure involves the simultaneous submission of the dossier to all states selected by the applicant. The total procedure duration in the reference state does not exceed 140 working days, and in the concerned states, 50 working days.[3] This procedure is used less frequently, primarily when a simultaneous product launch in several countries is required (**Figure 3,** p. 17).

Section VII of the EAEU rules for marketing authorization provides for special procedures for orphan medicinal products, medicines for the treatment of life-threatening diseases, and other cases where the full set of data cannot be submitted at the time of application.[3,21] A summary of each procedure is presented in **Table 1** (p.18). The validity of the marketing authorization for each procedure is valid for five years, though the validity of the marketing authorization for products under exceptional circumstances is subject to revocation.

Pre-registration strategy

Type and characteristics of the medicine

The type of medicine indicated in the marketing authorization application determines the composition and scope of the registration dossier, as well as the required studies. Selecting the appropriate product type directly affects the timeline for bringing the product to market and the likelihood of a successful expert examination. These requirements are detailed in Appendix No. 1 in the EAEU regulation establishing the procedures and requirements for marketing authorization.[3]

For reproduced medicines (i.e., generics), which are the most common application type, it is critically important to correctly identify the reference product and to do so consistently across all modules of the dossier. In practice, there are cases where applicants indicate different reference products across modules, which contradicts the requirements and leads to regulator inquiries.

For example, the author observed that during one expert examination, the applicant specified one reference product in Module 5 and another in Module 2. The expert committee subsequently designated the correct reference product, requiring substantial revision of a significant portion of the dossier and re-justification of the reproduced product status.

Table 2 (p. 19) describes the EAEU product types, dossier requirements, and practical considerations for applicants. Reproduced medicines, also known as generic medicines, are the most common application type. A stepwise approach is

Figure 2. Mutual recognition procedure (sequential submission)

CONC STATE, concerned states, **REF STATE,** reference state, **wd,** working days.
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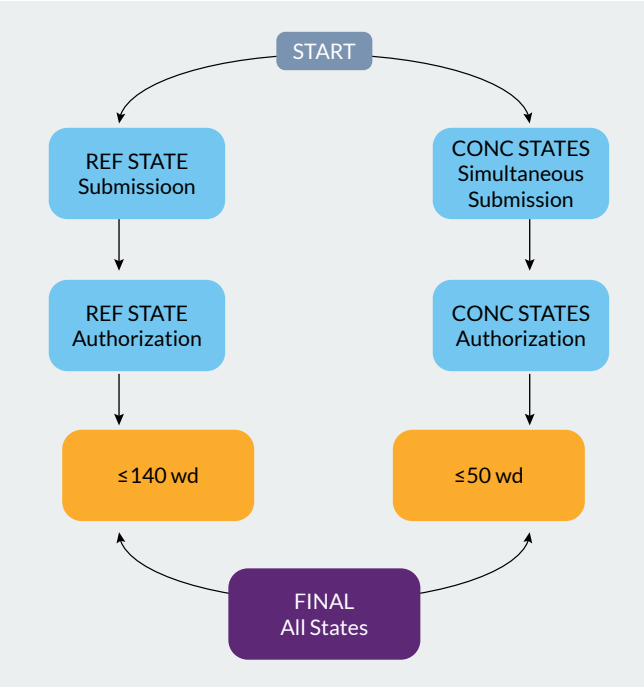
Figure 3. Decentralized procedure (simultaneous submission)



CONC STATE, concerned states, **REF STATE,** reference state, **wd,** working days.

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applied to reproduced medicines, aligning with the US Food and Drug Administration and European Medicines Agency. This stepwise approach, based on similarity in qualitative composition, quantitative composition, and microstructure, is supported by in vitro release testing (IVRT) and followed by assessment of therapeutic equivalence. IVRT data generated for other jurisdictions are generally acceptable.

Hybrid products typically receive more inquiries than average because they are a relatively new product type under EAEU rules, and the need for additional data often leads to more regulatory questions.

Recognition of international studies

Paragraph 36 of the EAEU regulation establishing the procedures and requirements for marketing authorization establishes the criteria for recognition of clinical studies conducted outside the EAEU.[3]

Studies completed before 2016 are recognized if they were conducted in International Council for Harmonisation (ICH) member states prior to 1 January 2016, and if the product based on these studies is authorized in ICH countries.[3] Studies initiated after 2016 are recognized, subject to the condition that at least one clinical study is conducted fully or partially in the EAEU territory, and that all studies (including those conducted outside the EAEU) are performed in accordance with ICH good clinical practice standards, which are harmonized with EAEU law.[3]

In practical terms, for products under development, it is necessary to plan for the inclusion of EAEU research sites within the clinical development program.

Orphan medicinal products

In the marketing authorization application, orphan status is indicated as a separate item, regardless of the product type. For products intended for the treatment of rare diseases, the EAEU rules provide for special provisions.[3] In accordance with Section VII of the rules (as amended by Decision No. 36), orphan medicinal products may be eligible for conditional marketing authorization, marketing authorization under exceptional circumstances, and accelerated examination.[3,21] A key limitation applies where an orphan indication is included in the list of rare diseases of only one member state; in such cases, the product is authorized exclusively for circulation in the market of that state.[3]

Trade name

When selecting a trade name, the requirements of the EAEU's guideline on the selection of trade names for medicinal products must be considered.[25] The proposed name must not be confusingly similar to an already authorized product, particularly a product with a different composition and action. Failure to comply may result in the refusal of marketing authorization, or a requirement to change the name during expert examination.

A practical example observed by the author in 2025 involved an application that required changing the trade name due to visual and phonetic similarity with an authorized product of a different composition, which posed a risk of prescribing errors. Changing the name during the expert examination required revising a significant portion of the dossier (including Module 1, package mock-ups, the summary of product characteristics, and the package leaflet), adding several months to the authorization timeline.

Selection of the reference state

The applicant independently selects the reference state.[3]

Table 1. Special marketing authorization procedures in the Eurasian Economic Union

Procedure	Regulatory basis	Conditions for application	Authorization timeline
Conditional marketing authorization	Section VII, S ubsection VII.III, Decision No. 36[21]	– Medicines for severe or life-threatening diseases, including orphan medicines, with unmet medical need – Positive benefit-risk balance despite incomplete clinical data	140 working days
Marketing authorization under exceptional circumstances	Section VII, Subsection VII.II, Decision No. 36[21]	– Ultra-rare pathologies or cases where comprehensive efficacy data cannot be obtained for objective reasons (e.g., ethical limitations, state of scientific knowledge)	140 working days
Marketing authorization with additional requirements	Section VII, Subsection VII.I, Decision No. 36[21]	– Situations where additional safety or efficacy data must be generated after market entry	140 working days
Accelerated examination	Paragraph 16 of the rules as amended by Decision No. 36[21]	– Orphan medicines; – Treatments for life-threatening diseases; – Pediatric use; or – Products of special significance for the healthcare system (e.g., antibody-drug conjugates for oncology indications)	100 working days
Marketing authorization at the initiative of a competent authority	Decision No. 93 of November 26, 2025[4]	– Product is not authorized in the member state; – No alternatives are available; and – Obtained written consent of the marketing authorization holder	40 working days

Russia remains the largest market and is the most frequently chosen. Alongside Russia, applicants also select Belarus and Kazakhstan, particularly when focusing on local markets, due to their market commercial potential, regulatory capacity, and manufacturing site location.

Risk assessment and gap analysis

The outcome of marketing authorization is largely determined by decisions made prior to dossier submission. Gap analysis should therefore not be limited to checking dossier completeness but should also assess the compliance of each document with current EAEU requirements. Identifying gaps at this stage helps reduce regulator inquiries and can significantly shorten overall review timelines. Particular attention should be given to Module 3 (quality), which typically generates the highest number of regulatory comments. Typical dossier gaps are presented in **Table 3** (p. 20).

For example, during the registration of a reproduced product, the author observed that the applicant received a request for additional justification of the impurity profile and for validation of the analytical methods, even though the original dossier contained a standard set of data. Preparing the response took several months, which significantly increased the overall registration timeline. Systematic analysis of comments from completed

Table 2. Eurasian Economic Union product types and associated dossier requirements and considerations

Product type	Dossier requirements	Practical considerations
Innovator (i.e., original)	Full package of preclinical and clinical studies for a new active substance[3]	– Conduct scientific advice consultations at early stages of development
Reproduced (i.e., generic)	Bioequivalence studies in a a ccordance with Decision No. 85[10] biowaiver possible for additional strengths and certain dosage forms, and for BCS Class I and III substances subject to criteria[10]	– For systemic products, the most frequent error is insufficient justification for a biowaiver – BCS Class III substances require prior agreement with the expert committee – For topical products (e.g., gels, ointments, creams), standard bioequivalence studies may not be applicable
Biosimilar	Stepwise approach with comparative in vitro and in vivo studies in accordance with Decision No. 89[22]	– The main risk is selecting a reference product that is not authorized in the EAEU. In such cases, additional comparability justification is required, and in complex situations, prior consultation with the expert committee
Hybrid	Applied when differences exist relative to the reference product; requires additional preclinical and/or clinical studies[3]	– Typical cases include new indications, changes in dosage, route of administration, or pharmaceutical form compared to the reference product
Well-established use	Substance use for at least 10 years in three or more member states. Studies may be replaced by references to scientific literature[3]	– Saves resources but requires a thorough literature search – Important to confirm that the safety profile is fully studied and reflected in the scientific literature
Fixed-combination	Preclinical and clinical study data justifying the rationale for the combination[3]	– Main focus of the expert review is the justification of the combination's advantages over monoproducts – Without clinical data, demonstrating rationale is challenging – Where authorized monoproducts exist, literature references may be acceptable
Reference product	Selection according to paragraph 18 of Decision No. 85[10] (innovator product authorized in the EAEU, or an alternative agreed with the expert committee)	– Incorrect justification of status leads to rejection at the validation stage – Additional risks include legal disputes and disagreements between member states

BCS, Biopharmaceuticals Classification System, **EAEU,** Eurasian Economic Union; **IVRT,** in vitro release testing.

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Table 3. Dossier assessment focus and gap analysis

Area	Assessment focus	Potential gaps
Quality	Compliance with EAEU Pharmacopeia; stability; impurities	Absence of data on genotoxic impurities in accordance with ICH M7;[23] insufficient stability data (less than 6 months at the time of submission);[15] lack of validation of analytical methods[17]
Preclinical studies	GLP compliance, data completeness	Absence of reproductive toxicity studies; absence of carcinogenicity studies for products intended for long-term use
Clinical studies	GCP compliance, study design	Insufficient data on subgroups (pediatrics, elderly, specific ethnic groups)
Pharmacovigilance	Existence and adequacy of an RMP	Absence of an RMP adapted to regional specificities[11]
Labeling	Compliance with Decision No. 76[12]	Missing provision for sticker/label space; noncompliance with font requirements; incorrect translation of mandatory labeling elements (e.g., dosage, storage conditions, expiry date, warnings)

EAEU, Eurasian Economic Union; **GLP,** good laboratory practice; **ICH,** International Council for Harmonisation; **RMP,** risk management plan.

registrations helps identify typical errors and adjust the approach to preparing new dossiers.

Scientific advice

Scientific advice is provided by the competent authorities of the member states, not at the level of the Eurasian Economic Commission, and is of a nonbinding, explanatory nature.[10] Its conclusions may or may not be taken into account during subsequent expert examination of the registration dossier. Scientific advice should be regarded as a supportive, rather than a guaranteed, tool for mitigating regulatory risks. It is recommended to document any scientific advice received and include it in Module 1 of the registration dossier; however, there is no guarantee that it will be considered during expert examination.

Registration dossier preparation

The EAEU has adopted the common technical document (CTD) format, which corresponds to the ICH CTD structure. Modules 2-5 are harmonized with international requirements, while regional specifics are concentrated in Module 1.[3] Since 2021, dossiers have been submitted exclusively in electronic format as eCTD (version 3.2.2, harmonized with ICH).[14] The structure and specific EAEU requirements are outlined in **Table 4** (p. 21).

Practical recommendations by module

The following section summarizes practical recommendations for each module of the registration dossier, based on regulatory requirements and observed best practices.

Module 1

If a manufacturing site inspection is scheduled during expert examination, the regulator may request the inspection results. The absence of a valid good manufacturing practice (GMP) certificate may suspend the procedure.

At the time of submission, it is sufficient to provide a GMP certificate from the country of manufacture and a package of documents in accordance with paragraph 30 of the rules of marketing authorization. Since 21 June 2025, amendments have entered into force that allow manufacturers to undergo inspection for compliance with EAEU GMP requirements within three years after product registration, rather than prior to dossier submission.[26] Failure to comply with the three-year deadline may result in the revocation of the marketing authorization.

Changes to the package leaflet during the expert examination stage may require additional user testing if they affect the de-

Table 4. Structure and requirements of the Eurasian Economic Union registration dossier

Module	Specific EAEU requirements
Module 1: Administrative information	– Must be in the state language of the reference state – Justification of the application type (Section 1.8.2) – EAEU GMP certificate or a package of documents in accordance with Rule 3 – User testing of the package leaflet[13] – Draft quality standard – Information on the pharmacovigilance system and RMP[11]
Module 2: CTD summaries	– Reduced content may be acceptable for reproduced (generic) products – Must be translated into Russian[3]
Module 3: Quality	– API master file may be submitted – CEP may be accepted where the monograph is included in the EAEU Pharmacopeia[24] – Requirements for assessment of genotoxic impurities[23] – Stability testing data must be provided[15] – Submission of a quality standard document[17]
Module 4: Preclinical study reports	– For reproduced products, bibliographic references may be substituted for full reports – Documentary and remote inspections possible – A summary in the state language[3]
Module 5: Clinical study reports	– Bioequivalence studies required per Decision No. 85[10] – For biosimilars, comparative clinical studies required per Decision No. 89[22] – GCP inspections may be conducted – Summary in the state language[3]

API, active pharmaceutical ingredient; **CEP,** certificates of suitability; **EAEU,** Eurasian Economic Union; **GCP,** good clinical practice; **GMP,** good manufacturing practice; **RMP,** risk management plan.

sign or layout. The summary of product characteristics (SmPC) and package leaflet should follow the structure and content of the reference product's documents, as unjustified discrepancies in indications are a common reason for queries.

Module 2

In Module 2, translation quality is a critical factor, as errors in the summaries may lead to additional questions and delays in expert examination. Based on the author's experience, it is recommended to engage professional translators with regulatory expertise. Automated tools should not be solely relied upon alone, as they often fail to capture context, nuance, or the specific regulatory terminology of the EAEU.

Module 3

The most common reasons for Module 3 queries include noncompliance of specifications with EAEU Pharmacopeia requirements, incomplete method validation (especially the absence of a full description of chromatographic columns, such as manufacturer and catalog number), absence of data on genotoxic impurities in accordance with ICH guidelines on assessment and control of DNA reactive impurities,[23] insufficient stability data (less than six months at the time of submission),[15] and absence of photostability data. Ensuring these elements are adequately addressed will reduce the likelihood of regulatory queries.

Module 4

For Module 4, if a preclinical study was conducted outside the EAEU, the applicant should ensure that a GLP certificate recognized in the Union is available. Compliance with GLP standards is required to confirm the validity and acceptability of nonclinical study data for regulatory assessment.[9]

Module 5

For clinical studies after 2016, at least one study involving patients from the EAEU is mandatory.[3] It is recommended

that the inclusion of local study sites be planned at the protocol development stage.

- For bioequivalence studies, the reference product must be authorized in the EAEU (per paragraph 18 of Decision No. 85).[10] If a different reference product is used, applicants should allocate budget and time for a bridging study.
- For biowaivers, the analysis should begin with verification of compliance with the criteria set out in Appendix No. 4 to Decision No. 85.[10] For Biopharmaceutical Classification System Class III substances, applicants should allocate time for prior agreement with the expert committee.
- For biosimilars, the choice of a reference product authorized in the EAEU is a critical decision affecting the entire scope of the program. When planning studies, the requirements for immunogenicity data for the EAEU population must be considered. If the study is conducted globally, a justification for extrapolation should be provided.
- For topical products (e.g., gels, ointments, creams), standard bioequivalence studies measuring plasma concentration are often not applicable. It is recommended to incorporate a stepwise approach based on similarity in qualitative composition, quantitative composition, and microstructure, supported by IVRT, and followed by assessment of therapeutic equivalence (Appendices No. 11–13 to Decision No. 85).[10] IVRT data obtained for the European Medicines Agency using validated methods are generally accepted.

Overall, early alignment of study design with EAEU regulatory expectations is essential to reduce the risk of additional requirements during expert examination.

General recommendations

The following recommendations complement the module-specific considerations outlined above and highlight additional cross-cutting procedural and technical requirements applicable to EAEU registration dossiers.

For foreign applicants, the appointment of an authorized representative within the EAEU territory is mandatory.[3] The authorized representative must be registered in the same state where the application is submitted and must have documented authority to act on behalf of the applicant. Their responsibilities include submitting documents, interacting with regulatory authorities during expert examination, and obtaining the marketing authorization. When selecting a representative, it is recommended to consider their experience with product registration in that state, knowledge of local documentation requirements, and technical readiness to work with the eCTD system.

The pharmacovigilance system master file is submitted with the first product, while for other dossiers, a brief description of the system is sufficient.[11,14] In addition, strict adherence to the eCTD submission chronology is required. The sequential order of dossier versions throughout the product lifecycle must be maintained. Failure will result in validation errors in the XML dossier and, as a result, make it impossible to submit to the regulatory authority.

Postmarketing obligations

Renewal of the marketing authorization

For initially authorized products, the marketing authorization is issued for five years.[3] An application for renewal must be submitted no earlier than 140 working days before the expiry date of the authorization in the reference state, but no later than the expiry date itself.[3] Upon successful renewal, an unlimited validity marketing authorization is issued.[3] For products authorized under special procedures, the five-year cycle is maintained with the possibility of re-issuance.

Simultaneous variation submission with renewal

Paragraph 144 of the EAEU rules on marketing authorization allows the combination of renewal and variation procedures in a single application, provided that the variations are classified as type IA, IAIN, or IB in accordance with Appendix V to Annex No. 19.[3] In the EAEU variation system, type IA and IAIN correspond to minor changes that can usually be implemented with postimplementation notification, while type IB variations are minor changes necessitating notification and regulatory acknowledgment prior to implementation.

This combined approach is particularly relevant where commitments from a previous assessment include minor variations (types IA, IAIN, or IB). The classification of variations is therefore critical, as it determines whether they can be carried out within the renewal procedure or will require a separate application.

The classification of variations is critical, as it determines whether a variation can be included in the renewal application or will require a separate procedure. Reference

to Appendix V is therefore essential for correct procedural planning. An important distinction is that if variations affect product quality and are classified as type II (i.e., a major change variation), they will require a separate submission. However, parallel processing of renewal and type II variations is permitted, but requires special attention to document version control to avoid conflicts between the submitted versions.

