Whitepaper

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Success in 2023:
Understanding Recent Regulatory Updates

MMS Regulatory Services Team

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Introduction

Ben Kaspar, Director of Regulatory Affairs

As 2022 winds down and thoughts turn to planning for the first quarter of 2023, MMS has been preparing for what promises to be an exciting year of regulatory change and opportunity. One of the main challenges in regulatory work is knowing what to prepare for and what is coming next.

Working closely with our sponsors and health authorities, the MMS Strategy, Regulatory Affairs, and Regulatory Operations teams have identified key areas where preparation for change will lead to a smoother and more successful 2023 for Sponsors.

The Prescription Drug User Fee Act (PDUFA) VII goals letter consistently garners a lot of attention, as it provides a clear window into upcoming changes and opportunities. This year FDA has outlined upcoming new regulations and guidance to advance treatments for rare and serious conditions, streamline and harmonize regulatory submissions, leverage pathways for accelerated approval, increase the diversity of clinical trials, and ensure compliance with recent data standards. Other upcoming changes for FDA include the CDISC Standard for the Exchange of Nonclinical Data (SEND) requirements for US INDs, specifically the new requirements for CBER, which go into effect next year.

While PDUFA VII continues to accelerate the approval of new drugs and biologics, a significant initiative in the European Union promises to do the same for clinical trial applications (CTAs). On that theme, we review progress on the actualization of the EU Clinical Trials Regulation (CTR) through the Clinical Trial Information System (CTIS) with a focus on best practices for cross-functional planning and preparation for successful submissions.

We give special emphasis to the role of a strong Regulatory Operations team and the importance of regulatory information management systems for compliance and expedited development across all regions.

Overall, this white paper aims to provide a high-level overview of changes to the regulatory landscape that will begin in 2023. The strategic topics addressed herein are intended to give practical support to planning development programs in an ever-changing regulatory environment.

Strategies to Leverage Key PDUFA VII Changes

The Prescription Drug User Fee Act (PDUFA) VII, the 6th reauthorization of PDUFA, was signed by President Biden on September 30, 2022. In addition to the standard content that ensures the FDA has the necessary resources to provide a predictable and efficient review of human drugs and biologics, PDUFA VII has several enhancements that were discussed at a public meeting on September 28, 2021.

PDUFA Goals Letter

The Prescription Drug User Fee Act, or PDUFA, was created by Congress in 1992 and must be reauthorized every five years. After PDUFA is signed, the FDA releases its "performance goals and procedures," commonly referred to as the "goals letter" or "commitment letter." The performance and procedural goals and other commitments specified in this letter apply to aspects of the human drug review program that are important for facilitating timely access to safe, effective, and innovative new medicines for patients.

The FDA is committed to meeting the performance goals specified in this letter and to continuously improving its performance in other important areas specified in relevant published documents relating to pre-approval drug development and post-approval activities for marketed products.

You can find the goals letter for PDUFA VII here .

Split Real-Time Application Review (STAR) Pilot Program

By: Ben Kaspar, Director of Regulatory Affairs & Dr. Amanda Beaster, Associate Director of Regulatory Strategy

The FDA announced its intention to expand its programs further to expedite patient access to safe and effective drugs and biologics for serious conditions with an unmet medical need.

The goal of the STAR pilot program will be to decrease the time from the date of the complete submission to the PDUFA action date for established therapies.

This newest pilot program joins existing programs that allow for differing degrees of rolling review, such as Breakthrough Therapy Designation (BTD), Fast Track Designation, Regenerative Medicine Advance Therapy (RMAT) Designation, and Real-Time Oncology Review (RTOR).

It closely aligns with RTOR, an oncology-specific program that allows for a rolling review. Thus, experience with a rolling review, especially RTOR, may help prepare regulatory leads for the intricacies of this type of submission. Unlike RTOR, STAR will be available to applications across all therapeutic areas and review disciplines. Under STAR, initial reviews will be conducted by the relevant review division (Center for Drug Evaluation and Research) or office (Center for Biologics Evaluation and Research) based on discipline.

STAR will only apply to efficacy supplements, meaning that efficacy data is being submitted for a drug that already has approved labeling for another indication or population in the US. Neither Breakthrough Therapy Designation (BTD) nor Regenerative Medicine Advanced Therapy Designation (RMAT) is required, but the criteria for the clinical evidence are similar.

