CMC Strategies for Expedited Program Development — Regulatory Perspectives

Session 1 of a CMC Strategy Forum

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In response to increasing demands for expedited availability of biotherapeutics around the world — and with the ultimate goal of patient benefit — health authorities have developed accelerated regulatory pathways to reduce development timelines to product licensure. Because of the complexity and unique nature of each program and product modality, some solutions must be worked out case by case between sponsors and regulatory agencies.

On 13 October 2020, CASSS–Sharing Science Solutions presented a virtual session overviewing currently available regulatory pathways in the United States, Europe, and Canada and general considerations for accelerated product development. Health-authority representatives shared experiences with reviewing requests and submissions under expedited programs. Presenters also provided examples and case studies for different therapeutic modalities to illustrate the applicability of expedited programs. Topics of discussion included comparability assessment, process validation strategies, specification setting, expectations for regulatory submissions, and emerging approaches to facilitate a common understanding of chemistry, manufacturing, and controls (CMC). The "Participants" box lists chairs, presenters, and panelists for this virtual meeting.

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US Programs

Expedited programs are intended to facilitate development and review of new drugs that address unmet medical needs in the treatment of serious or life-threatening diseases and conditions. US Food and Drug Administration representatives Susan Kirshner (Office of Pharmaceutical Quality, Center for Drug Evaluation and Research (CDER)) and Robin Levis (Office of Vaccines Research and Review, Center for Biologics Evaluation and Research (CBER)) presented the expedited program pathways currently available from the FDA (**1**). They described the qualifying criteria and regulatory advantages for CDER's and CBER's pathways.

Fast-track designation can be granted to a product if nonclinical or clinical data demonstrate its potential to address an unmet medical need. **Breakthrough-therapy designation** requires preliminary clinical evidence indicating that a drug could provide substantial improvement over existing therapies on one or more clinically significant endpoints.

The **Accelerated Approval Program** applies to products with demonstrated effects on surrogate endpoints that are considered to reasonably predict clinical benefit — or clinical endpoints that can be measured early and are reasonably likely to predict such an effect. This program requires a sponsor's commitment to conduct postmarketing confirmatory trials.

Priority-review designation can be granted to a drug that treats a serious condition and that (if approved) would provide significant improvement in safety and effectiveness over available alternatives. This designation shortens the review timeline (to six months from the 60-day filing date, from 10 months otherwise).

The relatively new **Regenerative Medicine Advanced Therapy (RMAT)** expedited development program was created under the 21st Century Cures Act. RMAT designation can be granted to an investigational drug if it meets the definition of a regenerative medicine

therapy; if it is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and if preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such a disease or condition.

With certain specifics applicable to each program, all those options allow for early and more frequent interactions with the agency (multidisciplinary meetings and communications with a review team and senior management) to facilitate efficient development programs and discuss critical issues. They also may provide potential for priority review and submission of a "rolling" biologics license application (BLA) or new drug application (NDA) (**1**). That means a drug company can submit sections of its application for review by the FDA as they are completed rather than waiting until the entire dossier is ready to submit the full application.

Vaccines for Emerging Diseases

Vaccine development against emerging infectious diseases follows the same paradigm as that for other preventive vaccines, with unique considerations if development occurs in a public health emergency such as the COVID-19 pandemic. At a minimum, a development strategy must include a well-defined process to ensure product quality and consistency of manufacture, along with product-related data, preclinical and clinical trial data, documented compliance with quality and current good manufacturing practice (CGMP) requirements, and a pharmacovigilance program for after product licensure.

Licensure pathways for vaccines include traditional and accelerated approvals based on clinical benefit and animal-rule approval based on animal studies with specific "eligibility" criteria and associated requirements. The path to licensure depends on disease incidence and available data. Demonstration of manufacturing consistency and product quality as well as clinical safety and effectiveness is required for approval by all pathways, although some differences exist in approaches to demonstrate efficacy.

Emergency-use authorization (EUA) is a relatively new regulatory pathway for drugs developed under emergency conditions — e.g., for the COVID-19 pandemic (**2**). For EUA determination, specific criteria apply along with a unique submission-package structure, specific steps for issuance of a letter of authorization; and particular conditions for use, revision, and revocation.