Prior to the submission of a renewal application, it is recommended that applicants:

- Verify the validity of all licenses and GMP certificates of manufacturing sites (otherwise, the expert examination may fail even with formal compliance);
- Confirm the existence and correctness of periodic safety update reports;
- Ensure compliance of the SmPC and package leaflet with current requirements (taking into account the latest amendments to Decision No. 88); and
- If there are commitments from expert authorities, check whether they relate to variations of types IA, IAIN, or IB in order to include them in the renewal application (paragraph 144 of the EAEU rules).[3]

When applied correctly, this combined procedure reduces administrative burden and speeds up marketing authorization maintenance across the EAEU.

Variations to the registration dossier

Throughout the product lifecycle, the marketing authorization holder may introduce variations to the registration dossier. The classification of variations (types IA, IB, II) and associated submission procedures are established by Section VIII of the EAEU rules.[3] Detailed lists of variations are provided in Appendix V.[3]

The following is a list of other key considerations regarding variations to the registration dossier:

- When multiple variations are submitted in a single application, the review timeline is determined by the most complex variation.[3]
- A significant simplification introduced by Decision No. 34 is the possibility to initiate variations to the registration dossier both before and during the mutual recognition procedure in the member states.[26] Previously, such actions required a separate procedure and significantly delayed product entry into the markets of the concerned states.
- Since December 2025, minor technical corrections, such as the correction of typographical errors, may be permitted provided they do not affect product quality, safety, or efficacy. Such corrections must be justified in the cover letter.[3]
- With regard to pharmacovigilance documentation, the pharmacovigilance system master file is submitted with the first product of the marketing authorization holder and is subsequently maintained within that dossier as a type IB variation. For other dossiers, a brief description of the pharmacovigilance system is sufficient, and changes to this system are submitted as type IAIN variations.[11]
- Although the applicant determines the type of variation, the regulator may reclassify it. In the case of uncertainty, scientific advice is recommended.

For example, the author observed an applicant who included several amendments in a variation application, considering them to be technical amendments, but did not explain their nature in the cover letter, and did not confirm that they did not affect product quality. The regulator regarded them as unsubmitted variations and rejected the application.

Pharmacovigilance

Requirements for the pharmacovigilance system are established by Decision No. 87.[11] The following obligations are imposed on the marketing authorization holder:

- Ensure the functioning of the safety monitoring system;
- Designate a qualified person for pharmacovigilance;
- Develop and maintain a risk management plan and periodic safety update reports at a frequency established by the regulator; and
- Interact with national pharmacovigilance centers.

The risk management plan must contain EAEU-specific risk minimization measures. For high-risk products, it is advisable to consult the regulator on the draft plan prior to dossier submission.

For example, in one observed case, the applicant submitted a risk management plan that did not describe routine risk minimization measures in detail, particularly how risks were reflected in labeling and the SmPC. As a result, the

regulator requested revisions, which added two months to the expert examination timeline.

Conclusion

The transition to unified EAEU registration rules, completed on 31 December 2025, has formed a new regulatory environment for pharmaceutical manufacturers.[3,4] In 2026, the primary focus of regulatory work is on the registration of new products and the lifecycle management of already authorized medicines.

Experience from regulatory practice confirms that registration success is largely determined at early development stages. The choice of product type, reference state, and timely gap analysis directly impacts time-to-market. Studies conducted outside the union are recognized, subject to compliance with EAEU requirements.[10] The largest number of regulatory queries continues to relate to Module 3, particularly concerning data on impurities, stability, and method validation.[15,17,23] Overall, the EAEU registration system is predictable with proper preparation, as reflected by the more than 11,500 marketing authorizations currently in the unified register.[1,2]

Looking ahead to 2026-2028, further digitalization of document flow is expected, in line with the approved EAEU development roadmap to 2030, which includes measures for digital transformation in technical regulation and product labeling.[26] Continued harmonization with international standards, including implementation of ICH guidelines, is also anticipated. In parallel, attention to pharmacovigilance and oversight of postmarketing obligations will increase, as evidenced by ongoing training programs for regulators.[27]

Abbreviations

API, active pharmaceutical ingredient; **BCS,** Biopharmaceutics Classification System; **CEP,** certificate of suitability to the European Pharmacopoeia; **CTD,** common technical document; **EAEU,** Eurasian Economic Union; **GCP,** good clinical practice; **GLP,** good laboratory practice; **GMP,** good manufacturing practice; **ICH,** International Council for Harmonisation; **INN,** international nonproprietary name; **MA,** marketing authorization; **MAH,** marketing authorization holder; **PL,** package leaflet; **RMP,** risk management plan; **SmPC,** summary of product characteristics.

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Comparability protocols as a strategic tool for postapproval CMC changes

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This article discusses how comparability protocols provide structured, pre-approved plans for managing postapproval chemistry, manufacturing, and controls (CMC) changes while ensuring product quality. These protocols explain the scientific rationale for the proposed change, outline the analytical strategy to demonstrate comparability, define the acceptance criteria, and specify the recommended reporting category. The use of comparability protocols aligns with the principles outlined in International Council for Harmonisation (ICH) guidelines, which stress risk-based decision making and strong lifecycle quality management. This article also discusses the advantages and limitations, differences between the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approaches, and practical implementation considerations for comparability protocols.

Keywords – CMC, comparability protocols, lifecycle management, pharmaceutical quality system, postapproval change

Introduction

Comparability protocols are important tools for systematically and scientifically managing postapproval CMC changes. In this article, the term *comparability protocol* refers to the written plan submitted to a regulatory authority that describes the strategy for assessing a postapproval manufacturing or analytical change and the evidence required to confirm that the change maintains product quality.

International standards, such as ICH Q9(R1), Q10, and Q12, recognize comparability protocols as part of the pharmaceutical quality system, linking them to change management, knowledge management, and management review.[1-3] Through the use of scientific reasoning and lifecycle monitoring, comparability protocols help organizations implement changes successfully while maintaining quality and meeting regulatory requirements.

Scope and regulatory foundations

In October 2022, the FDA published final guidance updating its 2016 draft to assist the pharmaceutical industry in submitting protocols for postapproval manufacturing changes.[4,5] The guidance explains the types of protocols, their limitations, and the required information, including risk assessments, analytical plans, and acceptance criteria. It also explains how to implement and report changes after protocol approval.[6]

The use of comparability protocols to plan and assess postapproval manufacturing changes closely aligns with process validation concepts applied throughout a product's lifecycle. According to the FDA's 2011 guidance, manufacturers are required to implement continued process verification (Stage 3) through the routine collection and analysis of process data during commercial manufacturing. Stage 3 is defined as

the ongoing, statistically based monitoring of process performance and quality attributes to verify that the validated manufacturing process performs consistently over time.[7] Real-time monitoring after implementing a change under an approved protocol is important, as it ensures the change works as planned and prevents unexpected problems.

In practice, this involves tracking concrete metrics, such as process capability indices (e.g., CpK) for critical quality attributes and monitoring out-of-specification rates. *CpK* measures how consistently a process operates within its predefined specification limits, accounting for both process variability and process centering. In pharmaceutical manufacturing, a CpK value of 1.33 or higher is commonly used as an indicator of a capable, well-controlled process. Maintaining a CpK above 1.33 or demonstrating a stable or reduced out-of-specification rate after implementing a change can provide strong assurance of ongoing process stability. Regular checks of these quality attributes help maintain product consistency, build patient trust, and support good clinical outcomes.[6,8]

When to use the comparability protocol

FDA guidance states that comparability protocols are suitable for quality-only changes.[3] These include expanding manufacturing networks, relocating production sites, or updating analytical methods, provided analytical comparability and risk assessments proved no impact on product quality. Protocols are not appropriate for changes that may impact clinical outcomes or when analytical comparability is uncertain. They work best when processes and controls remain the same, and verification or process performance qualification studies are conducted.

For example, when moving finished dosage form manufacturing from one location to another, a comparability protocol helps maintain product quality by documenting the change, establishing process checks, and creating analytical comparability plans with acceptance criteria. This can speed up reviews, reduce downtime, and make transitions easier without requiring additional clinical data when the protocol criteria are met.[9] Protocols can also support changes to raw materials or active pharmaceutical ingredient suppliers when supported by strong data and risk assessment.[5,10]

However, the guidance clearly states that comparability protocols are not appropriate for changes requiring clinical or nonclinical evaluation, or for modifications outside the scope of CMC topics, such as labeling changes, formulation changes impacting efficacy, or changes to the dosing regimen.[10] The following section addresses the characteristics of a strong protocol and how its structure fulfills regulatory requirements.

Creating a strong comparability protocol

A strong comparability protocol uses product and process knowledge to create a clear, testable plan. It explains the scope and rationale for the change, lists what will change and what will stay the same, and retains a narrow focus to lower the risk of rejection. The protocol should clearly connect proposed changes to critical quality attributes, explain why supporting studies are needed, and link identified risks to relevant data or control measures.[10]

A strong comparability protocol uses product and process knowledge to create a clear, testable plan.

The protocol must have an analytical comparability plan that lists the methods to be used, explains why they are suitable, and sets clear acceptance criteria. It should describe how results will be compared with specifications and past data. The FDA expects a well-justified statistical approach, including sample size, power, and margins.[10,11]

If process verification or process performance qualification is required, the protocol must specify the number of lots to be tested, the sampling approaches, and the statistical criteria to be used. It should explain how continued process verification (Stage 3) will monitor performance after the change. The protocol should also specify success criteria, a reporting plan, and pass-or-fail standards. It must also state the proposed Step 2 (the postimplementation reporting step per FDA comparability protocol guidance), including the reporting category and a list of the data to be submitted upon completion of the protocol.[10]

The protocol should clearly show how it integrates within the pharmaceutical quality system. This includes describing the change control process, documentation practices, deviation management, and management review activities. It

should explain how the protocol will be carried out, how it can be reused for future changes, and how it will be updated when needed. Organizations should align comparability protocols with existing change control templates and internal quality procedures. Centralized documentation and version control help track revisions, approvals, and all related records. It is also important to define clear roles and responsibilities for executing the protocol, including review and approval by quality assurance, regulatory affairs, and manufacturing.[10]

Risk-based tools should support decision making in change control, helping teams determine when a protocol is appropriate and when to escalate an issue. Staff involved in designing, implementing, and monitoring the protocol must be properly trained so that procedures are consistently followed. Regular assessments of protocol performance during management meetings support continuous improvement and encourage knowledge sharing across sites or product lines.

Whenever possible, comparability protocols should be linked to senior management review cycles, such as quarterly or annual reviews, to ensure their effectiveness, outcomes, and ongoing suitability are evaluated routinely. Integrating this evaluation into established review processes reinforces lifecycle ownership and helps maintain regulatory compliance, ultimately leading to fewer complaints and fewer recalls. By applying these practices, comparability protocols become scientifically sound and fully integrated into the pharmaceutical quality system.[12]

Benefits of comparability protocols

A key benefit of comparability protocols is the potential to qualify for a lenient FDA reporting category, thereby resulting in faster implementation of postapproval CMC changes. For example, a change to critical manufacturing equipment usually requires submission as a prior-approval supplement. However, if a comparability protocol is approved in advance and successfully executed, the same change may be submitted under a Changes Being Effected in 30 Days (CBE 30) pathway, speeding up implementation. When a protocol has clear, defined criteria and demonstrates that product quality is maintained, the FDA's 2022 guidance allows sponsors to request a lower reporting category. By setting data expectations, methods, and acceptance criteria in advance, comparability protocols make regulatory processes more efficient and transparent.[6,10,13]

Comparability protocols also improve the efficiency of FDA review by specifying in advance the data required for a postapproval CMC change, thereby minimizing the postapproval review burden and need for iterative exchanges during the review process. Before the adoption of comparability protocols, a typical postapproval change could involve multiple regulatory queries. With a robust protocol, the number of queries can be reduced, since most information is predetermined and documented. According to FDA guidance, comparability protocols enable the agency to avoid repeated comprehensive reviews of similar changes, thus reducing the administrative burden associated with postapproval submissions. As a result, organizations benefit from receiving fewer FDA information requests and experience more predictable review timelines, as the testing strategy, acceptance criteria, and risk rationale are established in advance.[6,10]

When a protocol has clear, defined criteria and demonstrates that product quality is maintained, the FDA's 2022 guidance allows sponsors to request a lower reporting category.

Limitations of comparability protocols

The FDA's 2022 comparability protocol guidance emphasizes that approval of a protocol allows a sponsor to propose a lower reporting category, but this outcome is not guaranteed. Reduced reporting is granted only when the protocol results meet the predefined acceptance criteria. If the criteria are not met, the sponsor may need to submit a higher-level supplement or conduct additional studies to address the issues identified. Sponsors should be prepared for this possibility. If the protocol fails, having a clear plan for next steps, such as submitting a prior approval supplement or generating additional supporting data, helps ensure a structured, timely response. Describing this backup plan within the protocol sets realistic expectations and promotes smoother interactions with the FDA.[14]

Suitable versus unsuitable CMC changes

According to FDA guidance, some postapproval CMC changes are suitable for a comparability protocol because they primarily rely on analytical comparability and risk-based scientific reasoning. However, some CMC changes

are not covered if they could affect clinical performance or if analytical data alone cannot resolve the uncertainty.[6]

As a result, comparability protocols work best for well-understood, lower-risk changes that have solid analytical evidence and significant historical data. In contrast, more complex or higher-risk changes, especially those involving biologics and advanced therapies, frequently require additional evidence beyond a comparability protocol to meet FDA requirements for product quality and patient safety.[6] **Table 1** summarizes which types of postapproval CMC changes are generally suitable for a comparability protocol and highlights key limitations or conditions that may apply.

Lifecycle management of comparability protocols

After approval, managing a comparability protocol requires implementation, ongoing monitoring, reporting, and regular review within the pharmaceutical quality system. Doing these steps well ensures regulatory predictability and protects product quality and patient safety. This integrated lifecycle-based management of comparability protocols transforms the comparability protocol from a mere regulatory requirement into a useful quality management tool that supports continuous improvement.[10] **Figure 1** (p. 31) illustrates the lifecycle of a comparability protocol, showing how approval, implementation, verification, and ongoing monitoring integrate within the pharmaceutical quality system. In the figure, maroon ovals represent key regulatory decision or submission steps, light blue ovals indicate execution and ongoing monitoring activities, and purple ovals denote points where predefined criteria are not met, and further risk reassessment, escalation, or protocol revision is required.

Comparison of FDA and EMA approaches

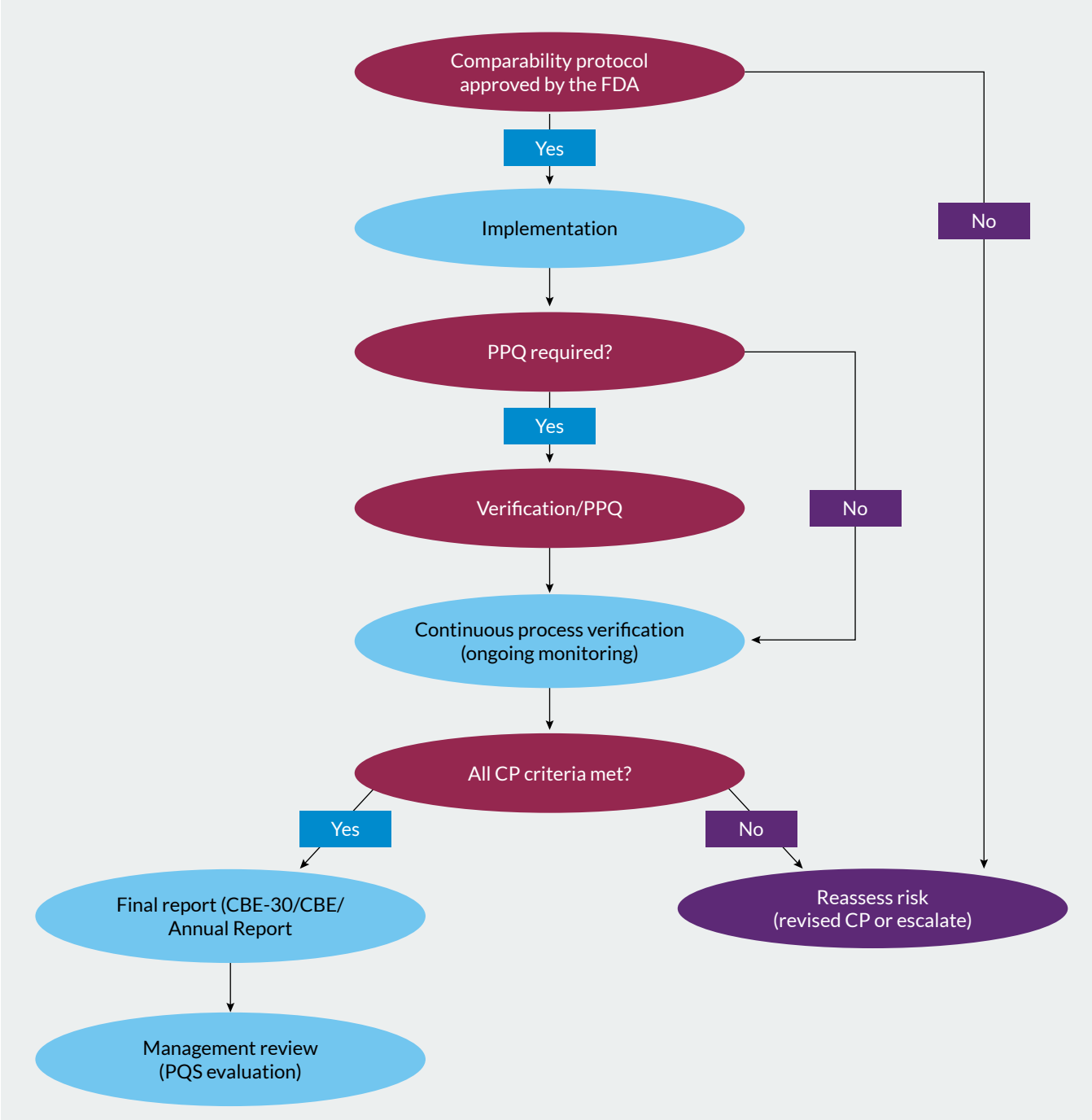
Both the FDA and EMA use pre-agreed procedures to

Table 1. Suitable versus unsuitable CMC changes for comparability protocols

Change type	Suitable under CP?	Remarks
Formulation changes (SUPAC Level I and II)	Yes	Allowed only if the formulation change is justified with in vitro study data.[6] Postapproval Level I changes are minor, while Level II changes carry moderate risk.
Site transfer changes	Yes	Allowed only when the proposed site has a strong inspection history and experience with the proposed dosage form.[6]
Noncritical manufacturing changes	Yes	Critical manufacturing changes in NDA or BLA submissions should be discussed with the FDA.[6]
Equipment changes	Yes	The CP should address differences in equipment design and operating principles.[6]
Analytical method upgrades (e.g., HPLC to UPLC)[3]	Yes	The CP should demonstrate method equivalence between the HPLC and the UPLC method.
New raw material or API supplier	Yes	The CP should address risk-based materials characterization and demonstrate analytical comparability. The proposed API drug master file should have scientific assessment status.[6]
Minor packaging/device tweaks	Yes, case by case	The CP should include appropriate analytical testing and performance checks.[6]
Clinical assessment changes[3]	No	–
Cellline switch or major upstream revamp	Often no, or CP + extra data	Analytical assessments often require supplementation with pharmacokinetic and/or clinical data.[15]
Cell gene therapy process variability issues	Often no, or tailored approach	Limited material availability and immature potency changes with potency/assays restrict the ability to establish analytical comparability.[12]

API, active pharmaceutical ingredient; **BLA,** biologics license application; **CMC,** chemistry, manufacturing, and controls; **CP,** comparability protocol; **FDA,** Food and Drug Administration [US]; **HPLC,** high-performance liquid chromatography; **NDA,** new drug application; **SUPAC,** scale-up and post-approval changes; **UPLC,** ultra-performance liquid chromatography.

