FDA's Strategy Document on Facilitating Chemistry, Manufacturing, and Controls Readiness for Products with Accelerated Clinical Development

I. Executive Summary

As part of the *Prescription Drug User Fee Act (PDUFA) Reauthorization Performance Goals and Procedures Fiscal Years 2023-2027 (PDUFA VII)*, the U.S. Food and Drug Administration (FDA) committed to activities that facilitate Chemistry, Manufacturing, and Controls (CMC) development for drugs and biological products that are intended to diagnose, treat, or prevent a serious disease or condition where there is an unmet medical need and may have accelerated clinical development timelines. In connection with this effort, FDA committed to the following actions:[1]

(1) Issue a new MAPP on approaches to address CMC challenges for drug and biological products regulated by the Center for Drug Evaluation and Research (CDER) with accelerated clinical development timelines (Status: published December 7, 2022)

(2) Implement, starting in FY 2023, a CMC Development and Readiness Pilot (CDRP)[2] to facilitate, where warranted by anticipated clinical benefit of earlier patient access, the expedited CMC development of products under an investigational new drug (IND) application (Status: commenced in April 2023)

(3) Conduct a public workshop[3] on CMC aspects of expedited development, to include best practices and lessons learned from, and stakeholder input on, the CDRP and its goals (Status: conducted on September 10, 2025)

(4) Issue a strategy document that outlines the specific actions the agency will take, including proposed timeframes, to develop or revise, as appropriate, relevant MAPPs, SOPPs, or other documents to incorporate lessons learned (Status: This strategy document meets this fourth and final commitment)

As PDUFA VII draws to a close, FDA will stop accepting new applications for admission to the CDRP at the end of April 2027, though the program will continue for Investigational New Drug applications (INDs) previously accepted. However, the potential to engage in enhanced communication between FDA and sponsors of drug and biological products with expedited program designations, especially Breakthrough Therapy (BT), Regenerative Medicine Advanced Therapy (RMAT), and Fast Track (FT) designations, will remain in effect.[4]

Lessons learned from the pilot will be incorporated into quality assessment practices for drug and biological products in expedited programs and other new or ongoing FDA programs.

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[1] See PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 through 2027 (PDUFA VII Commitment Letter), available at https://www.fda.gov/media/151712/download.

[2] See the pilot web page at link: https://www.fda.gov/drugs/pharmaceutical-quality-resources/chemistry-manufacturing-and-controls-development-and-readiness-pilot-cdrp-program.

[3] The web page for the meeting is at link: https://healthpolicy.duke.edu/events/lessons-learned-chemistry-manufacturing-and-controls-cmc-development-and-readiness-pilot-0.

[4] See the guidance for industry, *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014), available at link: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics. See also the draft guidance for industry *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions* (September 2025) at link: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-regenerative-medicine-therapies-serious-conditions-0. When final, this guidance will represent the FDA's current thinking on this topic. We update guidance periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

II. Discussion

Accelerated clinical development frequently does not follow the traditional Phase 1, 2, and 3 development timeline. For instance, in certain cases the results of Phase 2 trials may provide substantial evidence of effectiveness adequate to support regulatory approval of a marketing application (e.g., a New Drug Application (NDA) or Biologics License Application (BLA)). This significantly reduces the time available for product development, including CMC aspects of development. Cell and gene therapies, where, according to one analysis, product development timelines have on average decreased from around ten to six years,[5] are a case in point. These therapies have had demonstrable success in treating diseases that were previously considered terminal. Since these early successes, there has been a rapid increase in the number of IND applications, and the numbers of BT and RMAT designations granted.

More generally, in section I.N.4 of the PDUFA VII Commitment letter,[6] FDA recognized that products with accelerated clinical development often face challenges in expediting CMC development activities to align with the accelerated clinical timelines. FDA agreed to the CDRP pilot because overcoming CMC challenges in accelerated programs often requires additional interaction with FDA during product development and the use of science- and risk-based regulatory approaches so that the clinical benefits of earlier patient access to these products can be realized. Early FDA engagement can help sponsors navigate challenges by establishing clear CMC targets, which is especially critical for accelerated programs. While every applicant must provide sufficient information in the application to demonstrate and ensure product quality, FDA may be able to exercise case-by-case flexibility in support of expedited programs, making early and frequent dialogue critical.

As a PDUFA VII commitment, FDA agreed to undertake the four actions listed above to assist sponsors and applicants in addressing issues with accelerated development programs. With the publication of this strategy document, FDA has now fulfilled all four commitments.