Expedited Pathways in Europe and Canada

In Canada: Jason Fernandes of Health Canada's (HC's) Biologic and Radiopharmaceutical Drugs Directorate overviewed the expedited review pathways available in Canada. **Priority review** is applicable for new drugs intended for treatment or prevention of severe, life-threatening, or severely debilitating diseases and conditions.

The **Access to Drugs in Exceptional Circumstances** pathway can be initiated by a federal, provincial, or territorial chief public health officer when an urgent public health need is identified. This pathway provides access to drugs that have received market authorization in the European Union or United States, but it does not grant market authorization in Canada.

Canada's **Special Access Programme** can be initiated by healthcare providers to provide access for drugs to treat patients with serious/life-threatening conditions and for whom conventional treatments either are unavailable or have failed. All these Canadian pathways require complete CMC/clinical packages.

In September 2020, Canada issued an interim order regarding drugs for COVID-19 (**3**). For such new medicinal products, sponsors are required only to submit known CMC and clinical information. The interim order provides a distinct pathway for drugs approved by a trusted foreign regulatory authority, allows for rolling submissions, and authorizes HC to compel submission of information/material both before and after authorization, which is not possible under regular pathways.

In Europe: Mats Welin from Sweden's Medical Products Agency (MPA) presented an overview of regulatory approaches for accelerated product development in the European Union. The most widely used regulatory pathway for biologics submissions is the centralized procedure, which is handled by the European Medicines Agency EMA and involves all EU regulatory bodies.

Europe's **PRIME priority medicines scheme** was launched in 2016 to enhance support for development of medicines that target unmet medical needs. Similar to the breakthrough-therapies mechanism in the United States, PRIME provides enhanced interactions between sponsors and regulatory representatives for early dialogue and scientific advice. It also enables potential approval through accelerated assessment.

The PRIME pathway has been used for COVID-19 medicinal products during the current pandemic. For such products the EMA also has considered some additional flexibilities: e.g.,

Participants

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- Jason Fernandes, a biologist evaluator for Health Canada's Biologic and Radiopharmaceutical Drugs Directorate
- Veronika Jekerle, head of the European Medicines Agency's Pharmaceutical Quality Office
- Susan Kirshner, division director in the division of biologics research and review at the FDA Center for Drug Evaluation and Research's (FDA-CDER's) Office of Pharmaceutical Quality
- Robin Levis, deputy director in the division of viral products at FDA-CBER's Office of Vaccines Research and Review
- Mikhail Ovanesov, research biologist and principal investigator in the division of plasma protein therapeutics at FDA-CBER's Office of Tissues and Advanced Therapies
- Kimberly Schultz, chief of the gene therapy branch in the division of cellular and gene therapies at FDA-CBER's Office of Tissues and Advanced Therapies
- Mats Welin, a senior expert in biotechnology at Switzerland's Medical Products Agency.

implementating supply chain changes for authorized products, postponing on-site inspections while performing distant assessment of facilities' GMP status, using a risk-based approach for quality assessment, postponing certain types of testing, and allowing rolling submission of sponsor data in segments for expedited review.

Conditional marketing authorization (CMA) can be granted in an emergency if a sponsor complies with the following requirements of the Committee for Medicinal Products for Human Use (CHMP):

- a positive benefit/risk balance for a product
- an applicant's ability to provide comprehensive data
- intention for the medicinal product to fulfill unmet medical needs
- a benefit to public health of the product's immediate availability on the market that outweighs risks related to the need for further data.

Mutual Considerations

All presenters emphasized that the major difficulties with expedited development programs relate to limited product understanding and significantly shortened CMC development timelines. In a pandemic, rapid shifts in global knowledge about an infectious agent, disease pathology, and relevant immune responses will drive product development. Increased understanding of the pathogen may require manufacturing changes (e.g., scale-up, moving from clinical to commercial processes, coordination with contract manufacturers, development of container–closure systems); requirements to plan and execute comparability studies and process qualification work under compressed timelines with limited validation data available; and setting specifications with few lots produced in total and even fewer tested in clinical trials.