Figure 1. Lifecycle of a comparability protocol



CBE, changes being effected; **CBE 30,** changes being effected in 30 days; **CP,** comparability protocol; **FDA,** Food and Drug Administration [US]; **PPQ,** process performance qualification; **PQS,** pharmaceutical quality system.

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manage postapproval CMC changes, but their systems differ in scope, process, and regulatory context. The FDA's comparability protocol allows applicants to submit a written plan to assess a proposed change and its impact on product

quality. The FDA guidance covers new drug applications, abbreviated new drug applications, and biologics license applications, and states that the protocol can support reduced reporting categories when sufficient scientific understanding is available. The FDA's approach is flexible and allows changes that affect identity, strength, quality, purity, or potency as described in the guidance.[6]

The EMA's postapproval change management protocol (PACMP) has a narrower scope. It is rooted in the EU Variations Regulation[16] and the associated guidance. The EMA framework limits PACMP use to quality changes that do not require clinical or nonclinical assessment and do not result in a line extension. A *line extension* refers to a change that creates a new presentation of a medicinal product, such as a new strength, dosage form, or route of administration, which requires separate regulatory approval. The EMA requires that PACMPs be submitted as variations under the EU system. In the EU system, postapproval changes are submitted as *variations*, which are formal regulatory applications used to notify or seek approval for changes to an approved marketing authorization. Although PACMPs can reduce variation during implementation, their use is constrained by the European variation classification, which categorizes changes as Type IA, IB, or Type II.[17]

Both agencies follow ICH Q12 lifecycle management principles; however, the EMA more clearly incorporates PACMPs within the ICH Q12 framework, while the FDA encourages manufacturers to use knowledge- and risk-based strategies that align with ICH principles.

In summary, the FDA framework is broader and more flexible in adjusting reporting categories. In contrast, the EMA system is more structured and limited to quality-only changes, but it offers predictable categorization within the EU variation system after PACMP approval. **Table 2** compares the FDA and EMA frameworks for pre-approved and postapproval change protocols, highlighting key differences in scope, submission pathways, evaluation stages, and reporting flexibility.

Protocol for removing blend uniformity testing

The following illustrative example is included to demonstrate a potential regulatory approach for justifying the removal of routine blend uniformity testing within a comparability protocol framework.

In this hypothetical example, the sponsor proposes a compatibility protocol that provides a pre-approved plan to remove blend uniformity testing from routine in-process controls after abbreviated new drug application or new drug application approval, provided the protocol is successfully carried out. This justification is supported

Table 2. Comparison of FDA and EMA approaches to pre-agreed change protocols[6,17]

Category	FDA's CP	EMA's PACMP
Regulatory basis	FDA guidance on comparability protocols for postapproval CMC changes (October 2022)	EMA guideline and Q&A on PACMPs (January 2026)
Scope	CMC changes impacting quality attributes	Quality only changes; no clinical/nonclinical
Submission pathway	Original ANDA/NDA/BLA or PAS	Variation application, usually Type II for protocol approval
Evaluation approach	Strategy reviewed first, data may be reviewed postimplementation	Two-step process: Step 1 (strategy), Step 2 (data)
Reporting flexibility	May justify a lower reporting category (e.g., PAS to CBE)	Enables 'onecategorylower' reporting for the implementation step once PACMP is approved

ANDA, abbreviated new drug application; **BLA,** biologics license application; **CBE,** changes being effected; **CMC,** chemistry, manufacturing, and controls; **CP**, comparability protocol; **EMA,** European Medicines Agency; **FDA,** Food and Drug Administration; **NDA,** new drug application; **PACMP,** postapproval change management protocol; **PAS,** prior approval supplement.

by a well-understood blending process that has shown consistent results across exhibit batches. Finished product content uniformity and assay results have consistently met specifications, with little variation between batches. There have been no blend-related deviations, out-of-specification results, or unusual findings during manufacturing.

Routine in-process controls, such as checking blend time, blender load, and mixing speed, along with finished product testing, still ensure uniformity. Ongoing monitoring of assay and content uniformity during finished product analysis, in accordance with United States Pharmacopeia requirements, will continue to confirm that product quality meets the required standards.

Supporting information and analysis

Three exhibit batches (EB1-EB3) were evaluated for blend uniformity, and all batches met the set acceptance criteria. The %RSD was well within the limit. *Percent relative standard deviation* (%RSD) is a statistical measure of variability that describes how consistently sample results cluster around the mean. A low %RSD indicates uniform mixing and good process control. Values within predefined limits demonstrate acceptable blend homogeneity. In this hypothetical example, the drug product is not classified as a narrow therapeutic index or lowdose product, which reduces the risk associated with removing routine blend uniformity testing and supports reliance on finished product testing.

In this example, the drug product is not classified as a narrow therapeutic index or lowdose product, which reduces the risk associated with removing routine blend uniformity testing and supports reliance on finished product testing.

As per United States Pharmacopeia guidance on uniformity of dosage units, the company must continue to monitor assay and content uniformity during finished product analysis to ensure product quality meets the required standard. Exhibit batches EB1–EB3 met all predefined limits set by the United States Pharmacopeia guidance and internal quality standards (blend uniformity individual 90–110%, mean 95–105%, %RSD ≤ 5%; acceptance value ≤ 15; assay 90–110%), demonstrating consistent blend performance and finished product uniformity.

The sponsor in this example should submit three exhibit batches of blend uniformity data, and, if possible, compare them with assay and content uniformity data to demonstrate a robust manufacturing process.

Comparability protocol for the proposed CMC change

Following approval of the comparability protocol, the sponsor must demonstrate that batches made without routine blend uniformity testing are analytically comparable to those made with the testing. The sponsor will continue releasing products and performing stability testing in accordance with approved quality control methods and sampling plans.

Proposed reduced reporting category

Given the low risk and a strong control strategy, the applicant suggests reporting the removal of blend uniformity testing for commercial batches in CBE 30 after completing this comparability protocol. A final report will be submitted in CBE 30, summarizing the risk assessment, batch data, comparative study, and confirmation that the acceptance criteria were met.

This hypothetical example shows how a welldesigned comparability protocol can support the removal of blend uniformity during routine testing while maintaining a strong control strategy and regulatory compliance.

Recommendations for sponsors

A good comparability protocol should be based on scientific and risk-based principles, clear operations, and full integration with the pharmaceutical quality system. Sponsors should clearly define the rationale, statistical methods, acceptance criteria, and continued process verification triggers to reduce FDA questions and support a lower reporting category. For changes such as removing blend uniformity testing, demonstrating strong process performance, consistent content uniformity and assay results, and solid historical data, the likelihood of the FDA accepting a CBE 30 pathway is high after the protocol is completed.

Conclusion

Comparability protocols offer an effective method to manage certain postapproval CMC changes by specifying the evidence required to demonstrate that product quality

is maintained. When based on strong scientific reasoning, proper analytical comparability, and clear acceptance criteria, these protocols can help achieve lower reporting categories and faster implementation. They are even more useful when incorporated into the pharmaceutical quality system through risk assessment, ongoing process monitoring, and management review, which support consistent quality control. For suitable, lower-risk changes, comparability protocols improve regulatory predictability, encourage continuous improvement, and protect patient safety.

Abbreviations

CBE 30, changes being effected in 30 days; **CMC,** chemistry, manufacturing, and controls; **EMA,** European Medicines Agency; **EU,** European Union; **FDA,** Food and Drug Administration; **ICH,** International Council for Harmonisation; **PACMP,** postapproval change management protocol.

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Regulatory roadmap for NCE commercial IND submissions in academia: A case study

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This article presents a case study outlining the development and submission of a commercial investigational new drug (IND) application for a new chemical entity (NCE) developed at The Ohio State University (OSU). Drawing on their experience as academic drug developers directly involved in the project, the authors describe the regulatory pathway from academic discovery to IND submission. They explore the unique challenges and opportunities for academic drug development and provide valuable insights for other academic institutions embarking on similar paths to an IND submission. Key lessons include the importance of thorough preparation, regulatory strategy, interdisciplinary collaboration, regulatory expertise, and the ability to swiftly respond to feedback.

Keywords – academic drug development, interdisciplinary collaboration, investigational new drug, new chemical entity, regulatory strategy

Introduction and background

The goal of drug development is to bring new therapies to patients, addressing unmet medical needs and thereby improving health outcomes. Biotech and pharmaceutical companies are the primary drivers of this process, consistently innovating and producing a significant proportion of new treatments. However, academic institutions also have a unique opportunity to leverage their research and development strengths to contribute meaningfully to therapeutic innovation. Although academic centers often participate in early-stage research, they typically lack the substantial financial resources, infrastructure, and regulatory expertise needed to support the later stages of preclinical and clinical development for NCEs.

Nevertheless, it is possible to harness the unique capabilities of an academic medical center to transition an internally developed molecule (i.e., *homegrown molecule*) from discovery to a first-in-human (FIH) clinical trial. In this context, a homegrown molecule is an NCE discovered, optimized, and advanced through nonclinical development within academia. This includes the initial identification of a lead compound, subsequent medicinal chemistry optimization, and the generation of supporting pharmacology, pharmacokinetics/pharmacodynamics (PK/PD), toxicology, and chemistry, manufacturing, and controls (CMC) data necessary for an IND submission.

Unlike repurposed agents or externally sourced compounds, homegrown molecules originate entirely from academic research efforts and are developed without prior licensing or external sponsorship. To fully appreciate the insights from the case study in this article and to provide a valuable regulatory roadmap for other academic institutions embarking on similar paths, it is essential to first examine the fundamental disparities in drug development approaches

between academic institutions and pharmaceutical companies, including differences in standards, resources, and timelines.

Industry approach to drug development

Drug discovery and development by pharmaceutical companies is focused on expeditiously advancing new therapeutics by enabling well-funded, staffed, and equipped teams to meet defined project milestones while adhering to strict internal and external standards and processes. This robust support system enables pharmaceutical companies to successfully advance programs through the so-called *valley of death* in nonclinical drug development – a critical phase where many potential drugs fail to translate from early preclinical research in a laboratory to an FIH clinical trial.

Against the backdrop of the resource-intensive, highly structured pharmaceutical model described above, it is important to clarify how pharmaceutical companies and biotechnology companies are referenced throughout this article. While they are sometimes used interchangeably as a contrast to academic drug development, they are not single, uniform entities. Rather, there are meaningful differences between pharmaceutical and biotechnology organizations, particularly with respect to regulatory timelines, internal governance, and the resources available to advance programs to clinical trials.

There are meaningful differences between pharmaceutical and biotechnology organizations, particularly with respect to regulatory timelines, internal governance, and the resources available to advance programs to clinical trials.

Biotechnology companies, which are often smaller and less encumbered by rigid internal processes, tend to operate with greater flexibility and decision-making autonomy than large pharmaceutical organizations. This agility can enable more rapid IND preparation and submission. As a result, pharmaceutical companies sometimes license or acquire assets that have been advanced by biotechnology teams, leveraging their speed and innovation while applying pharmaceutical-scale resources to later-stage development. This distinction also helps frame the broader industry emphasis on rapid advancement and efficiency discussed in the following section.

Generally, the drug development industry, and particularly biotechnology companies, prioritize rapid project advancement to meet market deadlines and maximize return on investment while preserving the duration of intellectual property protection and, therefore, market exclusivity. This focus on efficiency can inadvertently limit opportunities for in-depth scientific exploration. In other words, commercial drug developers may need to adhere to predetermined project timelines, restricting their ability to delve into unexpected findings or pursue tangential research avenues that could lead to significant breakthroughs. While this approach ensures timely progress, it may also hinder the discovery of innovative solutions and novel drug candidates.

For example, it is not uncommon for multiple companies to pursue the same indications for agents with the same or similar mechanisms of action. This strategy is often driven by the perception of risk versus reward, including the existence of regulatory precedents, which can facilitate and expedite the US Food and Drug Administration (FDA) approval process, providing a clearer regulatory and clinical pathway to market for new therapies. An undesired consequence of this rush to market may be that a thorough exploration of alternative label indications can inadvertently be limited.

Consider the case of Bruton's tyrosine kinase (BTK) inhibitors, which were initially pursued by commercial drug developers as a therapeutic strategy for rheumatoid arthritis based on the role of B-cell signaling in autoimmune disease.[1] Subsequent mechanistic studies – many conducted outside the constraints of a single, indication-driven development program – revealed broader relevance of BTK signaling in malignant B-cell proliferation, ultimately leading to the successful development of BTK inhibitors for oncologic indications. This example illustrates how an early emphasis on a single, time-bounded commercial indication can delay recognition of alternative or higher-impact therapeutic applications. A development paradigm that prioritizes the fastest path to market may therefore limit systematic exploration of a drug's full biological and clinical potential, placing disproportionate weight on speed, perceived risk, and near-term market considerations.

Academic approach to drug development

In contrast, drug development in an academic environment offers unique opportunities for scientific exploration, in part because academic research is supported by funding mechanisms that differ fundamentally from those of for-profit pharmaceutical companies. Academic investigators are typically funded through government grants, foundation support, philanthropic donations, and institutional resources, which prioritize scientific merit, innovation, and public health impact rather than commercial profitability. As a result, investigators can pursue novel development opportunities, such as exploring new indications for established mechanisms of action or interrogating unexpected biological findings. This relative freedom from the pressure to deliver rapid, market-driven results fosters a culture of intellectual curiosity and innovation, which is a defining hallmark of academic research.

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Another strength of drug development in academia is the access to a wide range of subject-matter experts, both clinicians and basic researchers. These open collaborations can unlock the aforementioned exploration of alternative indications, the discovery of biomarkers to guide clinical trials, and the assessment of novel combination treatments. While this type of exploration can be time-intensive, it can substantially increase the impact of a new therapeutic. Nevertheless, there should be a fine balance between the length of preclinical exploration and patent life, so that new therapeutic options can be delivered to patients while also allowing for a return on investment for the commercial partners.

However, these advantages come with their own set of challenges. Academics often juggle multiple responsibilities beyond drug development, including mentoring trainees, writing grants, teaching, attending to clinical responsibilities, and publishing. These additional areas of focus can divert attention and resources away from drug development, potentially slowing progress when compared to the more streamlined paradigm employed by the pharmaceutical industry.

Additional challenges in advancing academic drug development programs from the laboratory to market can arise when the FIH Phase 1 study is conducted as an investigator-initiated trial (IIT). In such trials, the principal investigator serves as the sponsor. The reduced cost structure of an IIT typically reflects institutional pricing models at academic medical centers, where hospitals often charge investigators substantially lower-per-patient fees, overhead, and start-up costs than those applied to industry-sponsored trials. These lower costs are made possible by the use of existing clinical infrastructure, subsidized research personnel, and streamlined administrative processes designed to support academic research rather than generate commercial margin.

While this cost structure aligns with the limited budgets typical of academic settings, IITs often lack the financial and operational resources to support comprehensive data management, monitoring, and quality systems required for later-stage drug development. As a result, data generated by IITs may not be suitable for supporting a future new drug application (NDA), potentially requiring a commercial partner to repeat early-phase human studies to meet regulatory expectations.

As a result, this deviation from industry standards poses a risk to potential private-sector licensing partners. In contrast, academic assets developed using industry-aligned approaches – such as commercial INDs formatted in electronic common technical document (eCTD) structure, independent third-party clinical trial monitoring and auditing, and validated electronic data capture systems – are perceived by licensing partners as having higher value because the resulting clinical data can be directly leveraged for regulatory submissions. This higher perceived value reflects reduced regulatory risk, shorter development timelines, and avoidance of duplicative clinical costs, making such assets more attractive for licensing, partnership, or acquisition by private-sector developers.

Additionally, while many university-based medical centers are skilled in clinical operations essential to conducting

human clinical trials, they rarely have the internal expertise required to obtain regulatory clearance for NCE INDs and the study-may-proceed notification from the FDA. Because the development of a new therapeutic from bench to bedside solely by a university is rare, it is not cost-effective for most university medical centers to develop and maintain the internal regulatory expertise needed to advance NCEs. Furthermore, it is difficult for academic researchers to obtain the significant funding required to conduct IND-enabling safety and toxicity studies or to undertake a CMC campaign to transform a laboratory research molecule into a good manufacturing practice (GMP)-certified, formulated drug product ready for administration to patients.

Given these strengths and limitations, universities typically focus on basic research, exploring novel therapeutic concepts, and generating nonclinical data. Their emphasis lies in understanding disease mechanisms and identifying potential drug targets, often working with academic collaborators and small-scale research teams. In contrast, pharmaceutical companies possess larger-scale operations, dedicated R&D and quality departments (whose standards and standard operating procedures differ from academia), and substantial financial resources. These companies are primarily driven by marketing approval and commercialization, transitioning promising research findings into marketable drugs through rigorous clinical trials and regulatory submissions.

Case study: Commercial NCE IND in an academic setting

The case study presented in this article will outline the challenges and lessons that we learned through developing a commercial FDA IND application for a novel oncology NCE small-molecule inhibitor, developed entirely at OSU and advanced into clinical evaluation at OSU's The James Cancer Hospital (The James). In contrast to the typical academic approach of pursuing research INDs, our objective from the outset was to adhere to the regulatory standards required for a commercial NCE IND, with the explicit intent of licensing the therapeutic candidate to a commercial partner capable of advancing it toward market authorization.