If upon review of their clinical trial outcome data, a Sponsor believes that their upcoming Supplemental New Drug Application (sNDA) or Supplemental Biologics License Application (sBLA) may qualify for review under the STAR program, they should submit a STAR Entry request as an informal pre-submission teleconference with FDA and provide FDA with topline trial results and proposed labeling. At this meeting, the only topic will be whether the application is eligible for STAR (no meeting minutes will be generated, but a formal decision letter will be issued).

FDA also indicates that sponsors can request a STAR as part of the pre-sNDA or sBLA meeting, which would be most appropriate if the Sponsor has other questions for the FDA regarding the content or format of the upcoming submission.

This means that if a Sponsor is working on an existing program and wants to use STAR, they should consider having a draft label ready to go by the time topline results are available and take a "fill in the blanks" approach when it comes to the data-reliant portions of the label (e.g., Section 14).

Applicants will also do best if they have lean processes for drafting the topline summary and approving the draft labeling.

Advantages of STAR

"Split:" Allows sponsors to split their sNDA/sBLA into two key submissions, submitted up to two months apart.

"Real-time:" Allows FDA to initiate review before receiving the complete submission.

FDA will initiate a review of the data upon receipt of the Part 1 submission. Although the PDUFA timeline will begin upon receipt of the Part 2 submission (i.e., the complete application), under STAR, FDA intends to target taking action at least one month earlier than the applicable priority 6-month PDUFA goal date.

For STAR applicants, the filing meeting is to be scheduled within 30 days of receipt of the Part 2 submission, and sponsors will be notified of the intended action date (along with the PDUFA goal date) in the filing letter.

Part 1
All components of the sNDA or sBLA submission, including complete datasets, proposed labeling, clinical protocols and amendments, and a topline efficacy and safety results (a document providing topline results for each of the adequate and well-controlled studies), except those submitted in Part 2.

Part 2

Final clinical study reports (CSRs) for the adequate and well-controlled trials and related the Electronic Common Technical Document (eCTD) module 2 clinical summaries (2.5 and 2.7). Note that if the Part 2 CSRs do not impact Module 2 clinical summaries, they should also be a part of the Part 1 submission. FDA also indicates that the Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) will be included in Part 2.

Specific Criteria for Applicants

To be considered for STAR, applications must meet each of the following criteria:

1. Must include clinical evidence from adequate and well-controlled trials
2. Similar to BTD and RMAT, it must include evidence that the drug may demonstrate "substantial improvement on a clinically relevant endpoint(s) over available therapies," and the drug must be intended to treat a "serious condition with an unmet medical need."
    - While this qualifying standard is the same as required for BTD or RMAT, the FDA has provided some notably specific details regarding the types of evidence that may, or may not, support the demonstration of "substantial improvement."
    - The FDA anticipates that most non-inferiority trials will not demonstrate substantial improvement; thus, Sponsors of non-inferiority trials should consider designing non-inferiority trials with built-in superiority analysis if they wish to pursue STAR.
    - Additionally, the FDA has clarified that real-world evidence (RWE) will not be accepted to demonstrate substantial improvement under STAR.
3. No aspect(s) of the application can require a longer review time. This would include things such as a novel Risk Evaluation and Mitigation Strategy (REMS) proposal.
4. No CMC information that requires a manufacturing site inspection outside of the US will be accepted. However, US site inspections may be allowed if they can be conducted in the expedited time frame.

Other Key Points to Keep in Mind

- Part 2 will not be accepted any later than three months after Part 1
- Suppose FDA determines that the Part 1 submission is incomplete during the filing review (except for the planned components of Part 2). In that case, the review will not be initiated under the STAR program (i.e., review will not initiate until a materially complete application is submitted and the application is removed from STAR).
- The FDA's STAR public-facing webpage went live in October 2022. You can find it here: Split Real Time Application Review (STAR) | FDA
- The STAR program will be available in 2023 but likely will not be fully implemented until 2024

More to Come: Related PDUFA VII Commitments

FDA has committed to conducting an interim assessment of STAR by the end of 2025 and a public workshop by the end of Q2 2026.

At that point, they plan to discuss the potential value and feasibility of expanding STAR to specific New Molecular Entity (NME) NDAs and BLAs.

They will also request feedback from industry stakeholders who experienced the STAR pilot program and will follow up with a publicly available summary of overall metrics (the percentage of applications accepted/submitted and the percentage of applications with an action date at least one month in advance of the priority 6-month PDUFA goal date) and external stakeholder feedback received.

What is RDEA and What Does it Mean for Rare Disease Research?