Other challenges in accelerated development include the use of unqualified/unvalidated assays, especially for new technologies and products with unique testing requirements. Emerging new concepts can require development of relevant test methods and/or innovations in formulation and/or container–closure systems. Limitations on the amount of available manufacturing and stability data bring uncertainty to the task of establishing a product's shelf life. Despite all the related uncertainties, products under expedited development are expected to be safe and efficacious and to present a positive benefit/risk ratio.

DESPITE all the related uncertainties, products under expedited development are expected to be safe and efficacious and to present a positive benefit/risk ratio.

Building quality into a manufacturing process early is crucial to the success of expedited programs. Rapid process development can be facilitated by early and well-planned activities relating to product quality and manufacturing. Early understanding of a drug's mechanism of action (MoA) is helpful, as are timely identification of its critical quality attributes (CQAs), assessment of container–closure system compatibility with the product formulation, and planning for manufacturing changes to minimize the need for comparability studies later on. Sponsors should develop reference materials and achieve standardization and validation of critical assays as early as possible.

Control strategies should include more attributes, process parameters, and assays, and can be revised later on when more knowledge is gained. Leveraging design of experiments (DoE) for small-scale and quality-by-design (QbD)–based studies along with prior knowledge and process modeling can enable flexible control strategies and help companies streamline their manufacturing process development and qualification work. Other helpful mechanisms for streamlining process qualification include the use of comparability protocols, concurrent validation approaches, postapproval life-cycle management plans, and performance of certain activities in parallel that are normally performed sequentially.

Platform technologies can be useful in accelerated process development by providing validated unit operations with predictable critical process parameters (CPPs) and CQAs, rapid phase-to-phase process improvement and comparability assessments, and predictable yields and scale-up. Platforms also are helpful for safety evaluations (e.g., based on the safety record of platform-related impurities, qualification of cell banks, and clinical experience with adjuvants) and for quality control (e.g., applicability of existing assay validation work to a new product, potential adaptability of established specifications of platform-related products, and assessments of stability and container–closure compatibility). It is important to justify the applicability of any platform used for a new product based on substantial experience and demonstration that products share MoA, proof of concept, and similar stability profiles.

When **setting specifications** and establishing dating periods in expedited development, companies must leverage the target product profile (TPP), MoA, CQA understanding, real-time and forced-degradation stability data, and platform knowledge. Under accelerated programs, acceptance criteria for specifications are set based on limited manufacturing data, so their ranges may not represent normal process variability. That increases the risk for out-of-specification (OoS) results in commercial manufacturing. If broader acceptance ranges than what apply in production of clinical trial materials need to be proposed, they would need to be justified with evidence that the consistency of clinical performance (safety and efficacy) will be assured.

Assessment of CQAs and their potential effects on safety and efficacy — along with a positive balance of potential benefits and risks — becomes fundamental for setting acceptance criteria in accelerated programs. Prior knowledge can be a powerful tool, but its applicability to a new product must be justified. Stability models based on platform understanding can be used in assigning release requirements for specification parameters to assure acceptable levels at the end of a product's shelf life. Risks associated with setting specifications early can be alleviated in

the postmarketing phase, when more lots will have been manufactured to capture data that can be assessed to verify or revise the original acceptance criteria. Sponsors of expedited products must have a clear plan for revising those criteria — with postapproval change-management protocols (PACMPs) at prespecified timepoints (**4**) — and must discuss those proposals with regulators either in advance of submission or in the course of review.

Expedited product development requires balancing regulatory flexibilities with strategies to ensure product quality. It is crucial to identify phase-appropriate CMC concerns and prioritize concerns as development proceeds. Regulatory scrutiny in the early stages of development should focus on issues that confirm proof of concept and affect safety, compatibility of container–closure systems with product formulations, and approaches to comparability assessment and specification setting. Use of prior knowledge in later stages can help identify how sponsors will bridge their manufacturing processes (e.g., identifying critical unit operations for process validation and assays for control of CQAs), identify alternative approaches to consistency assessment, determine shelf life, and support their final benefit/risk assessments to balance gaps of data.

Concurrent process validation can be allowed provided that a well-defined protocol is established and interim data are made available. Certain aspects of process validation can be abbreviated if supported by data, such as supportive validation results from platform-related products if platform relevance and applicability to the new product are demonstrated. Sponsors might consider a prioritization-based approach for validation of critical and noncritical assays.