The initial IND sponsor for this project was our academic institution rather than a university-affiliated startup company (also referred to as a university-founded or university-licensed company) specifically tasked with advancing drug development and raising external capital. The development and regulatory strategy were deliberately structured to meet commercial expectations, recognizing that academic funding alone would be insufficient to support later-stage development activities such as Phase 2 and Phase 3 clinical trials and the submission of an NDA. In this case study, we hope to demonstrate that academic centers can conduct IIT FIH Phase 1 trials under a commercial IND application rather than a more traditional research IND, thereby facilitating the transfer of clinical development to a commercial partner. We also hope to demonstrate to industry partners that drug development conducted within academic institutions can yield assets (e.g., small-molecule inhibitors, biologics, and cell-based therapies) with genuine potential to improve patient outcomes. The information presented in this article may be particularly relevant to regulatory professionals supporting academic regulatory submissions or to industry professionals involved in the acquisition and licensing of university-originated therapeutics.

The development and regulatory strategy were deliberately structured to meet commercial expectations, recognizing that academic funding alone would be insufficient to support later-stage development activities.

Finally, the small-molecule featured in this case study is a dihydroorotate dehydrogenase (DHODH) inhibitor, which was named HOSU-53 during its development at OSU. HOSU-53 was licensed to Jabez Biosciences after the commercial IND discussed here was cleared. After licensing, HOSU-53 was renamed JBZ-001. Details on the FIH Phase 1 clinical trial at OSU's The James using this compound can be found on the clinicaltrials.gov database (NCT 06801002).[2]

Repurposed agents versus NCEs

In contrast to this case study, many INDs obtained by hospitals are for drugs that already have FDA NDA approval or for agents already being investigated in other clinical trials by a pharmaceutical sponsor (i.e., an IND had previously been obtained). In these scenarios, a clinician (i.e., the investigator-sponsor) is interested in seeking a novel indication or a novel drug combination for a drug that has already obtained IND clearance. This practice is sometimes

referred to as repurposing a drug for a different indication.[3] Because repurposed agents have already undergone FDA review, their regulatory packages differ from those of NCEs, which have never been studied in humans.

Finding new uses for approved drugs allows investigators to use existing documents to support the IND application process, making the regulatory development pathway for the repurposed agent faster, cheaper, and less risky than that for NCEs. For example, a repurposed drug may use a package insert or already existing investigator's brochure (IB), rather than having to draft an original IB as required for NCEs. Likewise, a variety of sections in the repurposed drug's IND application may be borrowed from its original IND package via cross-referencing.[4]

Academic institutions may benefit from adopting eCTD formatting proactively, even though it is not currently mandated for noncommercial research IND submissions.

When moving into the clinic, some repurposed drugs are used in IITs. IITs at The James are not typically FIH trials and therefore do not necessitate the creation of a comprehensive regulatory package based on original data demonstrating the agent's safety and potential efficacy. It is also important to underscore that the research INDs – in contrast to the commercial INDs used in the case study – supporting these IITs are not intended for commercialization purposes. The research IND's primary objective is to advance scientific understanding rather than to facilitate product commercialization.[5,6]

Leveraging use of the eCTD

Another important point regarding IND submissions by academic institutions is that, although eCTD formatting is not currently mandated for non-commercial research IND submissions,[4] academic institutions may benefit from adopting it proactively. Strategic use of the eCTD offers regulatory foresight, anticipating future FDA requirements that may eventually extend to research INDs, and facilitates smoother transitions to commercial partners who expect documentation in this format,[7] including the accompanying IND-enabling toxicity data submitted in the standard for exchange of nonclinical data format.[8]

Moreover, using eCTD submissions from the outset aligns with regulatory expectations for commercial INDs,[9] minimizing reformatting delays. Despite these advantages, many academic centers lack the internal infrastructure and expertise to generate eCTD submissions, often requiring external regulatory support. Nonetheless, investment in eCTD capabilities may prove valuable for academic programs contemplating eventual commercialization.

Having established the regulatory distinctions between repurposed agents and NCEs, as well as research versus commercial INDs, we will now describe our process for developing the NCE at OSU, focusing on the strategic regulatory planning and preparation undertaken during the pre-IND and IND submission phases.

Optimizing the hit compound

The development of this small-molecule inhibitor as an oncolytic agent began in 2017 at OSU with the screening of compounds in acute myeloid leukemia cell lines in the laboratory of John Byrd, MD, then the senior advisor for cancer experimental therapeutics and distinguished university professor at The James. After the initial compound evaluation, Byrd and colleagues engaged the OSU Drug Development Institute (DDI) to spearhead the optimization of the identified *hit compound* (i.e., a molecule identified through early screening that demonstrates measurable biological activity against a target but requires further optimization) to a bona fide preclinical candidate with suitable drug-like characteristics and substantial in vivo anti-cancer efficacy.

These efforts spanned a period when the COVID-19 pandemic significantly disrupted drug development research. Lockdowns and social distancing measures hindered in-person collaborations and lab access, with additional impact on essential research materials and reagents, causing delays in research timelines. Despite these challenges, the team identified a promising candidate.

Pharmacokinetic and pharmacodynamic (PK/PD) studies across multiple species and GMP manufacturing of the drug substance (DS) were conducted following optimization of the small-molecule preclinical candidate. Because of these efforts, by 2022, the OSU DDI had developed an orally bioavailable, small-molecule, competitive enzyme inhibitor

as a new chemical entity for treating solid tumors and hematologic malignancies. Ready to transition from the preclinical to the clinical stages, the DDI sought guidance on regulatory strategy for an IND application.

After consultation with internal OSU teams, the DDI engaged external regulatory and development experts to guide the upcoming NCE FDA regulatory interactions, as it was not cost-effective for OSU to maintain comprehensive internal regulatory support for rare internally developed NCEs. In November 2022, external consultants recommended a regulatory plan that included a Type B pre-IND interaction with the FDA in 2023, followed by an eCTD NCE commercial IND in 2024. Following this advice, preparations for the pre-IND FDA package began in December 2022.

Pre-IND process

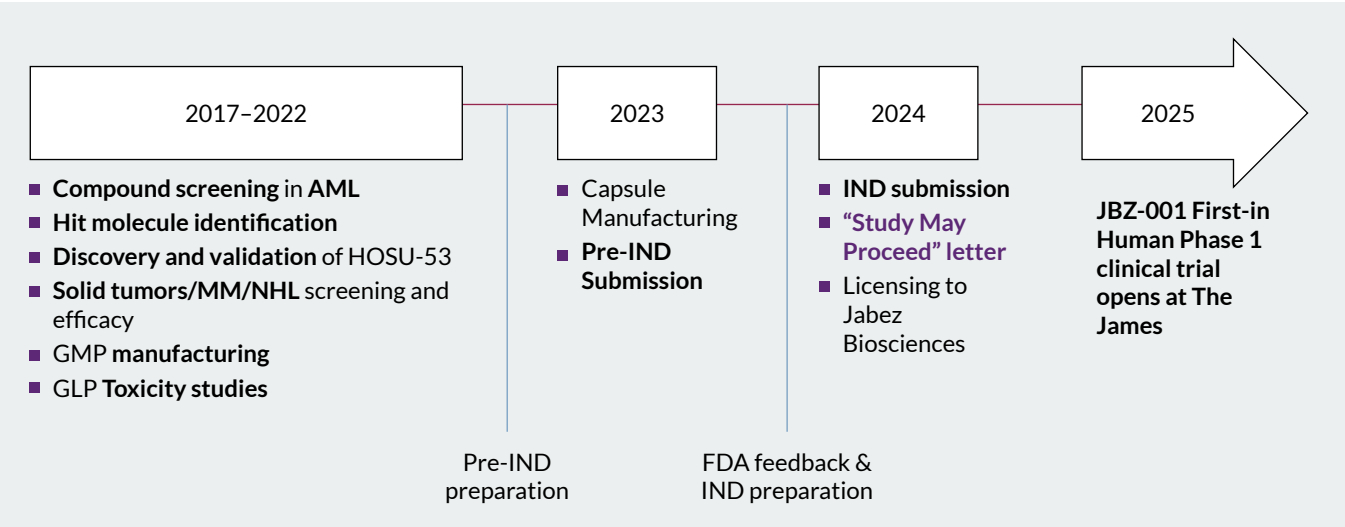
The goal of the 2023 Type B pre-IND[10] interaction with the FDA was to obtain feedback on several critical areas that would be part of the IND submission planned for 2024. Feedback was sought through 10 carefully crafted questions in the briefing document submitted to the agency. Specifically, we sought guidance on three main aspects of development:

- CMC strategy for both the drug substance (i.e., the active pharmaceutical ingredient in its desired salt and crystal form that provides pharmacological activity) and drug product (i.e., the finished dosage form that contains the drug substance, generally in association with inactive ingredients);
- Nonclinical pharmacology, PK/PD, and toxicology package, which were designed to justify the indications, starting dose, and therapeutic window; and
- Clinical protocol design (including indications, inclusion/exclusion criteria, dose-limiting toxicity criteria, and dose levels).

From January to July 2023, our efforts focused solely on assembling all necessary data and completing all formal study reports required for the FDA pre-IND package (see **Figure**). During this period, we also conducted additional preclinical studies to address data gaps identified in discussions with regulatory consultants, which were deemed important for a pre-IND interaction with the FDA.

The preparation of the pre-IND package highlighted the extensive expertise required for an NCE submission. It should be noted that the FDA does not specifically prescribe the exact number or order of sections in a pre-IND application. After general information on the meeting request and the program,[11] the subsequent two sections of our FDA briefing document described the program's

Figure. Timeline and key activities leading to eCTD pre-IND and IND submissions[a]



AML, acute myeloid leukemia; **eCTD,** electronic common technical document; **GLP,** good laboratory practice; **GMP,** good manufacturing practice; **IND,** investigational new drug; **MM,** multiple myeloma; **NCE,** new chemical entity; **NHL,** non-Hodgkin lymphoma.

[a]The clinical candidate (HOSU-53) was licensed to a commercial partner and renamed (JBZ-001) after the FDA study-may-proceed letter was obtained.

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clinical and preclinical strategy, the therapeutic agent, and the rationale for its development in light of the chosen indication's standard of care. Key strategies learned from developing these two sections were:

- Clearly describing and articulating the new chemical entity and characterization not only aids regulators in understanding the mechanism of action (MoA), but also sets the stage for comparison with similar agents (which may be either under development or already approved);
- Providing a robust rationale for the entity's development, which emphasizes its potential to address unmet medical needs and is crucial for gaining the agency's support in granting an IND; and
- Thoroughly analyzing the standard of care for the chosen indication, which reveals treatment gaps that the new entity could fill, reinforcing to the FDA the need for the agent's clinical development.

To shape the most compelling narrative for regulators, the team worked with an external medical writer with experience in NCEs, as well as internal clinical oncologists at The James, to ensure comprehensive research in this area was clearly communicated.

Questions for the FDA. One of the most critical sections in the pre-IND briefing documents is the drafting of the questions for the FDA. The questions must be carefully crafted to elicit thoughtful and constructive feedback from the agency, which is the primary purpose of a pre-IND submission. Each question is accompanied by the sponsor's position, which provides justification and context for the question. There are four important elements to consider when writing sponsor positions:

- Rationale for the questions: explaining why the questions are being asked and their relevance to the drug development process;
- Current status of the issue being addressed: describing what has been done so far to address the question, including any studies or data collected;
- Future plans: outlining what the sponsor plans to do next in the development of the drug to address the question; and
- Scientific and regulatory justification: providing a rationale for why the chosen approach is valid from both a scientific and regulatory perspective.

This comprehensive context facilitates precise, relevant FDA feedback that can aid in the successful submission of an IND application.

Chemistry, manufacturing, and controls section. The CMC and GMP campaign data for both the drug substance and the drug product comprise this section of the pre-IND briefing document. The drafting of this section required assistance from our external GMP manufacturing vendor to ensure the data were correctly formatted for the FDA submission, including drug substance and drug product stability data, which is highly recommended at this stage. Understanding the composition and production of the drug substance and drug product was vital for a comprehensive CMC package at the pre-IND stage. Our GMP drug product campaign (using the previously manufactured GMP drug substance) was timed so that pilot stability data would be available for the pre-IND submission and more extensive stability data would be available for the subsequent IND submission.

The stability data demonstrate to the FDA that the drug substance and drug product will remain within acceptable identity, strength, and purity limits throughout the clinical trial. Typically, IND applications include at least one month of stability data at the time of submission.[12] Cross-functional communication among the internal medicinal chemist, the external CMC consultant, and the contract research organization (CRO) manufacturing the drug substance and drug product provided the team with a more comprehensive understanding of potential CMC challenges and the ability to respond to FDA concerns that could arise during data review.

Clinical trial synopsis sections. The next sections of our pre-IND package comprised a clinical trial protocol synopsis, drafted in close collaboration with the principal investigator and subinvestigators at OSU. While previous pharmaceutical industry programs used the same MoA to treat hematologic malignancies and COVID-19, failing to yield any FDA approvals (this context was tabulated in a subsequent section summarizing previous clinical trials of DHODH inhibitors), our academic scientists and cancer center clinical team, in collaboration with an external consultant, explored promising novel indications based on the extensive nonclinical efficacy data generated at our institution.

Detailed exploration of the trial's eligibility criteria was aimed at enhancing clinical trial accrual (i.e., patient recruit-

ment and enrollment). The trial design, namely the dose finding and optimization, was based on the FDA's Project Optimus guidelines.[13] Project Optimus aims to reform the paradigms for dose optimization and Phase 2 dose selection in oncology drug development.[14] The goal of the project is to move towards a model that continues to prioritize safety but also provides data regarding the potential efficacy of a drug (as early as FIH Phase 1). Inherent in the rationale underpinning this FDA program is a shift from the traditional toxicity-centric goal of finding a maximum tolerated dose (MTD) to the more pragmatic goal of identifying a dose or dose range that provides the best balance of benefit and risk (i.e., the optimal biological dose) through a broader exploration of multiple dose levels in larger patient cohorts.[15,16]

The Oncology Center of Excellence first announced Project Optimus in 2021, during our pre-IND preparation, which required changes to the original clinical trial design, highlighting the importance of a flexible clinical strategy to meet regulatory requirements. The protocol synopsis's design had to be revised to use our broader scope of indications and to highlight not only safety and tolerability but also the efficacy and PK/PD findings that target the optimal biological dose rather than the MTD. One consequence of pursuing dose optimization and potential efficacy signals during an FIH trial is that more patients are required in Phase 1 studies than in traditional FIH escalations to the MTD. Because of this, accrual velocity (i.e., how quickly patients can be recruited) becomes an important factor in clinical trial design and operations, potentially influencing the choice of index indication for malignancies that accrue patients more quickly, especially in single-center trials.

Summary of nonclinical pharmacology and toxicology. The last section of our pre-IND package summarized in vitro and in vivo studies related to pharmacology, PK/PD, and toxicology, including some good laboratory practice (GLP) toxicology data needed for the IND submission. Although preclinical study reports need not accompany a pre-IND submission, the data should be available if the agency requests its review. While working on this section, we learned that it is important to strategically select and present the most relevant information, aiming to provide the FDA with sufficient data to assess the safety and efficacy of the investigational drug without overwhelming regulators with unnecessary details. By focusing on essential pre-clinical data, sponsors can streamline the review process, comply with regulatory principles, and increase the likelihood of a timely IND approval. This approach not only saves time and resources but also demonstrates a clear understanding of the regulatory requirements and a commitment to efficient drug development.

FDA pre-IND feedback

The format of the pre-IND FDA feedback we obtained from this interaction is termed *written response only* (WRO). For a WRO, the FDA mails the sponsors a list of answers to their questions rather than having a face-to-face or virtual meeting. Anecdotally, WRO feedback has been increasing for early-stage programs but varies by FDA office. The feedback had a significant impact on our subsequent IND submission, providing crucial insights and guidance that helped us refine our clinical protocol design and ensure alignment with FDA expectations. The feedback also validated our CMC strategy, confirming that no issues were present in the drug substance and drug product CMC approach.

The pre-IND FDA feedback had a significant impact on the subsequent IND submission, providing crucial insights and guidance that helped refine the clinical protocol design and ensure alignment with FDA expectations.

This pre-IND interaction with the FDA enabled us to streamline the preparation of our IND package and emphasized the importance of a comprehensive, well-organized submission, ultimately making our IND application more robust and likely to succeed. By incorporating the FDA's recommendations, we were able to de-risk our program and ensure that our clinical trial design met regulatory standards, paving the way for a smoother transition into the clinical phase.

IND submission process

Following the pre-IND feedback, we embarked on the meticulous task of writing the required modules for an eCTD commercial IND package for the NCE. The FDA IND final package, after incorporating all necessary sections and study reports, totaled about 6,700 pages. This extensive documentation underscores the diverse expertise required to compile a successful small-molecule, NCE IND for

submission to the FDA. This section delves into the key lessons learned from the development and submission of each of the five core modules of our NCE IND.[17] By sharing these insights, we aim to provide information that could increase the chances of a successful IND application for researchers and academic institutions embarking on similar regulatory development pathways.

Module 1. This module includes, among other administrative documents, the IB, which is designed to assist clinicians in running the trial by providing a summary of preclinical data and safety precautions. This module also contained our official pre-IND WRO feedback.

Our aim for the IB was to provide investigators with a clear, concise, and easy-to-understand document that would help them reference potential drug-drug interactions, concomitant medications, and food effects on drug administration. The drafting of the IB varies depending on the type of IND. Repurposed drug INDs sometimes use the package insert for the FDA-approved drug in place of the IB. For our brochure, we enlisted the expertise of external consultants with extensive industry experience to ensure the document's quality. In our experience, a well-written pre-IND briefing document provides the organization, structure, and foundation of the IB.

Module 2. This module contains an introductory section providing an executive summary of the IND; a clinical overview with information on the product development rationale; an overview of the clinical trial, potential benefits, and risks; and risk mitigation strategies. This section also provides tabulated summaries of nonclinical pharmacology, PK/PD, and toxicology studies, the aspects of which are detailed in the accompanying **Table**.

Module 3. This module details the GMP CMC campaign and includes stability data for both the drug substance and the drug product. Academic institutions pursuing IND submissions frequently rely on CROs or contract development and manufacturing organizations (CDMOs) for GMP production of the drug substance and drug product. While these external partners generate the technical documentation required for the CMC module, academic sponsors are responsible for verifying that all aspects of the manufacturing process – including key steps, critical quality attributes, specifications, analytical methods, and control strategies – are accurately and comprehensively described.

For this case study, the critical oversight was led by one of the authors, Chad Bennett, who has pharmaceutical industry experience in process chemistry and GMP-compliant active pharmaceutical ingredient manufacturing for FIH clinical trials. Bennett played a pivotal role in reviewing, authorizing, and signing numerous protocols and reports to ensure the integrity and regulatory compliance of the

Table. Overview of tabulated summaries in Module 2

Aspect	Details
Purpose	Provide an at-a-glance view of essential nonclinical studies that will allow regulators to determine the potential risks and benefits to trial participants
Content	Good practice for drafting these tables is to highlight key findings from each study, including data demonstrating: – In vitro and in vivo potency and efficacy – Pharmacokinetic parameters – Pharmacodynamic effects – Available absorption, distribution, metabolism, and excretion data – Toxicology observations
Interpretation	The tables should also provide a brief interpretation of the nonclinical data, including any potential implications for the clinical trial design and safety monitoring
Practical tips	Accurate and complete tabulated summaries take time to create. Proactively communicate timelines with academic collaborators and the contract research organizations that will contribute to these tables and their supporting study reports. Consider drafting these tables in advance to save time during the submission process.