By: Dr. Amanda Beaster, Associate Director of Regulatory Strategy, Ben Kaspar, Director of Regulatory Affairs, and Dr. Christine Clarke, Senior Global Regulatory Affairs Manager

Under PDUFA VII, FDA intends to roll out the Rare Disease Endpoint Advancement (RDEA) Pilot Program next year. This program is intended to address some of the unique challenges rare disease researchers face when determining endpoints to assess the efficacy of drug products in clinical trials.

These programs require intensive collaboration with the FDA due to a lack of validated clinical trial endpoints.

Discussions with the FDA around complex topics such as mechanisms of action, pathogenesis, diagnostics, animal models, natural history, etc., are critical to understanding the disease and selecting clinically-relevant endpoints.

Rare disease researchers must work creatively as there is a limited patient population to contribute to advancing various therapeutic options through enrollment in clinical research. Many rare disease programs also struggle with funding and additional roadblocks to reaching viable therapy.

Applying the Type A/B/C meeting format to intensive scientific discussions and the inevitably incremental resolution of key development questions in an environment of scarce resources requires creative solutions.

By supporting the development of robust efficacy endpoints, especially those that may be applicable across multiple related rare diseases or those with similar manifestations, FDA hopes to drive the general advancement of rare disease drug development.

To this end, the RDEA pilot is intended to aid researchers as they work through the known challenges to understand and characterize the key signs and symptoms of a particular rare disease. Whether these be direct measurements of how patients with rare diseases feel, function, or survive or surrogate endpoints.

The goal of this pilot is to provide the opportunity for repeated, intensive interactions with the FDA by offering additional engagement opportunities to rare disease researchers that meet specific criteria.

Under PDUFA VII, FDA has committed to developing its capacity to execute the complex and intensive reviews necessary for novel endpoint development.

Key Advantage of the RDEA Pilot

The key advantage of the RDEA pilot is it allows applicants to participate in up to four focused meetings with relevant FDA staff to discuss endpoint development.

The additional input gained at these meetings may be strategically used to ensure that development programs are in full alignment with FDA expectations, but also to avail inexperienced applicants to the wealth of knowledge at the FDA providing the opportunity to speak with experienced drug developers who now work for the FDA.

It is important to understand that while helpful, FDA advice provided in the RDEA pilot is considered non-binding and does not guarantee approval for subsequent applications that utilize the efficacy endpoints discussed during RDEA meetings.

After the four meetings have been conducted, or when the applicant does not have additional endpoint-focused discussions, the development will continue through the respective pathways. Additional input can be requested using the existing mechanisms for formal meetings with the FDA.

Status of the Program

To be considered for the pilot, rare disease programs should have an active Investigational New Drug (IND) Application, pre-IND, or a natural history study utilizing a proposed endpoint for discussion with the FDA. Applicants developing innovative or novel endpoints for common diseases may also apply if they can provide sufficient justification that the endpoint could apply to a rare disease.

Criteria: The Endpoint(s)

The proposed endpoint must be novel—meaning that either it has not been used to support drug approval or is a substantial modification of another endpoint (one that has been used previously to support drug approval). It also should be intended to establish substantial evidence of effectiveness in a rare disease drug program.

FDA also clarified that it would preferentially consider programs intended to have multiple uses, either through relevance to other diseases or those that may lead to the development of a range of different types of endpoints.

FDA will also consider surrogate endpoint proposals, especially those that include a new approach to clinical data collection in the pre-market stage to allow for the validation of these endpoints.

Applicants intending to submit a surrogate endpoint proposal should consider requesting a Type C Surrogate Endpoint meeting first.

The Pilot

FDA is committing to selecting very few proposals, only one in 2023 and one per quarter (maximum: three per year) for the rest of the fiscal years under PDUFA VII—although FDA has stated that, depending on staffing, they may expand beyond this number of selected proposals.

Researchers may, however, benefit from this program even if not directly selected for participation. Firstly, FDA is committing to conducting up to three public workshops by the end of the fiscal year 2027 to discuss various topics relevant to endpoint development for rare diseases, such as multi-domain analysis methods.

Secondly, FDA may issue additional supportive materials and present the novel endpoints developed through RDEA in public forums (e.g., guidance document(s), website(s), or public workshops).

Timelines for Submissions and Meetings

FDA commits to confirming receipt of the initial proposal within 14 days and will notify the applicant of the selection decision no later than 60 days following the end of the fiscal year quarter during which it was submitted.

For this reason, it is in the applicant's best interest to submit early enough in the quarter to ensure adequate time for the proposal to be reviewed before the end of the quarter.