A. CDER's MAPP on Quality Assessment for Products in Expedited Programs (2025)

MAPP 5015.13[7] discusses risk-based approaches and the regulatory flexibilities that CDER's Office of Pharmaceutical Quality may consider. For example, FDA may consider:

- Flexible approaches to process validation – including concurrent release of process performance qualification lots, or certain unit operations within the initial Stage 2 process validation being qualified at a reduced scale with a follow-up at commercial scale.
- Clinical-scale batch marketing – based on product-specific considerations, in certain circumstances, permitting marketing of batches made with the clinical manufacturing process where scale-up activities would otherwise delay commercial launch of the product.
- Alternative approaches to stability studies – for example, providing stability updates during the review cycle; use of data from batches of a different size than recommended in ICH Q1A(R2); leveraging data from batches other than the primary stability batches (i.e., supportive stability data); and alternative approaches to stability based on modeling using data from accelerated studies (for small-molecule products in NDAs).

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[5] See Laptiva L, Purohit-Sheth T, Serabian M, Puri RK. Clinical Development of Gene Therapies: The First Three Decades and Counting. Molecular Therapy Methods & Clinical Development. 2020 December 20;19: 387. doi: 10.1016/j.omtm.2020.10.004. Available at https://doi.org/10.1016/j.omtm.2020.10.004

[6] See the PDUFA VII Commitment Letter, available at link: https://www.fda.gov/media/151712/download, pp 50-52.

[7] MAPP 5015.13 Rev. 1 *Quality Assessment for Products in Expedited Programs*, available at: https://www.fda.gov/media/187958/download.

B. Stakeholder Feedback from the CDRP Program Workshop

On September 10th, 2025, FDA co-sponsored a public workshop hosted by the Duke-Margolis Center for Health Policy titled "*Lessons Learned from the Chemistry, Manufacturing, and Controls Development and Readiness Pilot (CDRP) Program*." The workshop convened FDA officials and pharmaceutical industry representatives to discuss their experience with different science- and risk-based approaches and early engagements employed during the pilot. Regulators and industry representatives discussed the current challenges and opportunities with expediting CMC readiness in light of accelerated clinical development timelines, and shared ideas on how practices like those employed in the pilot could alleviate these barriers.

Overall, stakeholder feedback indicated that:

- The CDRP provided an opportunity for sponsors to engage FDA early and solicit feedback on alternative approaches to accelerate CMC development. The CDRP's efforts helped companies receive timely feedback from FDA, address CMC development challenges, and develop robust submissions. Faster feedback in earlier stages of development was valuable, especially for smaller companies with less experience or fewer resources to invest in navigating the regulatory process.

However, stakeholders also noted:

- It was hard for sponsors to see how the additional engagement provided through the CDRP offered benefit beyond what was already available through the BT, Fast-Track FT, and RMAT Designation programs, which already provide opportunities for engagement via Type B meetings.
- A key barrier to expediting CMC development is that doing so typically entails a significant upfront investment of time and resources to plan and conduct the development activities as well as to engage in the discussions with FDA. Manufacturers may have limited resources and, due to unresolved uncertainties around approval and market demand, may be uncertain whether the long-term expected return justifies that investment.

C. Reflections on the CMC Development Readiness Pilot (CDRP)

The purpose of the CDRP was to help sponsors with expedited clinical timelines accelerate CMC development and provide a complete application, as well as to inform how FDA could better facilitate CMC development for products in expedited programs in general and in the future.

During the CDRP, sponsors and FDA collaboratively explored science- and risk-based approaches to accelerate CMC development. As part of applying for the pilot, sponsors outlined their plan for CMC development and identified anticipated challenges. Once accepted into the pilot, FDA reviewed these plans for completeness and provided feedback on ways sponsors could address their anticipated issues, as well as any additional issues identified by the sponsor or FDA during CMC-focused Type B meetings and short-turnaround follow-up discussions.

1. CDRP Participation Was Limited Relative to Capacity

Overall, participation in the pilot in the first three years was limited and below the maximum of nine new IND-stage drug or biological products per year, across both Centers. Over those 3 years, CDER had a total of 13 requests to participate and accepted 5 while CBER had 8 requests and also accepted 5, for a total of 10 accepted products, out of a possible total capacity of 27 (i.e., up to nine products per year over three years).

The Pharmaceutical Research and Manufacturers of America (PhRMA), and the Biotechnology Innovation Organization (BIO) conducted an interim survey of their members about the pilot in April 2024. Survey respondents reported that the main barriers to applying to the pilot were (1) uncertainty due to the limited number of available spots and eligibility criteria, (2) the specific eligibility criterion that the sponsor still be "at least two years" away from submitting an NDA/BLA, (3) the time and effort required to apply to (e.g., providing a CMC development plan up front), and then to participate in the pilot, (4) concerns related to signing a disclosure letter, and (5) potential delays in FDA decisions on acceptance to the pilot. Based on this feedback, FDA incorporated programmatic changes for the pilot's third year. These included:

- Removing the requirement that the product be at least two years away from NDA/BLA submission
- Reducing the maximum possible FDA review time for applications to the pilot from 180 to 90 days
- De-emphasizing sponsor inexperience as a selection criterion
- Shortening and simplifying the description of the "CMC development plan" – e.g., from "comprehensive" to an "outline"

Additional industry feedback suggested that the pilot's promise of two additional Type B meetings did not offer any obvious additional benefit to sponsors whose drug or biological product had already received a BT or RMAT designation.