Flexible use of PACMPs may be allowed as a mechanism to facilitate acceptance of postapproval process validation data and scale-up or introduction of new manufacturing sites. In stability assessment, sponsors can assign short initial shelf lives to allow for rapid product use, then refine those upward based on data obtained later. Companies can consider using predictive stability models, stability data under stressed conditions, extrapolation of data from different presentations, and postapproval commitments to facilitate application progression.

Panel Discussion

Following the presentations, the four speakers were joined by Veronica Jekerle (EMA), Mikhail Ovanesov (FDA-CBER), and Kimberly Schultz (FDA-CBER) for a panel discussion to address attendee questions.

For submission of **rolling BLAs,** the FDA regulators on the panel emphasized that sponsors and the agency should reach agreements up front — during the pre-BLA meeting (before any data are submitted) — on plans for timing the submission of required items. The rolling BLA process allows sponsors to submit modules separately; however, the official review clock does not start until all complete modules are submitted. The agency may refuse to accept the filing (or start the review clock) if critical sections of the BLA are found to be incomplete, thus precluding the substantive final review. Submission of a complete Module 3 is preferred strongly (**5**). Neither the MPA, EMA, nor HC has specific presubmission conditions, but information initially submitted at the start of review is expected to be sufficiently broad and conclusive, including sufficient clinical data.

Whether to use **small-scale models** (SSMs) depends on which characteristics are being modeled, the criticality of their parameters, and the complexity of the modeled operation. SSMs can be used for risk assessments or as preliminary studies in comparability assessments and can enhance and streamline the qualification process. However, SSMs are not a substitute for at-scale process performance qualification (PPQ). SSMs are not particularly useful for cell-based products considering the dependence of cell growth on culture method and conditions. The scalability of a model and potential limitations should be evaluated to demonstrate the model's relevance to a given unit operation, and the scope of planned studies to be performed at full scale should be described clearly.

For **analytical testing** at early stages to support phase 1–2 clinical development, panel members recommended assessing as many parameters as is reasonably possible with a broad range of assays and prioritizing the rational investment of limited resources for assay development and validation. Studying only a few parameters with robust methods carries the risk of missing important information in the absence of a full criticality analysis. Even if assays are not validated fully, they can provide useful information as long as they are well controlled. It is important to establish a robust sample-retention program to allow for subsequent bridging studies. For cell and gene therapy products, a higher level of assay qualification is expected early in development (e.g., for dose determination) to assess important safety attributes and ensure safe dosing in the eventual commercial process.

Forced-degradation studies are useful in product characterization. They help sponsors assess the suitability of a stability program and/or product formulation given limited amounts of data from limited numbers of manufactured lots. These studies can be used in determining whether analytical tools are suitable and sensitive enough for control of CQAs. Identifying product-degradation pathways through forced-degradation studies early in development can help sponsors determine the effects of degradants in vivo, design pharmacokinetic (PK) studies, and develop necessary control strategies. Forced-degradation studies also are critical to understanding how product quality for global supplies might be affected when the cold chain is not robust (e.g., insufficient time to develop cold storage infrastructure in a pandemic).

However, forced degradation may not fully represent normal product degradation pathways and therefore cannot replace requirements for long-term stability studies to support shelf-life claims. Accelerated stability studies can provide valuable information in comparability assessments to support process changes. They are also useful in determining robustness of a product stability profile under challenged

storage conditions to support a proposed shelf life.

Quality Remains Paramount

Accelerated programs must never sacrifice product quality in favor of speed. Sponsors are advised to engage with regulatory agencies and plan early so that they can come to agreement on an appropriate accelerated path. Regulators should communicate their expectations and requests for information early and often and provide enhanced guidance to sponsors of expedited products. Collaborative efforts across regulatory agencies toward the goal of regulatory convergence and mutual recognition between industry and regulators are vital for successful CMC development under these programs and ultimately for providing worldwide access to medicines faster during emergencies such as pandemics.

Disclaimer

The content of this manuscript reflects discussions that occurred during the CMC Strategy Forum. This document does not represent officially sanctioned FDA policy or opinions and should not be used in lieu of published FDA guidance documents, points-to-consider documents, or direct discussions with the agency.

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