For those selected, meetings will typically be scheduled within 45 days following the FDA's receipt of the meeting request and complete briefing document.

If the topics and questions are focused, the timeline could potentially be expedited at FDA's discretion. There is no set requirement for the time between meetings; rather, it will depend on when new issues or questions arise and how quickly an adequate request and briefing materials can be submitted.

Transparency

As mentioned above, FDA intends to share information gained from these programs publicly to promote innovation and the evolving science of efficacy endpoint development and use.

The FDA and the applicant will have to agree on the information that the FDA may share publicly before the initial RDEA meeting. If no such agreement can be reached, the proposal will no longer be part of the RDEA pilot program.

What Does RDEA Mean for the Rare Disease Community?

We reached out to members of the rare disease-focused drug developers and patient advocacy communities to ask what this new initiative meant to them and their attempts to find treatments and cures for their patient groups.

This is what they said:
For A-T Children's Project, the RDEA program could dramatically improve drug development for A-T and other rare diseases.

Ataxia-telangiectasia (A-T) is a rare disease that causes muscle control and balance loss, cancer, lung disease, and immune system problems in children and young adults, shortening their lives. The non-profit A-T Children's Project partners with academic and industry investigators to develop potential treatments. Brad Margus, the founder of the non-profit and father of two sons battling A-T, believes that the FDA's pilot program could dramatically improve drug development for A-T and other rare diseases.

"The ability to get direct input from the FDA early on, while endpoints for clinical studies are being selected, will be a game-changer, making our trials ***more precise and relevant to everyday life while avoiding discouraging missteps.*** *It can be brutally disappointing to families of A-T kids when a trial fails because it technically missed an endpoint that they felt didn't accurately reflect efficacy in their children or when we didn't fully understand the FDA's views of the endpoint until after the fact. The opportunity to work closely with the FDA on what's meaningful to patients – before a trial begins – will be wonderful."*

Brad Margus
Founder of the non-profit A-T Children's Project

For Parasail LLC, a clinical-stage rare disease company, the RDEA program could uniquely benefit from assessing the therapeutic efficacy of their VAL-1221 antibody-enzyme fusion in Lafora Disease.

"Lafora is a devastating genetic childhood epilepsy with no current treatment. Glycogen accumulation in the brain drives the hallmark symptoms of this disease, including increasing seizure frequency, progressive dementia, and loss of functional mobility. While extremely severe and progressive individually, these symptoms collectively advance at different rates; therefore, ***FDA programs such as RDEA would be especially beneficial in identifying therapeutic endpoints for a pivotal trial.****"*

Vicki Wong, MPH
Co-Founder & Vice President, Parasail LLC

For the patient advocacy group Chelsea's Hope, the RDEA program could benefit them when partnering with potential drug development partners to open new pathways for treatments for rare diseases like Lafora disease.

"Our community has been working tirelessly to move promising treatments out of the lab and into human trials for our children. In fact, multiple therapy modalities have been developed and shown effective in animal models. However, a significant roadblock exists because getting approval for meaningful clinical endpoints can be an arduous process. We are very excited about the FDA Rare Disease Endpoint Advancement Pilot Program, which ***directly addresses this need and supports communities in the most critical part of the regulatory submission process.*** *The program has the potential to open new pathways for treatments for rare diseases like Lafora disease."*

Kit Donohue, Scientific Director
Chelsea's Hope, Lafora Children Research Fund

Updated FDA Meetings

By: Dr. Christine Clarke, Senior Global Regulatory Affairs Manager, and Dr. Amanda Beaster, Associate Director of Regulatory Strategy

Sponsors receive FDA feedback and advice on their drug development program via formal FDA meetings. These meetings allow Sponsors to learn the FDA's current thinking on a specific topic and to amend their development program based on FDA's recommendations appropriately.

The Recent PDUFA VII Commitment goals letter outlines several additions and enhancements to existing formal PDUFA meetings and related procedures:

- Type D
- Initial Targeted Engagement for Regulatory Advice on CBER products (INTERACT)
- Procedural changes and clarifications
- Updated guidance
- Opportunities to contribute

These help clarify sponsor expectations and encourage communication using the correct channels and time frame.

Type D Meetings

Per PDUFA VII, a new meeting type, Type D, is focused on a "narrow set of issues." By this, FDA means these will typically be granted for discussion of one or maybe two issues (but no more than that).

This does not mean that Sponsors can only ask two questions but that questions should all be associated with at most two focused topics.