CMC documentation. The drug substance and drug product used in our Phase 1 clinical trial were manufactured under phase-appropriate current GMP conditions at a qualified CDMO, and the manufacturing campaign was completed prior to IND submission. The ongoing FIH trial, currently in the dose-escalation phase, is using a phase-appropriate GMP-compliant drug product managed by our institution's investigational pharmacy. Collectively, these efforts – namely, the extensive cross-functional planning required to coordinate external CDMO GMP manufacturing with internal expert oversight by Chad Bennett – underscore the importance of early planning, interdisciplinary collaboration, and experienced leadership in assembling a robust and compliant CMC package for timely IND submission.

Module 4. This module contains the nonclinical study reports for all preclinical studies (GLP and non-GLP) used to support the safety and rationale of the proposed clinical trial cited in the IND application, along with tabulated summaries. Ensuring that all study reports are available, comprehensive, and complete can be a laborious, time-consuming process if nonclinical studies were conducted at various labs and/or by CROs. To save valuable time, each study should be documented in a finalized, signed report before the beginning of the pre-IND and/or IND package preparation. In addition, the preclinical study reports should include (but are not limited to):

- A prospectively written protocol and all protocol amendments (or a detailed methodology);
- A detailed description of the study design – a description of the in vitro or in vivo test system used, animal species/animal models, control and test articles administered, dose levels, detailed procedures for test article administration (including delivery device description), and collection of all study protocol parameters;
- Results for all parameters evaluated for each animal for in vivo studies; and
- Analysis and interpretation of the study data.

Collectively, this comprehensive nonclinical data package provides the scientific and safety foundation necessary to justify initiation of the Phase 1 clinical trial described in Module 5.

Module 5. This module comprises the full Phase 1 clinical trial protocol and the informed consent form. Our clinical trial protocol was written in collaboration with a variety of internal clinical oncology experts, as well as an external clinician with extensive pharmaceutical industry experience in FIH NCEs and Project Optimus. This clinical collaboration was crucial for ensuring the scientific rigor, ethical conduct, and practical feasibility of the study. Our OSU clinician team brought invaluable expertise in patient care, disease understanding, and real-world challenges. Their input helped refine the study design, identify relevant endpoints, and develop practical recruitment and retention strategies. Incorporating the suggestions of the clinical team at The James Phase 1 Clinical Trials Unit (i.e., clinical research manager, pharmacist, nurses, etc.) also fostered a shared understanding of the trial's goals and objectives, leading to what we hope will be a more robust and efficient enrollment rate.

FDA IND submission feedback

Obtaining an IND while avoiding a clinical hold necessitates thorough preparation, interdisciplinary collaboration, and the ability to respond swiftly to regulatory feedback. We submitted our IND in June 2024, and during the 30-day review period, we received 16 comments from the FDA, requiring prompt responses. These comments included minor technical requests (such as the electronic resubmission of certain data via the eCTD electronic portal), 12 potential clinical hold comments, and a few additional non-hold clinical and nonclinical comments. Throughout July 2024, we diligently addressed all the queries, ensuring that our responses were thorough and timely.

The guiding principle in stratifying studies is to determine whether they enable FDA reviewers to understand the potential benefits and risks associated with an NCE; hence, not all studies are critical from this perspective.

Since the FDA required timely responses to their questions,[18] which were sent on a rolling basis, it was important to remain alert to guarantee the agency's comments were quickly addressed in an organized and clear manner with the insight of our experts. Addressing each comment with supporting data while proactively seeking clarification on ambiguous comments increased the

likelihood of timely resolution, ultimately accelerating the IND clearance timeline. It should be noted that we received our study-may-proceed letter before the 30-day FDA review period concluded, marking a significant milestone in our journey to bring this NCE to a clinical trial.

Discussion of lessons learned

During the seven-year discovery, development, and regulatory path to an NCE commercial eCTD IND at our academic medical center, we learned several valuable regulatory lessons. The IND submission process took longer than anticipated due to the extensive learning curve required to navigate the NCE eCTD commercial IND, a regulatory pathway not commonly used in academia. Critically, the regulatory knowledge, infrastructure, and institutional experience gained through this process are expected to reduce the time and effort required for future FDA interactions led by our team, including pre-IND meetings, IND submissions, and subsequent regulatory communications for other internally developed programs, regardless of modality (e.g., small molecules, biologics, cell-based therapies, etc.).

Importantly, we now recognize that one of the first steps in the IND journey is to identify which nonclinical studies are essential to include in these types of interactions. The guiding principle in stratifying studies is to determine whether they enable FDA reviewers to understand the potential benefits and risks associated with an NCE; hence, not all studies are critical from this perspective. We highly recommend consulting seasoned regulatory and development experts to support this decision-making process.

Beyond procedural guidance, the pre-IND interaction served as a strategic alignment exercise, ensuring that our nonclinical, CMC, and clinical development plans were coherent, phase-appropriate, and responsive to FDA expectations. This alignment was particularly important in an academic setting, where resources are limited, and missteps at later stages can be costly and difficult to correct. Early FDA feedback helped organize our data, set a regulatory timeline, and conduct gap analyses of reports. Collectively, these benefits allowed us to advance the program with greater confidence, efficiency, and regulatory predictability as we transitioned toward IND submission.

The successful advancement of an NCE from discovery to IND requires a significant investment in both financial and human resources. While internal budgets at academic centers provide foundational support, philanthropic donations play a pivotal role in accelerating this regulatory process. By supplementing internal funding, philanthropic contributions can bridge funding gaps for the expensive GLP and GMP activities, expedite preclinical research, and enhance the quality and efficiency of academic IND applications. This additional support can significantly improve the chances of securing FDA approval and bringing life-saving treatments to patients in need.

Other time-consuming and resource-intensive elements include the study reports, GLP toxicology studies, and the GMP CMC package. Study reports must be available, comprehensive, complete, and signed for FDA submission. This endeavor was a time-consuming but essential task. Additionally, NCE INDs require both GLP toxicology studies and a GMP CMC package. Although these IND components are costly and require substantial coordination, they are crucial for de-risking the program, enabling and justifying the administration of the NCE to humans, and making an NCE attractive to investors.

A successful NCE IND submission at an academic medical center requires a large, interdisciplinary team of internal and external collaborators to gather the expertise needed. In our case, the list of experts included: disease area biologists, clinicians, medicinal chemists, pharmacologists, in vivo and in vitro assay specialists, CMC and formulation experts, medical writers, toxicologists, biostatisticians, and regulatory and clinical operations experts.

Although a successful NCE IND submission at an academic medical center requires collaboration with a large, interdisciplinary network of internal and external experts, the day-to-day scientific and regulatory decision-making in our program was driven by a small, core academic drug development team. This compact team structure – embedded within an academic environment – enabled rapid evaluation of data and efficient coordination across disciplines while leveraging specialized expertise from a broader group of collaborators as needed. The absence of multiple layers of corporate governance and formalized approval hierarchies allowed decisions to be made directly by the individuals closest to the data.

As a result, our team was able to respond quickly to evolving scientific, clinical, and regulatory insights, adapt strategies in real time, and maintain momentum toward IND submission.

This combination of broad interdisciplinary collaboration and a streamlined, empowered core team proved critical for advancing the program efficiently in a fast-paced regulatory environment, where timely decisions can meaningfully influence development timelines and program success.

The absence of multiple layers of corporate governance and formalized approval hierarchies allowed decisions to be made directly by the individuals closest to the data.

Conclusion

This case study offers a practical roadmap for academic institutions navigating the complex regulatory terrain of commercial IND submissions. While for industry professionals, this process may be more routine, our experience underscores the distinct challenges faced by academic centers, which often lack robust infrastructure and seasoned regulatory teams. By documenting the first eCTD-submitted, small-molecule NCE commercial IND by The Ohio State University Comprehensive Cancer Center, we aim to illuminate the unique regulatory and operational hurdles in academia and to demonstrate that, with strategic planning and interdisciplinary collaboration, they can be overcome. Building on these insights, we aim not only to inform industry stakeholders seeking to license academic innovations and regulatory consultants supporting university-led development, but also to encourage other academic institutions to pursue regulatory pathways for their scientific discoveries – ultimately contributing to the timely delivery of novel therapies to patients in need.

Abbreviations

CMC, chemistry, manufacturing, and controls; **CRO,** contract research organization; **DDI,** Drug Development Institute; **eCTD,** electronic common technical document; **US,** Food and Drug Administration [FDA]; **FIH,** first-in-human; **GLP,** good laboratory practice; **GMP,** good manufacturing practice**; IND,** investigational new drug; **IIT,** investigator-initiated trial; **MOA,** mechanism of action; **MTD,** maximum tolerated dose; **NCE,** new chemical entity; **NDA,** new drug application; **OSU,** The Ohio State University; **OSUCCC,** The Ohio State University Comprehensive Cancer Center; **PK/PD,** pharmacokinetics/pharmacodynamics; **WRO,** written response only.

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Strategic regulatory intelligence for cell and gene therapies

Padma Priya Togarrati, PhD, ASQ-CSSGB, RAC

This article is the first of two on strategic regulatory intelligence for cell and gene therapies (CGTs). It will examine how gaps between product approvals and patient access remain despite significant evolutions in the CGT landscape. Longer approval timelines and increasing product withdrawals underscore the need for robust regulatory intelligence frameworks that integrate geopolitical considerations, real-world evidence (RWE), artificial intelligence/machine learning (AI/ML) tools, and multistakeholder collaboration to build an effective regulatory strategy. The article examines the role of regulatory intelligence in advancing effective regulatory strategy across the full CGT and advanced therapy medicinal product (ATMP) lifecycles, including innovative clinical trial designs, chemistry, manufacturing, and controls (CMC) optimizations, and postauthorization surveillance across major global jurisdictions. The second article (p. 65) explores global CGT pricing and reimbursement models.

Keywords – artificial intelligence/machine learning, CGT, CMC, regulatory intelligence, regulatory strategy

Introduction

Regulatory intelligence operations have traditionally focused on collecting, analyzing, and summarizing information to inform regulatory strategy for product development. Regulatory intelligence supports regulatory strategy by providing actionable insights to cross-functional clinical, quality, safety, and commercial stakeholders, enabling evidence-based decisions throughout the product lifecycle while ensuring alignment with the organizational business goals.

However, advances in AI/ML and digital health technologies, alongside rapidly shifting and evolving geopolitics, trade dynamics, innovative clinical trial designs, real-world evidence and real-world data (RWD), adaptive licensing pathways, and payer-reimbursement landscapes are reshaping regulatory intelligence. Current regulatory intelligence activities encompass horizon scanning and analysis of global regulatory trends, evolving policies, and monitoring signals and alerts for a proactive regulatory strategy development to ensure timely execution of product development, launch pathways, pharmacovigilance, and postmarket surveillance.

The CGT field has also undergone scientific innovation and regulatory evolution over the past decade. As of January 2026, the US Food and Drug Administration (FDA) has approved 48 biologics, while the European Medicines Agency (EMA) has authorized 31 ATMPs.[1,2] However, the pace of global technological innovations and product approvals remains discordant with patient access to these therapies. In recent years, China's National Medical Products Administration has emerged as a dominant

force in the CGT space, reflecting its focus on increased investment in research and development infrastructure, supporting domestically developed innovations, efficient clinical trial designs, and progressively reshaping regulatory policies to align with international guidelines to have a global competitive edge.[3]

These regional divergences in approval rates and patient access reflect fundamental differences in evidence expectations, reimbursement architectures, and global regulatory system operations. For CGT and ATMP developers, navigating this landscape requires robust regulatory intelligence frameworks not only for approval requirements but also for patient access paradigms that ultimately determine a product's commercial viability.

In the US, the FDA groups CGTs under biologics, whereas the EU's EMA designates them as ATMPs.[4,5] Globally, CGTs/ATMPs account for the majority of accelerated and conditional approvals intended to address unmet medical needs. CGTs/ATMPs targeting rare diseases qualify for orphan drug designation, which provides benefits such as application fee waivers or reductions, enhanced regulatory interactions, rolling reviews, accelerated approval pathways, grant funding, tax credits, and 7 to 10 years of market exclusivity.[6,7] Of the 48 biologics approved by the FDA, 42 (87.5%) target rare diseases and 6 (12.5%) address non-rare conditions. Similarly, of the 31 ATMPs approved by the EMA, 24 (77.4%) received orphan drug status. The FDA also offers breakthrough therapy designations and regenerative medicine advanced therapy designations, while the EMA and Japan offer priority medicines and Sakigake designations, respectively. These designations facilitate more frequent regulatory interactions, priority and rolling review, and may allow accelerated approvals based on surrogate endpoints demonstrating early clinical efficacy.[8,9]

Despite these incentives, the median total clinical development time for novel orphan-designated drugs is approximately 7.2 years. Moreover, the median regulatory review time is shorter in the US (244 days) than in the EU (353 days).[10] The FDA and EMA require larger randomized controlled trials (RCTs) with confirmatory evidence of superior clinical efficacy over standard of care (SoC) treatments for non-rare indications, while innovative clinical trials using surrogate efficacy endpoints may support accelerated or conditional approvals for serious rare conditions with unmet needs.[11] However, even for conditional approvals, the EMA requires mature, robust, and comprehensive data demonstrating ATMP product quality, safety, and efficacy due to their inherently complex CMC and clinical development. This article examines the current regulatory intelligence paradigm to support effective regulatory strategy across the CGT/ATMP lifecycle.

Strategic framework for CGT clinical development

Increasing healthcare costs, limited budgets, rapid innovation in technologies, and severe unmet medical needs have led to growing regulatory expectations for smarter clinical trial designs. Regulatory intelligence aids in the development of appropriate clinical development, sequencing, and reliance pathways by tracking guidance, pilot programs, and regulatory precedents. This proactive approach can reduce the risk of late-stage regulatory challenges and enhance the efficiency of evidence generation.

Building upon foundational programs, including the Support for Clinical Trials Advancing Rare Disease Therapeutics and Rare Disease Endpoint Advancement Pilot Program, the FDA released three draft guidelines in late 2025 focusing on CGT development for rare diseases.[12-15] These guidelines address innovative trial designs (e.g., single-arm, disease modeling, adaptive approaches, plausible mechanism frameworks), expedited pathways, and postapproval data collection frameworks to accelerate approvals in small patient populations.

In parallel, the pharmaceutical industry has seen a profound shift from being driven by safety and efficacy endpoints and physician-centric drug development, to being driven by patient-centric development models. The EMA, along with the regulatory authorities in Japan, Australia, and Canada, has also increasingly embraced patient participation initiatives in scientific advisory meetings, efficacy endpoint design and evaluation, and benefit-risk assessments, ultimately focusing on developing products with increased patient access.

Since the FDA launched its patient-focused drug development (PFDD) initiative, there has been an unprecedented emphasis on including patient insights in all stages of drug development. This has led to the publication of a series of four PFDD guidance documents from 2020 to 2024.[16-19] The guidelines outline frameworks

for trial design, including rationale and context-specific application of patient-centered approaches. Additionally, the FDA recently announced a policy update outlining an enhanced regulatory flexibility to support pragmatic CGT development addressing unmet needs in rare and ultra-rare diseases, reflecting a shift toward more adaptive, evidence-based regulatory pathways.[20]

Rare and ultra-rare disease clinical development

The successful launch of CGT/ATMP for rare and ultra-rare diseases requires innovative and efficient clinical trial strategies, given the extremely limited global patient population, ethical constraints on control-arm assignment, incomplete understanding of disease pathophysiology, disease heterogeneity, and manufacturing constraints.

Single-arm trials, N-of-1 designs, disease progression models (DPMs), and the plausible mechanism pathway offer distinct and innovative approaches to address structural trial barriers by generating valid evidence of treatment effect through benchmarking against external controls, within-patient crossover comparisons, and incorporating natural history and RWD. Each approach is described in detail in the sections below.

Single-arm trial framework

For chronic rare disorders, patients enrolled in natural history registries with baseline data on disease-specific parameters can serve as their own controls by comparing pre- and posttreatment outcomes using identical measures. This approach can reduce reliance on concurrent control groups and is particularly valuable in generating early phase I/II clinical safety and efficacy evidence for rare and ultra-rare diseases where RCTs are practically and ethically impossible. This approach also opens avenues for cost-effective accelerated/conditional approvals for breakthrough personalized precision therapies and paves the path for the development of platform technologies.[21,22] Additionally, natural history registries and RWD/RWE can identify external controls with matched, context-specific baseline and follow-up parameters for use as comparators in nonrandomized rare disease trials.

N-of-1 trial framework

N-of-1 trials are personalized, single-patient study designs with randomized treatment order, alternating between active treatment and comparator across multiple treatment periods. In the context of CGT and ATMP development for rare and ultra-rare diseases, where conducting clinical trials using conventionally powered cohorts is not feasible, this design offers a scientifically sound alternative to chronic diseases with treatment response heterogeneity and sufficiently well-characterized underlying biological mechanisms. Regulatory agencies, including the FDA and EMA, have increasingly acknowledged such designs as acceptable evidentiary frameworks for rare and ultra-rare conditions.

DPM framework

As a component of the FDA's broader model-informed drug development framework, DPMs use robust mathematical simulations to integrate biomarker, SoC treatments, patient heterogeneity, dropout rates, disease baseline characteristics, disease progression data from patient registries, electronic health records, and RWE to map disease trajectories. This supports clinical trial design optimization, including endpoint selection, patient subgroup stratification, statistical power optimization, and treatment outcome prediction.[23] DPMs based on natural history data help predict patient behavior (e.g., dropout risk), optimize trial duration, justify dosage selections, support patient stratification, and enable extrapolation to pediatric populations when direct trials are infeasible.

Integrating N-of-1 studies with DPMs enhances drug development by providing natural history, treatment response grade, and placebo or SoC response data to evaluate treatment effects in small patient pools without a control arm. DPMs also have the potential to enhance N-of-1 studies by using delayed-start or wait-listed crossover designs for chronic rare diseases where disease progression remains relatively stable, and the goal is to assess disease modification rather than an immediate, permanent cure. This allows patients to act as their own controls, maximizing statistical power and trial efficiency despite limited patient populations, with promising findings that can be combined via DPM-based meta-analysis to extrapolate population-level efficacy.