While overall participation remained below capacity following the programmatic changes, the rate of applications for CBER products increased substantially in the first four months of year 4 (i.e., FY 2026).

2. Participating Sponsors Appreciated Opportunities for Iterative Feedback with Shorter Turnaround Times

Participants in the pilot who presented at the public meeting found that iterative communication (both formal and informal) helped reduce uncertainty and created an actionable path forward. In some cases, FDA staff responded to questions or provided preliminary feedback on aspects of CMC development plans via phone calls and email exchanges with sponsors participating in the CDRP. Participating sponsors noted that these communications facilitated more rapid feedback than would otherwise be available through Type B meetings alone. Participants also reported that this type of engagement builds shared understanding and can yield unanticipated insights. They reported that the opportunity for focused, fast-turnaround discussions was especially valuable when these conversations reduced uncertainty about FDA's expectations and how to choose among possible approaches to meet them.

3. CDRP Participation Enhanced Sponsor Preparedness and Regulatory Alignment Regarding CMC

Participating sponsors in the pilot emphasized that the CDRP added value by enabling earlier, more frequent, and more productive engagement throughout CMC development.

Enhanced FDA engagement depended on sponsors preparing a CMC development plan that described progress to date and the current status of their efforts to establish the various aspects of CMC readiness. Sponsors acknowledged that developing comprehensive CMC development plans in line with the CDRP program's early timeline required extensive internal coordination and significant upfront resources, typically going beyond their standard internal process, and involved providing FDA unprecedented transparency into their internal development activities.

Despite these demands, all participants who presented at the public meeting agreed that developing and sharing the CMC development plan justified the investment of time and resources. The exercise in early planning increased internal organizational alignment and offered early visibility into anticipated challenges. Early insight into sponsors' manufacturing strategies allowed FDA to identify potential issues that might lead to downstream delays, such as challenges with submission completeness or other readiness issues that could then result in deficiencies to be communicated in information requests (IRs) or even lead to a complete response (CR) letter. The background and context provided by the development plan allowed FDA to convey targeted and more informed feedback throughout development, helping sponsors reduce the risk of setbacks that could delay patients' access to a new treatment.

III. Action Plan Summary

The CDRP will cease accepting new applications to participate at the end of April 2027.[8] After review of the actions listed above, FDA has determined that it is not necessary at this time to develop or revise relevant MAPPs, SOPPs, and other documents. However, lessons learned from the pilot will continue to be incorporated into ongoing initiatives, programs, and activities, as described below:

A. Ways of Working and Communication

Enhanced communication, including the opportunity for CMC-focused Type B, C or D meetings, will continue to be available, including for drug and biological products with the BT, FT and RMAT designations. As lessons learned from the CDRP are incorporated into new or existing programs, these interactions provide opportunity for increased use of the following strategies in particular:

- Encourage sponsors to focus on their CMC development plan earlier in drug development. This includes:
  - Outlining a CMC development plan that identifies any anticipated CMC challenges and establishes a preliminary timeline for major milestones
  - Requesting an initial, CMC-focused meeting with FDA to discuss anticipated CMC challenges in the context of the preliminary plan
  - Holding follow up, CMC-only meetings, as needed throughout development
- Utilize available mechanisms for providing faster feedback on CMC-related follow-up questions through the use of Type D meetings and the recently announced Meeting Minute Clarification Opportunity[9] pilot program.
- Encourage expanded participation in programs, both current and emerging, that provide early engagement with FDA on select CMC topics, such as manufacturing and facility readiness, as appropriate, before submission of the full marketing application.

B. Regulatory Flexibility

Two recent policy initiatives reflect FDA's continued efforts to offer regulatory flexibility for drug and biological products on expedited timelines. For CDER, MAPP 5015.13, *Quality Assessment for Products in Expedited Programs* (2025), discussed earlier, remains in effect and, while the effectiveness of the flexibilities described will continue to be monitored, no additional updates to the MAPP are planned at this time. CBER will continue to extend flexibility on CMC requirements for biological products with accelerated clinical development timelines to advance

[8] FDA will continue to support INDs already in the pilot until their marketing applications are submitted or their INDs are withdrawn.

[9] Webpage: https://www.fda.gov/news-events/press-announcements/fda-pilots-faster-clarifications-meeting-minutes.

innovation in important fields. To that end, FDA has issued a guidance for industry titled *Chemistry, Manufacturing, and Controls Flexibilities for Developing Human Cellular and Gene Therapy Products for a Biologics License Application* (May 2026).[10] The flexibilities for cell and gene therapies fall into three main categories: (1) CMC expectations for investigational products in and during transitions between clinical phases 1, 2, and 3, (2) establishing commercial specifications, and (3) process validation.[11]

[10] Available at link: www.fda.gov/media/192321/download.

[11] See the full list of flexibilities at link: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/flexible-requirements-cell-and-gene-therapies-advance-innovation.