Plausible mechanism pathway

In 2026, the FDA's Center for Biologics Evaluation and Research released draft guidance describing a plausible mechanism pathway as an accelerated approval route for CGTs for rare and ultra-rare diseases. Under this pathway, accelerated approval may be granted if a CGT functionally corrects an established molecular or cellular anomaly underlying a rare disease, without requiring demonstration

of clinical benefit on a fully validated surrogate endpoint. The evidentiary standard rests on three elements: a well-characterized disease pathophysiology with a defined mechanistic target; functional correction of a specific target demonstrated through biomarker or cellular assay data; and a scientifically plausible link between mechanistic correction and expected clinical benefit.

This pathway is most applicable where disease is severe and rapidly progressive, with very small patient populations, where conventional endpoint-driven trials are not feasible, and mechanistic correction constitutes the most direct available evidence of therapeutic effect.[15] Sponsors pursuing this pathway are expected to generate confirmatory evidence of clinical benefit and safety through postapproval studies, structured long-term follow-ups (LTFU) programs, and patient registries within agreed timelines for full marketing approvals. **Table 1** (p. 55) shows some of the recent approvals using these innovative trial approaches.

Adaptive, Bayesian, and master protocol trials

A key challenge in rare disease trials is to derive robust and valid inferences from small, heterogeneous datasets, which conventional statistical approaches designed for large randomized studies do not address effectively. Approaches such as Bayesian methods, adaptive trial designs, and master protocols offer innovative approaches to trial design that are more efficient, flexible, and capable of producing evidence that meets regulatory standards despite limited patient populations.

Adaptive trials. Integration of model-informed drug development, DPM, and RWD strategies enables adaptive clinical trials in which predefined design elements may be prospectively modified based on pre-specified criteria using interim analysis of the current trial. This approach facilitates patient subtype enrichment, dosing optimization based on responses, sample size re-estimation, reduction of redundancy, and value-based decision making for trial continuation.[24,25]

Bayesian trials. Bayesian approaches incorporate adaptive design features but follow flexible, intuitive, continuously adjustable trial designs based on real-time data and probability data using prior knowledge from external controls, natural history registries, and RWE.[26] Adaptive and Bayesian designs allow modifications (e.g., sample size, randomization) during the study based on interim data, improving efficiency and enabling earlier go/no-go decision making.

Master protocol designs. Master protocol designs (including basket, umbrella, and platform trials) aim to evaluate multiple diseases, disease subtypes, or treatments under a single overarching clinical protocol.[27] Master protocols leverage prior knowledge from natural history studies, RWE, external controls, and patient registries while incorporating Bayesian and adaptive features to enhance operational efficiency, reduce costs, accelerate patient recruitment, enable more robust comparisons through shared control arms, and improve personalized treatment options.

Basket trials test one intervention across multiple diseases or subtypes sharing a common mutation or biomarker. *Umbrella trials* evaluate multiple therapies for one disease or subtype. *Platform trials* are long-term, adaptive trials that typically adopt Bayesian frameworks and common control arms, thereby reducing patient sample sizes and costs. These innovative trial design modalities are being currently used for dose optimization and interim efficacy analysis in ongoing clinical trials.[28-30]

Decentralized trials as part of the PFDD framework provide another paradigm to increase patient enrollment and retention while generating clinical data representative of geographically, ethnically, and socioeconomically diverse populations. These approaches leverage telemedicine follow-up visits, home phlebotomy and testing, local testing centers, AI-enabled digital health monitoring devices, online pharmacies, and mobile research units. Patient-reported preferences and outcomes, RWE/RWD, and natural history records provide invaluable insights for developing effective clinical protocols, including patient-preferred efficacy endpoints, which may improve the likelihood of regulatory approval in rare disease trials.[31,32]

Patient-reported outcomes collect patient health information to assess symptoms, quality of life, and overall well-being, helping gauge treatment effectiveness from the patient's perspective. Patient preference studies reveal patient values and quantify willingness to make trade-offs between benefits and risks, outcomes and convenience, and efficacy and side effects, and therefore play an important role in the effective clinical trial designs. Both PFDD and guidance on innovative trial designs advocate for broadening patient inclusion criteria by reducing overly restrictive eligibility requirements that hinder enrollment in limited patient populations. These policies also prioritize pediatric-focused clinical trial strategies in early development, reflecting the

Table 1. List of approved CGTs/ATMPs with innovative clinical trial designs

Product	Disease	Technology platform	Trial design features	Regulatory pathways
K-abe	CPS1D	In vivo base editing	– Natural history data – N-of-1 design for control group – Plausible mechanism pathway	– FDA emergency IND – Compassionate use
Waskyra	Severe WAS	Autologous HSC-based gene therapy	– Single-arm trial – Natural history data	– FDA accelerated approval – BT – Orphan drug – EMA conditional approval
BE-CAR7[a]	T-cell ALL	Base-edited allogeneic CAR-T	– Natural history data	– UK specials pathway
Zolgensma	Infantile-onset SMA Type 1	AAV9-based gene therapy	– Natural history data	– FDA accelerated approval – EMA conditional approval
Luxturna	LCA, RP	AAV2-based gene therapy	– Natural history data and natural history studies – Phase 3 delayed crossover RCT	– FDA accelerated approval – BT – Orphan drug – Rare pediatric disease designations – EMA conditional approval
Lenmeldy	Early onset MLD	Autologous HSC-based gene therapy	– Natural history data – Single-arm trial historical controls	– FDA accelerated approval – EMA conditional approval
Elevidys	DMD	AAV-based gene therapy	– External control group trials – Natural history data – DPM	– FDA accelerated approval
Kymriah	B-cell ALL (pediatric/young adult), DLBCL, FL	Autologous anti-CD19 CAR-T	– Natural history data	– FDA accelerated approval – EMA conditional approval
Yescarta	R/R LBCL, DLBCL, PMBCL, HGBL	Autologous anti-CD19 CAR-T	– Single-arm trials – Natural history data	– FDA accelerated approval – EMA conditional approval
Amtagvi	Unresectable or metastatic melanoma	Autologous TIL therapy	– Natural history data – Response rates – Single-arm trials	– FDA accelerated approval
Hemgenix	Hemophilia B	AAV5-based gene therapy	– Natural history data – single-arm trials	– FDA accelerated approval – EMA conditional approval

AAV, adeno-associated virus; **ALL,** acute lymphoblastic leukemia; **ATMP,** advanced therapy medicinal product; **BT,** breakthrough designation; **CAR-T,** chimeric antigen receptor T-cell therapy; **CGT,** cell and gene therapy; **CPS1D,** carbamoyl phosphate synthetase 1 deficiency; **DLBCL,** diffuse large B-cell lymphoma; **DMD,** Duchenne muscular dystrophy; **EMA,** European Medicines Agency; **FDA,** Food and Drug Administration; **FL,** follicular lymphoma; **HGBL,** high-grade B-cell lymphoma; HSC, hematopoietic stem cell; **IND,** investigational new drug application; **LCA,** Leber congenital amaurosis; **MLD,** metachromatic leukodystrophy; **PMBCL,** primary mediastinal B-cell lymphoma; **RCT,** randomized controlled trial; **RP,** retinitis pigmentosa; **R/R LBCL,** relapsed/refractory large B-cell lymphoma; **SMA,** spinal muscular atrophy; **TIL,** tumor-infiltrating lymphocyte; **WAS,** Wiskott-Aldrich syndrome.

[a]First-in-human but not true N-of-1 (therapy designed for broader CD7+ T-ALL population).

FDA's strategic shift toward personalized, flexible, evidence-supported approaches for rare disease products.

Regulatory intelligence related to innovative clinical trial designs – including adaptive, Bayesian, master protocol, single-arm, N-of-1 studies, decentralized designs, and plausible mechanism-based frameworks – can help sponsors select evidentiary strategies aligned with regulatory requirements, payer expectations, and reimbursement frameworks. As global regulatory authorities expand the use of model-informed drug development and consider mechanism-based and RWE, particularly in rare and ultra-rare diseases, up-to-date intelligence on precedents and regulatory guidance can support the design of fit-for-purpose pivotal programs.

For instance, single-arm trials that may be considered for pathways such as accelerated approval, integrated regulatory intelligence across clinical development, marketing authorization, and health technology assessment can help sponsors anticipate and address evidentiary gaps by planning for external or synthetic control arms, natural history data, or incorporation of platform trial elements, in line with evolving regulatory and payer expectations.

Non-rare disease development pathways

Given the complexity of CGT, traditional rigorous RCTs remain the recommended gold standard for non-rare disease indications. Dose selection and escalation studies are typically evaluated in Phase I trials (approximately 10-20 patients), followed by Phase II exploratory studies for efficacy assessment in expanded cohorts (approximately 50-100 patients).

For expedited programs such as breakthrough therapy designation and priority medicines designation, primary endpoints such as overall response rate from Phase II studies have served as evidence for conditional market approval.[33] However, Phase III confirmatory trials (typically 300-500 patients) are required to establish therapeutic benefit-risk profiles. Regulatory authorities increasingly require progression-free survival, event-free survival, and overall survival rate as evidence for therapeutic benefit in randomized, placebo/SoC-controlled trials. Recent trends also indicate the overall survival rate as an important evidentiary factor even for conditional or accelerated approval pathways.

CMC strategic framework

The majority of approved CGTs for oncology are chimeric antigen receptor T-cell (CAR-T) therapies, whereas gene therapies predominate in rare disease indications. 74% of the rejections of biologics license applications, clinical trial dossiers, and marketing authorization are due to manufacturing and CMC compliance issues. These issues are also a major reason for postlaunch viability failures.[34] CGT/ATMP CMC challenges include starting material heterogeneity, process and batch-to-batch variability, limited reference material availability, short product shelf-life, lack of validated potency assays reflecting clinical efficacy, insufficient stability data, manufacturing site inspection findings, technology transfer complexities, shortages of skilled personnel, and implementation of effective control strategies.

Regulatory authorities expect stringent adherence to current good manufacturing practice (cGMP) guidelines under 21 CFR Part 211, which requires robust process and product validation for clinical trials and marketing application approvals.[35] The FDA recently introduced flexibility for CGTs through a case-by-case assessment of CMC requirements.[20] For Phase I trials, the FDA made the cGMP guidelines optional for CGT manufacturing, creating advantages for small- and mid-size enterprises that traditionally invest heavily in in-house process development and in partnerships with contract development and manufacturing organizations (CDMOs). This flexibility extends to commercial process validation, including the potential for reduced manufacturing batches in certain circumstances.

Despite these flexibilities, the increasing issuance of complete response letters and nonapprovals based on CMC deficiencies is concerning. Most CGTs receive breakthrough or accelerated approvals based on early clinical efficacy endpoints that subsequently face challenges in confirmatory trials and postapproval success due to manufacturing and CMC validation barriers. CGT/ATMP CMC strategy development necessitates risk-based quality-by-design implementation with an end-in-sight approach by defining the target product profile at the program initiation stage. This is followed by risk-based identification of critical quality attributes and the development of manufacturing processes that consistently produce safe, efficacious, quality products that are comparable to pivotal trial products derived from a late-stage cGMP-compliant, validated process.

The advent of AI/ML-based technologies, closed automated systems, and in-process analytics that enable real-time process monitoring has expanded the scope of proactive,

cost-effective design, development, and control strategies for CMC manufacturing. Given the biological material's dynamics and heterogeneity, it is critical to prioritize robust control strategy development from early CGT process development stages, with meticulous real-time monitoring of critical process parameters linked to product critical quality attributes. Implementation of stricter starting material testing and traceability, quality raw materials, robust risk-based pre- and postchange process comparability testing, refined release test specifications, multiple potency assays reflecting mechanism of action, extensive product characterization assays, and comparable stability and sterility testing with cold-chain distribution, container closure, and shipping validation studies for multisite trials are highly recommended by regulatory authorities, as the product matures through clinical experience.

Manufacturing models and strategy

For small to mid-sized enterprises, resource-constrained, timeline-sensitive environments necessitate diligent regulatory and CMC strategy in weighing options between establishing in-house cGMP facilities or partnering with commercial contract research organizations and CDMOs, which may offer advantages through effective regulatory authority communications, comparability and control strategy development and implementation, regulatory intelligence expertise, skilled cGMP compliance professionals, process and analytical validation capabilities, and inspection-ready manufacturing services.

Increasingly, successful rare disease-targeting CGTs have been developed in small and academic settings focusing on personalized, cost-effective, timely therapeutic interventions through accelerated approvals (e.g., K-abe, Waskyra). Some European centers have manufactured patient-specific CAR-T products under Article 28 hospital exemptions using essentially N-of-1 treatment frameworks.[36] However, challenges persist in commercial translation and wider patient access due to scalability, development costs, and payer-mediated issues.

Recognizing severe unmet needs and a lack of suitable SoC for patients with rare and bespoke diseases, the FDA and EMA have initiated several programs. The FDA initiated the CMC Development and Readiness Pilot Program, which aims to accelerate complex product development, including CGTs, by increasing FDA-sponsor communication through FY 2027;[37] the Collaboration on Gene Therapies Global Pilot to advance global regulatory convergence on complex gene therapy development;[38] and the Platform Technology Designation program, which streamlines development pathways for validated delivery systems, allowing sponsors to reference precedent platform CMC and nonclinical data for new indications. The FDA and EMA jointly launched the Parallel Scientific Advice program and orphan drug cluster meetings. Both agencies have also explored decentralized manufacturing models, including point-of-care, distributed, and regional distribution models, to overcome supply chain and patient access challenges. **Table 2** (p. 58) presents key points of the FDA and EMA convergence and minor divergence regarding CMC manufacturing strategies.

Table 3 (p. 60) illustrates the major areas of divergence in CMC strategy across the two agencies. For starting materials and GMP requirements, early-stage trials in the EU involve higher costs and earlier implementation timelines due to the EMA's expectation for GMP compliance from the outset. Likewise, the divergence in potency assay expectations for first-in-human studies means that global sponsors must have a suitable potency assay developed before initiating Phase 1 studies.

Proactive regulatory intelligence is important for navigating these evolving frameworks. Continuous monitoring of the FDA's CMC flexibility frameworks, complete response letter trends, and CMC deficiency patterns can inform manufacturing investment decisions and CDMO selection without compromising inspection readiness or product quality. Furthermore, intelligence on the FDA's Collaboration on Gene Therapies Global Pilot program and platform technology precedents can help sponsors leverage established CMC data packages across new indications, thereby compressing development timelines, reducing duplicative validation efforts, and costs. As decentralized and point-of-care manufacturing models mature, global regulatory intelligence on GMP expectations will be essential for sponsors for developing multisite CGT manufacturing networks.

Postapproval benefit-risk monitoring

For full marketing approval, supplemental evidence and post-marketing safety and efficacy studies are necessary. In oncology indications, improvements in event-free survival, progression-free survival, and, in some cases, overall survival rate compared with SoC therapies are required beyond overall response

Table 2. FDA and EMA CMC strategy convergences and minor divergences

CMC criteria	FDA	EMA	Convergence or divergence
Cell viability specifications	Minimum acceptable viability is 70%, with supporting data needed if < 70%	Minimum acceptable viability is 70%	**Convergent**
Extractables/ eachables from single-use systems – bDtBPP	Testing required for bDtBPP	Testing required for bDtBPP	**Convergent**
RCV testing for retroviral vectors	Testing required for: – Vector producer cells – End-of-production cells – Vector stock – LV-modified cells Ex vivo cells cultured ≥4 days: RCV required as a release assay	Testing required for – Vector producer cells – End-of-production cells – Vector stock – LV-modified cells Same ≥ 4-day threshold as FDA: extensive RCV testing required	**Highly convergent** Both require a 15-year patient follow-up
CAR-T starting material collection (leukapheresis)	Excluded from cGMP: – Leukapheresis collection – Initial cell processing – Cryopreservation Subject to cGTP (21 CFR 1271)	Excluded from GMP: – Donation and collection of cells – Testing of cells GMP applies beginning at vector manufacture, cell purification/ processing, and MCB/viral seed stocks	**Convergent** Both exclude GMP requirements from early collection steps
Product nomenclature:	CGTs: – Cell therapy – Gene therapy – Tissue-engineered therapy	ATMPs: – GTMP – sCTMP – TEP – cATMPs	**Minor divergence**
Potency assay validation for pivotal trials	Quantitative functional potency assay required for release; must be validated according to ICH guidelines	Validated analytical methods; recommended but not strictly required; surrogate assays acceptable (e.g., functional characterization with demonstrated correlation)	**Minor divergence** EMA slightly more flexible; both require functional assay by MAA/ BLA
Manufacturing changes and comparability	Data-driven approach emphasizing: – Process performance qualification – Detailed control material documentation – Excipient specifications	Science-based, continuous improvement approach emphasizing: – Overall manufacturing strategy – Risk management – Lifecycle comparability	**Minor divergence** Both cite ICH Q5E (comparability)

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Table 2. (cont.) FDA and EMA CMC strategy convergences and minor divergences

CMC criteria	FDA	EMA	Convergence or divergence
		Specific guidance for GM cells: full vector sequencing, RCV absence, impurity comparison for starting materials	
Overall regulatory philosophy	Risk-based and pragmatic, emphasizing: – Graduated GMP compliance – Flexibility for Phase 1 – Data-driven decision making – Process performance qualification	Science- and quality driven, emphasizing – GMP compliance from early stages – Comprehensive lifecycle approach – Continuous improvement – Holistic risk management	**Minor divergence**

ATMP, advanced therapy medicinal product; **bDtBPP,** bis(2,4-di-tert-butylphenyl) phosphate; **BLA,** biologics license application; **cATMP,** combined advanced therapy medicinal product; **cGMP,** current good manufacturing practice; **CGT,** cell and gene therapy; **cGTP,** current good tissue practice; **CMC,** chemistry, manufacturing, and controls; **EMA,** European Medicines Agency; **FDA,** Food and Drug Administration [US]; **GM,** genetically modified; **GTMP,** gene therapy medicinal product; **ICH,** International Council for Harmonisation; **MAA,** marketing authorization application; **MCB,** master cell bank; **RCV,** replication-competent virus; **sCTMP,** somatic cell therapy medicinal product; **TEP,** tissue-engineered product.

rate alone. Consequently, the Prescription Drug User Fee Act dates have increasingly been extended to incorporate additional confirmatory evidence. The recent review of serious, adverse postapproval events of a high-profile gene therapy application for a rare pediatric condition highlighted the FDA's policy shift toward requiring stringent safety and efficacy endpoints for complex gene therapy approvals.[39,40]

For final approvals, the EMA requires extensive, more stringent confirmatory data from additional late-stage clinical trials that are generalizable across multiple EU regions. While the FDA primarily focuses on postmarketing safety (36.1%), the EMA also places significantly greater emphasis on postauthorization efficacy studies (47.1%), acknowledging that sustained clinical benefit and cure evidence for ATMPs require several years of monitoring.[41,42] CGTs/ATMPs approved under accelerated and conditional pathways are also subject to postmarketing monitoring. Both the FDA and EMA require 15 or more years of mandatory safety monitoring as part of pharmacovigilance and pharmacosurveillance programs, with risk-based approaches used to determine the duration of LTFU monitoring.[43] Factors such as DNA integration potential, duration of transgene expression, in vivo product persistence, and administration route influence regulatory decisions on LTFU duration and stringency. For example, therapies using genome-editing products and integrating vectors require 15 years of LTFU, whereas low-risk adeno-associated vectors require about 5 years of LTFU.

The FDA enforces a centralized approach using risk evaluation and mitigation strategy plans for high-risk CGTs, making decisions on the implementation and elimination based on postapproval benefit-risk surveillance. The EMA utilizes a decentralized pharmacovigilance system with region-specific compliance requirements across EU member states, requiring postauthorization safety and efficacy studies and a risk management plan that incorporates postmarketing surveillance of both efficacy and safety, with appropriate traceability systems. The EMA relies heavily on the European Network of Centers of Pharmacoepidemiology and Pharmacovigilance guidelines and registry-based studies for data gathering, especially when single-arm trials are the only feasible option. Both the FDA and the EMA recommend registry-based postapproval monitoring to assess the effectiveness of adaptive trial designs in clinical practice and to evaluate the effectiveness of these designs in smaller subsets and more heterogeneous patient populations.

Sponsors should perform feasibility assessments, collect continuous and uninterrupted data, transparently address missing data, and consider linking multiple data sources. Registries, electronic medical records, and claims data – capturing clinical, laboratory, demographic, genetic, histopathology, imaging, and digital health technology inputs – constitute common RWD sources. Key challenges include missing covariate data, patient dropout, unstructured data, and inconsistent or fragmented patient records.

Table 3. Major areas of divergence between FDA and EMA CMC strategies

CMC criteria	FDA	EMA	Divergence
Starting materials definition	Guidance refers to materials forming an integral part of the active substance, but does not provide a formal definition	Formally defined as materials that will become part of the drug substance (e.g., vectors, gene-editing components, cells)	**Major divergence**
Starting material (genome-editing components such as plasmids, mRNA, proteins); GMP requirements	Risk-based, flexible approach; non-GMP acceptable for Phase 1 with proper justification, step-wise increase in GMP compliance; full qualification and GMP validation at BLA and pre-license inspection	Stricter from outset, starting materials must follow GMP principles from early development; manufacturin sites subject to inspection; QP must ensure starting material quality	**Major divergence** EMA requires GMP from start while the FDA allows risk-based approach
Potency assay at FIH clinical trial	Flexible: if a potency assay is not available for release testing, other aspects of the control strategy may be accepted for potency assurance, including: – Manufacturing process controls – In-process testing – Material controls	Mandatory: a suitable potency assay must be in place when material for the FIH clinical trial is produced	**Major divergence** EMA requires potency assay earlier in development

BLA, biologics licensing application; **CMC,** chemistry, manufacturing, and controls; **EMA,** European Medicines Agency; **EU,** European Union; **FDA,** Food and Drug Administration [US]; **FIH,** first-in-human; **GMP,** good manufacturing practice; **QP,** qualified person.

Moreover, the FDA has provided draft guidance on decentralized data collection methods, including remote monitoring, telehealth, and local clinic assessments, to reduce patient burden as part of LTFU.[44]

Unless waived or deferred, the FDA requires sponsors to submit pediatric assessments per the Pediatric Research Equity Act. This act provides initial pediatric study plan exemptions for orphan designation applications, except for rare pediatric cancers under the amended Research to Accelerate Cures and Equity Act. As many rare disease CGTs/ATMPs target childhood-onset conditions, both the FDA and EMA require pediatric study plan submissions.[45] Deferred pediatric studies are mandated in pediatric populations after adult patient marketing approval.

Studies of drugs or biological products for life-threatening or severely debilitating pediatric diseases lacking adequate therapy could begin earlier than adult studies when urgency may justify early initiation despite limited adult safety and effectiveness information. The EMA requires a pediatric investigation plan submission for every new marketing application.[46] These submissions can be deferred until adult clinical efficacy data generation. Additionally, the EMA's 2023 pilot program allows sponsors to continue development with a partial pediatric investigation plan rather than waiting for more adult clinical trial data to support a full plan.

Conclusion

The CGT landscape demands a sophisticated, proactive regulatory intelligence framework. Higher FDA regulatory approval success rates alone are insufficient to ensure commercial viability; integrated strategies that address CMC robustness, RWE generation, multistakeholder collaboration, and region-specific market access are required. The convergence of AI/ML technologies, decentralized trial methodologies, patient-centric development frameworks, and regulatory flexibility initiatives creates unprecedented opportunities for accelerating CGT development.

However, success requires early, strategic, and proactive planning with an end-in-sight approach – particularly for CMC development, where 74% of regulatory failures occur. Emerging global dynamics necessitate comprehensive international regulatory intelligence that encompasses diverse regulatory frameworks, manufacturing paradigms, and market access strategies. The future of CGT development will be defined by

organizations that effectively integrate regulatory intelligence into strategic decision making across the entire product lifecycle, from early development through long-term postmarket surveillance, while maintaining flexibility to adapt to evolving regulatory landscapes as well as scientific and technological advances.

Ultimately, an effective regulatory strategy for CGTs requires balancing innovation with rigorous safety and efficacy standards, leveraging novel trial designs and RWE, and maintaining robust quality systems. Success also depends on fostering collaborative relationships among regulatory authorities, sponsors, patient advocacy groups, and healthcare systems to ensure these transformative therapies reach patients who need them most.

Abbreviations

AI/ML, artificial intelligence/machine learning; **ATMP,** advanced therapy medicinal product; **CAR-T,** chimeric antigen receptor T-cell; **CDMO,** contract development and manufacturing organization; **CGT,** cell and gene therapy; **CMC,** chemistry, manufacturing, and controls; **DPM,** disease progression model; **EMA,** European Medicines Agency; **FDA,** Food and Drug Administration [US]; **LTFU,** long-term follow-up; **PFDD,** patient-focused drug development; **RCT,** randomized controlled trial; **RWD,** real-world data; **RWE,** real-world evidence; **SoC,** standard of care; **cGMP,** current good manufacturing practice.

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Strategic regulatory intelligence on pricing and reimbursement models for cell and gene therapies

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This is the second of two articles on cell and gene therapies (CGTs). CGTs are among the most transformative and commercially complex therapeutics with their curative potential and one-time administration model. However, their extremely high research, development, and manufacturing costs create a unique set of regulatory and market access challenges not adequately addressed by the existing frameworks. The article synthesizes comparative regulatory intelligence across five major jurisdictions and discusses the corresponding health technology assessments (HTA), payer expectations, and reimbursement landscapes governing commercial access for approved CGT products. The first article, on p. 51, focuses on the role of strategic regulatory intelligence in shaping CGT strategy across the development lifecycle.

Keywords – cell and gene therapy, health technology assessment, outcome-based agreement, regulatory intelligence, risk-sharing agreement

Introduction

CGTs, a therapeutic category that includes cell, gene, and tissue-engineered therapies, differ from all other drug classes for which existing policies were originally intended.[1] These differences present unique challenges for regulatory science, HTA frameworks, and payer infrastructure across major global markets. The prospect of a single administration with potentially curative benefit, combined with high manufacturing costs and reliance on single-arm clinical studies in rare or refractory populations, represents a set of trade-offs that regulators have been willing to accept for CGTs. In contrast, these characteristics are often viewed as insufficient by HTA bodies and payers when recommending reimbursement.[2]

In this context, regulatory intelligence on regulatory agency expectations, HTA body methodologies, and payer decision frameworks across leading markets is an essential strategic requirement for improved patient access to these much-needed therapies. The regulatory intelligence challenge is further compounded by globally divergent and distinct policies. The US Food and Drug Administration (FDA) has established orphan disease, breakthrough therapy designation, and accelerated approval pathways that facilitate early authorization based on surrogate endpoints.[3] However, the absence of a formal national HTA process means that pricing and access decisions are fragmented across payers. These decisions are also subject to external review by organizations such as the Institute for Clinical and Economic Review (ICER), whose cost-effectiveness assessments carry no regulatory authority but might have substantial commercial impact.[4]

The European Medicines Agency (EMA) grants centralized marketing authorization for CGTs classified as advanced therapy

medicinal products (ATMPs) and offers conditional approval and priority medicine pathways.[5] Since January 2025, the European Joint Clinical Assessment (JCA) under Regulation EU 2021/2282 superimposes a harmonized comparative clinical evidence evaluation across 27 member states.[6] However, member countries apply their own HTA methodology, comparator selection logic, pricing negotiation, and reimbursement process.

Japan's Pharmaceuticals and Medical Devices Agency (PMDA) processes CGT applications through what is called an expedited Sakigake designation pathway[7] and mandates National Health Insurance (NHI) listing within 60 to 90 days following approval. However, the Ministry of Health, Labor and Welfare (MHLW) subjects listed products to biennial price revisions, which can materially erode commercial value over time.[8]

China's National Medical Products Administration has increasingly accepted multi-regional clinical trial data for CGT approvals, but reimbursement through the National Reimbursement Drug List (NRDL) requires separate annual negotiations with the National Healthcare Security Administration (NHSA). These negotiations are benchmarked against domestically approved CGTs priced at a fraction of global wholesale acquisition cost (WAC), a dynamic that has effectively excluded every major innovator CGT from public reimbursement.[9]

In South Korea, the Ministry of Food and Drug Safety links marketing approval to a structured HTA conducted by the Health Insurance Review and Assessment Service (HIRA), which applies formal cost-effectiveness thresholds prior to National Health Insurance System (NHIS) coverage decisions. A risk-sharing agreement (RSA) pathway for CGTs has enabled South Korea to become the first Asian market to formally reimburse multiple chimeric antigen receptor T-cell (CAR-T) products through public insurance.[10]

Across these five global markets, several recurring challenges occur. First, the evidentiary standard for regulatory approval and reimbursement decisions for CGTs frequently diverges. Regulators may accept single-arm trials with surrogate endpoints as sufficient evidence for conditional or accelerated approvals, whereas HTA assessments require comparative evidence against the standard of care, which is often complex for CGT trials.[11] Consequently, having an effective clinical development strategy for regulatory approval does not guarantee successful HTA assessment, contributing to systematic reimbursement failures across markets, regardless of the strength of the regulatory package.

Regulators may accept single-arm trials with surrogate endpoints as sufficient evidence for conditional or accelerated approvals. In contrast, HTA assessments typically require comparative evidence against the standard of care, which is often complex for CGT trials.

Additionally, timelines from regulatory approval to pricing and reimbursement decisions differ substantially across major global markets. Outcome-based agreements (OBAs) and RSA are among the major payer expectations for CGT coverage decisions, yet the supporting operational infrastructure to execute these agreements, including patient registries, outcome tracking systems, rebate administration, and data governance frameworks, is inadequate or fragmented in most markets.[12]

This article consolidates current regulatory intelligence on CGT approval, HTA, and reimbursement frameworks across the US, EU, Japan, China, and South Korea, and discusses the strategic regulatory intelligence implications for CGT sponsors navigating development, approval, and market access decisions across these markets simultaneously.

HTA and pricing policies

HTA and pricing pathways for CGTs/ATMPs diverge substantially across regions, reflecting differences in geopolitical policies, healthcare financing, and budget constraints. In the US, patient access to drugs has been shaped predominantly by payer-led value assessments and volume-based rebates, with the gradual adoption of OBA and RSA frameworks in the absence of a centralized HTA framework. European markets rely on nationally administered comparative cost-effectiveness evaluations, now partially harmonized through mandatory JCA, with managed entry access, OBA, and RSA widely deployed to address evidentiary uncertainty and budgetary impact. Across major Asia-Pacific markets, cost-effectiveness

analysis, RSA, and pricing discounts are increasingly used as price-adjustment mechanisms for high-cost ATMPs to enable patient access. These aspects have been described in detail in the subsequent sections.

United States

ICER, an independent, nonprofit organization, has emerged as a leading authority in the US for the clinical and economic evaluation of drugs to inform pricing and payer coverage decisions.[4] ICER develops recommendations for manufacturers, insurers, and providers prior to FDA approval, analyzing a drug's potential role in therapy, key patient subpopulations, pricing parameters, and payment schemes. For novel therapeutics such as CGTs with limited clinical evidence, ICER recommends that manufacturers and payers consider either a lower launch price with the potential for upward adjustment as evidence matures, or a higher launch price with OBA and RSA-based rebates that will reimburse payers if outcomes fall short of projections.[4,12] ICER also recommends the development of patient registries and planned long-term follow-ups for all patients treated with CAR-T therapies as part of postapproval commitments.

CGT sponsors are encouraged to engage with ICER proactively across scoping, evidence submission, draft reporting, follow-up data submission, and design of OBA structures. This early engagement can facilitate favorable price modeling and potentially achieve better commercial outcomes compared to a reactive response to postapproval ICER review.

Table. Health technology assessment frameworks and pricing decision criteria across the EU5[a] markets[13-15, 30-34]

Country	HTA body	Assessment method	Key decision factor	Binding for payer coverage
Germany	Joint Federal Committee	– Free pricing for first 12 months – Early benefit assessment – Reimbursement ceiling price after 12 months	– Short-term clinical benefit – Budget impact	Yes, after a 12-month free pricing period
UK	National Institute for Health and Care Excellence	Cost per quality-adjusted life year method: – £25,000-£35,000/ quality-adjusted life year – Up to £50,000 for end-of-life treatments	– Long-term quality-adjusted life year – Cost-utility effectiveness	Yes
France	Transparency Commission	Improvement in actual benefit method: – Substantial benefit (I-III) benchmarked against EU4[b] prices – Eligible for special hospital funding – Price discounts based on sales volume	– Long-term quality-adjusted life year – Cost-utility effectiveness	Yes, with price-volume agreements prioritized
Italy	Multiple[c]	– External reference pricing – Value-based outcome-based agreement – Region-specific final pricing	Budget impact	Not binding, recommendations only
Spain	Multiple[d]	– External reference pricing – Region-specific final pricing	Budget impact	Not binding, recommendations only

[a]EU5 comprises Germany, France, Italy, the UK, and Spain. [b]EU4 comprises Germany, Spain, Italy, UK. [c]One HTA for each of Italy's 21 autonomous regions. [d]One HTA for each of Spain's 17 autonomous regions.

European Union

Under the EU's HTA regulation, the European Commission coordinates a JCA, a single harmonized evaluation of the clinical evidence for an ATMP that can be utilized across all member states to produce a common relative effectiveness assessment.[5,6] The JCA evaluation of the comparative clinical effectiveness and safety of ATMPs against an appropriate comparator can therefore be used as the evidentiary foundation for national HTA and regional pricing decisions. For example, when the JCA's conclusion for a product is found to be insufficient in comparative evidence, the evaluation itself does not preclude national reimbursement, but it does substantially weaken the manufacturer's negotiating position across member states. Pricing frameworks in EU5 markets (Germany, France, Italy, the UK, and Spain) follow three broad HTA models as shown in the accompanying Table.

Germany. In Germany, manufacturer-set free pricing is applied for the first 12 months after launch. Manufacturer-set free pricing refers to the provision under which pharmaceutical manufacturers may unilaterally determine the launch price of a novel medicinal product for the initial 12 months following marketing authorization, with statutory payers obligated to reimburse at the manufacturer's stated price. The Federal Joint Committee then conducts a benefit assessment relative to a comparator therapy, rating the benefit as major, considerable, minor, nonquantifiable, or no added benefit. In situations where an ATMP is evaluated to have no added benefit, its long-term reimbursed price is capped at the cost of the reference or comparator therapy.[13] Following the 12-month free-pricing period, the National Association of Statutory Health Insurance Funds negotiates the final rebate price with the manufacturer. Germany primarily manages postlaunch evidence uncertainty through outcome-conditioned HTA reassessment, rather than formal outcome-based rebate schemes.

United Kingdom. In the UK, the National Institute for Health and Care Excellence conducts HTA based on full cost-per-quality-adjusted life year (QALY) appraisals, with a standard willingness-to-pay threshold of £25,000-£35,000 per QALY.[14] For most ATMPs, however, this threshold is extended to up to £100,000 per QALY.[15] ATMPs approved through conditional pathways also enter structured managed access coverage at a discounted price, commit to mandatory long-term outcome data collection, and undergo subsequent price negotiations at predefined review timelines.

France. France's HTA framework assigns an improvement in actual benefit (ASMR) rating of I-V, reflecting the degree of clinical improvement relative to existing therapies. The Economic Committee for Health Products then negotiates the list price with the manufacturer: ASMR I-III supports premium pricing, whereas ASMR IV-V aligns pricing with existing comparators. France also benchmarks drug prices using EU4 (i.e., Germany, Spain, Italy, UK) reference pricing.

Italy. The Italian Medicines Agency requires that every patient receiving a reimbursed CGT be enrolled in a national outcome registry. Furthermore, it uses this registry data to administer outcomes-based, payment-at-results, and cost-sharing agreements at the individual patient level, with manufacturers providing rebates when predefined clinical outcomes are not achieved at specified measurement points. Italy's framework represents one of the most operationally mature OBA frameworks for CGTs globally.

Spain. The Spanish Agency of Medicines and Medical Devices issues a therapeutic positioning report evaluating comparative clinical effectiveness. This is followed by pricing and reimbursement negotiations between the manufacturer and the General Directorate of the Basic Portfolio of Services of the National Health System and Pharmacy, leading to decisions on inclusion in the public National Health System's funding list, followed by final pricing decisions made by the Inter-ministerial Commission on Drug Prices (CIPM). However, for products associated with high budgetary impacts, access is frequently subject to agreements with regional authorities or individual hospitals, creating a de facto third access tier beyond the national commission decision.

Japan

Although the PMDA conducts marketing authorization review, pricing decisions in Japan are managed by the MHLW working through the country's HTA body, the Central Social Insurance Medical Council (Chuikyo). Upon PMDA approval, all products receive NHI listing within 60-90 days, making Japan one of the fastest formal national reimbursement market in the world for CGTs.[7,8] Accelerated Sakigake-designated products receive coverage within approximately three months of approval; for example, Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucell) were NHI-listed within 60 days of PMDA approval.

Under comparator-based pricing, NHI sets prices relative to the most comparable listed drug, with premiums or

discounts applied based on the assessed degree of improvement. Products demonstrating significant clinical improvement over existing therapies may receive premiums of up to 100% over comparable drugs. For most CGTs without close comparators, a cost-based pricing method is applied using a bottom-up cost calculation that incorporates manufacturing costs, distribution expenses, and a regulated profit margin.

The Japanese market has one of the fastest formal national reimbursement process for CGTs in the world: upon PMDA approval, all products receive National Health Insurance listing within 60-90 days.

Japan's biennial price revision involves MHLW revision of prices for all NHI-listed drugs every two years, based on actual market volumes, volume-price relationships, market share dynamics, and generic availability.[8] For high-cost CGTs with projected annual sales above approximately $100 million, a supplementary cost-effectiveness evaluation by the Committee on Drug Price Revision based on effectiveness is conducted mandatorily.

China

Following marketing approval by the National Medical Products Administration, the NHSA conducts a separate price negotiation process in which manufacturers submit dossiers and engage in direct price negotiation, after which products are listed in NRDL.[9] NHSA benchmarks proposed prices for foreign-manufactured products against domestically approved products, effectively using local CGT prices as ceiling thresholds in NRDL negotiations with foreign manufacturers.

South Korea

The Ministry of Food and Drug Safety approval is closely linked to a structured HTA process conducted by the HIRA, which evaluates all newly approved drugs for NHIS listing. HIRA applies formal cost-effectiveness criteria before pricing negotiations begin, using cost-per-QALY thresholds that are relatively low compared with global CGT launch prices. Products addressing high unmet need, severe disease, or lacking therapeutic alternatives are evaluated under more flexible criteria and are subjected to RSA.

The HIRA assessment requires manufacturers to submit a full health economic dossier, including a systematic literature review of clinical evidence, indirect treatment comparisons or meta-analyses of real-world evidence when no comparators exist, a full cost-utility model, a budget impact analysis, and a proposed RSA structure with defined outcome measures and rebate mechanisms.

Payer expectations and access barriers

Regulatory intelligence allows CGT sponsors to navigate the gap between regulators' expectations for marketing authorizations and the requirements of HTA bodies and payers prospectively, rather than reactively. A sponsor that designs its pivotal program solely to meet approval criteria, without anticipating region-specific HTA and payer expectations, will deliver a regulatory package that secures approval but fails to achieve reimbursement and commercial viability; this is highlighted by 29% (9 of 31) of EMA-approved ATMPs that have been withdrawn or not renewed due to commercialization failure driven by steep pricing (e.g., Provenge, ChondroCelect, Glybera, MACI), reimbursement negotiation deadlocks (e.g., Skysona and Zynteglo), and unfavorable postapproval confirmatory clinical results (e.g., Zalmoxis).[16] Proactive regulatory intelligence is critically important to continuously monitor shifts in pricing policies and reimbursement models that would facilitate drug development in alignment with payer expectations, prior to the product launch, rather than renegotiating under commercial viability pressure after approval.

United States

FDA approval of a CGT does not guarantee payer coverage or formulary listing in the US. The US operates under a fragmented, mixed-payer system in which public payers (e.g., Medicare, Medicaid, and the Department of Veterans Affairs) coexist with employer-sponsored and commercial private insurance, which together cover the majority of working-age patients. Each payer applies distinct pricing and coverage rules, and manufacturers set list prices freely at WAC, with no mandatory national price negotiation at launch.

Inpatient CAR-T infusions are reimbursed under Medicare Part A via a fixed inpatient CAR-T hospital payment category, with a base rate of approximately $48,000-$60,000, far below CAR-T WACs of $400,000-$475,000.[17] The Centers

for Medicare and Medicaid Services' (CMS) New Technology Add-on Payment program partially bridges this gap by covering 65% of costs exceeding the diagnosis-related group (DRG) threshold, but the eligibility is time-limited to two to three years postapproval and restricted to innovative products demonstrating substantial clinical improvement over existing treatment.[18]

Furthermore, Medicaid's DRG outlier payment covers approximately 80% of costs above a fixed multiplier of the base DRG rate; however, reimbursement is calculated using hospital-reported costs rather than drug WAC. Together, these mechanisms incompletely compensate institutions, particularly for community hospitals and newly certified advanced treatment centers lacking the administrative infrastructure to manage the reimbursement gap. This incomplete compensation leads many hospitals to decline Medicare CAR-T referrals and concentrate capacity on commercially insured patients.[19]

As payers in the US increasingly favor the outpatient setting, 340B-covered academic medical centers gain a structural financial advantage, resulting in access being concentrated at large urban institutions.

Outpatient CAR-T administration is reimbursed under Medicare Part B at the average sales price plus 6%. Under Section 340B of the Public Health Service Act, eligible safety-net hospitals and cancer centers may acquire outpatient drugs at statutory ceiling prices 20–50% below WAC and bill Medicare at the average sales price plus 6%, retaining the margin. As payers increasingly favor the outpatient setting, where co-insurance structures are more favorable than fixed inpatient DRG payments, 340B-covered academic medical centers gain a structural financial advantage over non-340B community advanced treatment centers and rural critical access hospitals. This results in access being concentrated at large urban institutions regardless of patient geography or disease burden.[20]

Given the high upfront costs and uncertainty surrounding long-term clinical efficacy, contemporary reimbursement models aim to mitigate financial risk by aligning critical patient access needs and payer expectations through linking payments to demonstrated therapy performance while preserving financial sustainability for healthcare systems. Some of these payer schemes are discussed in the following sections.

Inflation Reduction Act. Under the Inflation Reduction Act, CMS is authorized to negotiate a maximum fair price for high expenditure drugs beginning 11 years after FDA approval, with negotiated prices taking effect in year 13.[21] The One Big Beautiful Bill Act, enacted 4 July 2025, exempts CGTs approved exclusively for orphan indications from Inflation Reduction Act price negotiations, provided they have not received approval for another non-orphan indication.[22] Most of the currently approved CAR-T products (Kymriah, Yescarta, Breyanzi, Carvykti, Abecma, and Tecartus) and gene therapies for rare diseases (Hemgenix, Zolgensma, and Casgevy) have been approved exclusively for orphan indications and qualify for this exemption.

CGT Access Model Program. To address Medicaid access fragmentation, CMS recently launched the CGT Access Model Program, under which it negotiates OBAs with manufacturers on behalf of participating state Medicaid programs. Under this model, states pay upfront drug costs, which are linked to patient outcomes over time, and manufacturers provide rebates if therapies fall below prespecified thresholds.[23] The model also standardizes ancillary fertilization preservation service coverages to be covered by manufacturers and reduces state-level administrative burden. Bluebird Bio and Vertex Pharmaceuticals were the first manufacturers to enter agreements under this framework for sickle-cell disease. To date, 33 states, the District of Columbia, and Puerto Rico – representing 84% of Medicaid beneficiaries with sickle-cell disease – have enrolled.[23]

Value-based pricing models. To expand coverage for high-cost CGTs, payers and manufacturers have recently adopted value-based pricing models, including OBAs and RSAs. Luxturna, the first FDA-approved gene therapy in the US, has set the benchmark for success by implementing outcome-based pricing.[24] Similarly, in the case of Zynteglo (for beta thalassemia therapy), the manufacturer implemented a risk-sharing model under which it agreed to reimburse up to 80% of the therapy cost if a patient fails to achieve and maintain transfusion independence for at least two years

after treatment.[25] However, payer concerns regarding patient portability and member turnover have limited the willingness to extend the OBA beyond two years. In practice, risk-sharing models are primarily negotiated based on drug price-volume, budget, and clinical outcome metrics.

Other risk-sharing models. Some of the other risk-sharing models for high-cost CGTs include: subscription-based healthcare models in which a monthly or annual fixed fee covers unlimited direct primary care services;[26] stop-loss agreements in which payers pay part of the high-cost therapy payment on a per member basis, with the remaining amount covered by the employer;[27] risk pools stratification based models in which providers adjust payments based on intensity of the care needed based on disease severity levels;[28] and capitation payment models wherein payers provide a set per-member per-month fee to cover all care, forcing the employer to manage costs or pay for losses incurred by exceeding the budget.[29] These approaches, however, introduce operational and financial risks, including exposure to rare, high-cost cases (i.e., lightning-strike events), threshold-based coverage restrictions (i.e., lasering effects), and disproportionate financial burden on employers or smaller risk pools.[30] As a result, the adoption of these alternative models has remained limited.

European Union

All five major EU markets operate through predominantly publicly funded, tax- or social-insurance-funded healthcare systems in which statutory public payers are the primary providers of patient access to high-cost CGTs. Private health insurance exists across the EU5 but plays a peripheral role in CGT coverage; it is most developed in Germany, where approximately 11% of the population holds substitutive private insurance outside of Germany's statutory health insurance system (GKV), and in Spain and Italy, where voluntary private insurance supplements, but does not substitute for, public coverage. In the UK and France, private insurance is largely complementary (covering co-payments and amenities) and does not independently fund CGT access at list price. As a practical matter, CGT market access in all EU5 markets is determined by the statutory public payer, and a positive public reimbursement decision is a commercial prerequisite for meaningful patient volume.[31]

Reimbursement across the EU5 is governed by national payer systems that operate independently of centralized EMA marketing authorization. Although the EU JCA produces a shared comparative clinical evidence report, each member state retains full authority over pricing negotiation, reimbursement conditions, and coverage scope.[32] Managed entry agreements have become the standard commercial instrument for CGT access in all five markets, enabling conditional coverage in exchange for mandatory real-world outcome data generation and defined price review timelines.[33]

All five major EU markets operate through predominantly publicly funded, tax- or social-insurance-funded healthcare systems in which statutory public payers are the primary providers of patient access to high-cost CGTs.

Germany. In Germany, the GKV covers the majority of the population through competing nonprofit sickness funds, with rebate negotiations conducted centrally by the central federal association following the 12-month free-pricing period. Price negotiations are informed by the benefit rating assigned by Germany's national HTA and coverage authority as part of the early benefit assessment.

United Kingdom. The UK's National Health Service is a universal, tax-funded single-payer system that provides comprehensive coverage to the entire population with most services at no point-of-care cost. The NHS reimburses ATMPs through several routes: a standard technology appraisal conducted by the National Institute for Health and Care Excellence with a willingness-to-pay £25,000 to £35,000 per QALY; highly specialized technologies scheme for ultra-rare diseases with threshold up to £100,000 per QALY; managed access through the Cancer Drugs Fund and the Innovative Medicines Fund, each with £340 million budget, which provides interim coverage at a confidential patient access scheme price while outcome data accumulate over five years.[34] Products that do not meet modeled outcomes at the review point are subject to mandatory price renegotiation or delisting. The National Health Service also requires manufacturers of conditionally approved CGTs to participate in a managed access agreement that specifies data-collection obligations, outcome metrics, and review timelines as conditions for continued reimbursement.

Italy. Representing one of the most operationally mature outcomes-based reimbursement infrastructures for CGTs globally, Italy's National Health Service is a universal tax-funded public system administered through 21 regional health services, each with independent budget authority. The Italian Medicines Agency mandates enrollment of every treated CGT patient into a national outcome registry through which payment-at-results and cost-sharing agreements are executed automatically at the individual patient level.[35]

The UK's National Health Service reimburses ATMPs through several routes: a standard technology appraisal conducted by the National Institute for Health and Care Excellence, a highly specialized technologies scheme for ultra-rare diseases, and managed access through the Cancer Drugs Fund and the Innovative Medicines Fund.

France. The French National Health Insurance System is a statutory public health insurance system covering approximately 99% of the population, with complementary mutual insurance covering a substantial portion of co-payments for most beneficiaries but not independently funding high-cost CGTs. The Economic Committee for Health Products negotiates the list price based on the ASMR rating assigned by France's national HTA authority. ATMPs receiving ASMR I-III rating (moderate improvement) are eligible for coverage and are priced with reference to Germany, Spain, Italy, and the UK.[31] Price-volume agreements are the dominant contractual structure, increasingly complemented by OBA and RSA models.

Spain. The National Health System in Spain provides universal public coverage, but effective CGT access is further complicated by regional budget impact thresholds across 17 autonomous regions. As a result, national reimbursement authorization by the Inter-ministerial Commission on Drug Prices does not guarantee uniform formulary adoption across regions.[33]

China

China operates a mixed public-private insurance architecture in which public statutory insurance is the dominant payer for NRDL-listed drugs, while voluntary commercial supplementary insurance is the realistic near-term pathway for innovator CGTs that are not NRDL-listed. The statutory system comprises two mandatory public schemes: the Urban Employee Basic Medical Insurance, covering formally employed urban workers and their dependents through employer-employee payroll contributions, and the Urban-Rural Resident Basic Medical Insurance, covering the remaining population, including rural residents and the informally employed, through subsidized government premiums.

Together, these two schemes provide nominally universal coverage to approximately 1.4 billion people,[36] but reimbursement is limited strictly to drugs listed in the NRDL. Drugs not on the NRDL are not eligible under either statutory scheme, and patients must pay fully out-of-pocket or rely on voluntary supplementary commercial insurance products, including government-sponsored Huimin insurance, city-level schemes, and conventional commercial health insurance policies.[37] Innovative therapies, including several domestic CAR-T therapies, are also covered through the new national Commercial Health Insurance Innovative Drug List (Category C).[38]

The NHSA's annual NRDL negotiation benchmarks new drug prices against the lowest available comparable therapy price. For CAR-T products specifically, multiple domestically manufactured products (e.g., relmacabtagene autoleucel, equecabtagene autoleucel) and locally manufactured Yescarta have been commercially launched at prices ranging from ~$165,000, significantly below the global WACs of innovator products such as Kymriah (~$475,000) and Yescarta (~$400,000).[9] NHSA treats domestic product pricing as an effective ceiling benchmark in NRDL negotiations, rendering inclusion of innovator CGTs at global list prices commercially unviable although recently, few CAR-T therapies have been included in the new national Commercial Health Insurance Innovative Drug List (Category C). As a result, access to these products is limited to self-pay use, concentrated among high-income patients treated at Tier 3 academic medical centers in urban coastal provinces.

China's fixed-rate DRG payment system further compounds access inequities for administered CGTs. Fixed-rate bundle payment reimbursement models typically cover only a fraction

of the total episode cost for a CGT infusion, creating net operating losses for treating institutions. This financial disincentive limits institutional willingness to administer self-pay CGTs in the absence of manufacturer-sponsored access programs or supplementary provincial insurance coverage.

The National Healthcare Security Administration treats domestic product pricing as an effective ceiling benchmark in National Reimbursement Drug List negotiations, rendering inclusion of innovator CGTs at global list prices commercially unviable.

South Korea

South Korea's NHIS is a single-payer scheme covering the entire population, with drug prices subject to HIRA evaluation. Products that receive a positive HIRA evaluation enter direct price negotiation with the NHIS, whereas products that fail the HIRA evaluation are covered through out-of-pocket, RSA, and cost-effectiveness evaluation-based payment schemes. High-cost CGTs approved accelerated pathways are priced by implementing RSA.

Korea's RSA framework for CGTs incorporates four structural elements: utilization caps limiting the number of NHIS-reimbursed cases per contract period and expenditure caps, setting total annual expenditure limit for the drugs, with manufacturer/company refunding agreed percentage of amounts exceeding the annual reimbursement budget ceiling; outcome-based rebate obligations requiring manufacturers to refund a defined proportion of the drug cost if patients fail to meet predefined response thresholds within a specified post-infusion window; mandatory annual submission of real-world outcome data, including treatment response rates, progression-free survival, and safety data as a condition of continued listing; and conditional listing renewal, under which HIRA reevaluates the product approximately four years after listing and may require a price reduction or delisting if real-world outcomes do not support the originally modelled value.[39] This framework establishes NHIS coverage as a multi-year contract rather than a one-time access decision, with continued listing rights contingent on ongoing product performance.

Japan

Japan's NHI system provides universal, mandatory reimbursement for all PMDA-approved drugs within 60 to 90 days of marketing authorization, through a price-setting and listing process administered by the Central Social Insurance Medical Council (Chuikyo) and its drug pricing organization. Unlike any other major market, Japan has no separate coverage decision process, no formulary committee vote, and a rare possibility of outright payer rejection following marketing approval. Upon NHI listing, patient financial exposure is governed by income-stratified co-payment rules (generally 10%-30% of the treatment cost), alongside a high-cost medical expense benefit that caps individual monthly out-of-pocket expenditures. Together, these mechanisms effectively remove price as a barrier to patient access once a CGT achieves NHI listing. Kymriah and Yescarta were NHI-listed within 60 days of PMDA approval, demonstrating Japan's pace of formal access relative to other markets.[40]

However, the MHLW biennial and recent annual off-cycle drug price adjustments trigger downward price corrections, imposing a direct financial penalty on commercial success and incentivizing conservative volume projections in the initial NHI pricing dossier. CGTs with projected annual sales of approximately $100 million are additionally subject to mandatory cost-effectiveness reevaluation by the Committee on Drug Price Revision based on Effectiveness, which can mandate a price reduction at the subsequent biennial revision if the product is assessed as not cost-effective at its current NHI price. Postmarketing surveillance data, generated as a condition of conversion from conditional approval, are reviewed by payers to determine whether innovation premiums assigned at the initial listing remain justified, directly linking reimbursement sustainability to the quality and robustness of the real-world evidence program.

Conclusion

The global regulatory and market access landscape for CGTs operates under distinct frameworks of evidentiary standards, reimbursement expectations, and risk-allocation mechanisms. Regulatory approval, while imperative for market entry, is an insufficient parameter for patient access assurance. The gap between regulators' expectations for marketing authorizations and the expectations of HTA bodies and payers with respect to comparative effectiveness data, long-term follow-ups, and outcomes- and risk sharing-based agreements for pricing and reimbursement remains the central, unresolved challenge in CGT development strategy globally.

Regulatory intelligence trends indicate that payers across all major markets are moving toward evidence-based, outcomes-linked reimbursement schemes for CGT coverage. This shift demands CGT sponsors to design clinical development programs that not only align with the regulatory approval requirements but also with the payer expectations for real-world evidence infrastructure, patient registries, outcome tracking, and long-term follow-up protocols. Integrated regulatory intelligence, spanning global approval pathways alongside reimbursement frameworks, is therefore not a postapproval commercial function but a pre-IND strategic requirement. Decisions made during Phase 1/2 development, including comparator selection, registry integration with pivotal protocols, and the architecture of outcomes-based agreements negotiated at product launch, ultimately determine whether a conditionally approved CGT becomes both clinically accessible and commercially viable.

Abbreviations

ATMP, advanced therapy medicinal product; **CAR-T,** chimeric antigen receptor T cell; **CGT,** cell and gene therapy; **EMA,** European Medicines Agency; **FDA,** Food and Drug Administration; **HTA,** health technology assessment; **HIRA,** Health Insurance Review and Assessment Service; **ICER,** Institute for Clinical and Economic Review; **JCA,** joint clinical assessment; **MHLW,** Ministry of Health, Labour and Welfare; **NHI,** National Health Insurance; **NHIS,** National Health Insurance System; **NHSA,** National Healthcare Security Administration; **NRDL,** National Reimbursement Drug List; **OBA,** out-comebased agreement; **PMDA,** Pharmaceuticals and Medical Devices Agency; **QALY**, quality-adjusted life year; **RSA,** risk-sharing agreement; **WAC,** wholesale acquisition cost.

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