The examples that FDA cites are general questions about innovative approaches or follow-up questions that arise between meetings. Meeting background packages, or briefing documents, are to be submitted at the time of the Type D meeting request.

If a meeting is requested for several issues or a complex issue with multiple questions, FDA has stated that a Type C meeting is the most appropriate.

The other gating condition for granting a Type D is that the issue requires only input from three or fewer

disciplines or divisions. Suppose FDA disagrees with the Sponsor that the focus of the requested meeting meets these requirements. In that case, they will issue a notice of meeting-type conversion and allow the Sponsor the opportunity to accept or withdraw their request.

The target is for the FDA to respond to Type D meeting requests within 14 days and schedule meetings within 50 days. These goals are being phased in, with 50% of these meetings scheduled in 50 days in 2023, escalating to 90% in 2027.

INTERACT Meetings

INTERACT meetings are not new, but PDUFA goals for this meeting were only added in this reauthorization. Meeting background packages, or briefing documents, are to be submitted at the time of the meeting request.

INTERACT meetings focus on unique challenges and novel questions for CDER and CBER products for which existing FDA guidance or other information is available. These meetings provide FDA input on issues early in development, prior to IND filing and typically before the request for a pre-IND meeting, for issues that may hamper the progress or delay the initiation of IND-enabling studies in the absence of this early input.

Meeting questions may include complex CMC issues, design of IND-enabling toxicology studies, use of "cutting edge testing methodologies," "development of innovative devices to be used with a drug or biologic," or other development issues agreed upon by the FDA.

FDA will respond to an INTERACT meeting request within 21 days, and meetings will be scheduled within 75 days. These goals are being phased in, with 50% of these meetings scheduled in 75 days in 2023, escalating to 90% in 2027. If FDA advice changes because of an INTERACT meeting, then within 30 calendar days, preliminary responses will be annotated and resent. WRO serves as meeting minutes from FDA.

Procedural Changes and Clarifications

The FDA recommends that written meeting requests state the purpose of the meeting, as well as indicate the Sponsor's preference for a written response (WRO) from the FDA, or an in-person face-to-face, teleconference, or virtual meeting that enables audiovisual communication.

Challenging a WRO Response

Suppose a Sponsor receives a WRO in response to a pre-IND meeting request and believes a face-to-face meeting would be most valuable. In that case, the Sponsor may submit a follow-up correspondence to the FDA justifying the need for a face-to-face meeting.

If the Sponsor's request includes approaches in which there are no established precedents or novel approaches to clinical development, then the FDA may grant the Sponsor's follow-up request and convert the WRO to a face-to-face meeting.

Requesting Post-Meeting Clarification

Opportunities to follow up with the FDA are available to Sponsors who wish to clarify questions or confirm feedback in meeting minutes or WROs issued by the FDA.

The clarifying questions will be submitted in writing as a "Request for Clarification" to the FDA within 20 calendar days following receipt of the meeting minutes or WRO. Within 20 calendar days of receipt of the Sponsor's clarifying questions, FDA will respond in writing, referencing the original meeting minutes or WRO.

Only clarifying questions that meet the criteria will be issued a response; however, the FDA may exercise discretion regarding whether requests are permissible or in scope.

Updated Guidance and Opportunities to Contribute

The FDA plans to issue a revised version of the existing draft guidance, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," by September 30, 2023.

The updated guidance will contain information on Type D and INTERACT meetings and how to request post-meeting clarifications and trainings to communicate these best practices to the industry. All relevant Manuals of Policies and Procedures and Standard Operating Procedures and Policies will be updated.

A public workshop will be held on July 30, 2024, to discuss best practices for FDA meetings: important lessons from the Coronavirus Disease 2019 ("COVID-19") pandemic, including the use of virtual platforms for meetings and metrics and experiences

related to PDUFA activities, including Type D and INTERACT meetings.

Reported metrics include the number of granted or denied INTERACT meeting requests and the number of granted and denied in-person pre-IND, Type C, Type D, and INTERACT meeting requests.

Eighteen months after the public workshop, the FDA will update public documents, including publishing a revised draft or final version of the Guidance for Industry "Best Practices for Communication Between IND Sponsors and FDA During Drug Development."

Training is also planned to communicate best practices outlined in the guidances.

Existing Meetings

Existing meetings by which FDA provides guidance, advice, and feedback to Sponsor's drug development programs include Type A, B, and C meetings.

Type A meetings are "critical path" meetings that are reserved for otherwise stalled drug development programs to enable the development program to proceed. Other Type A meetings include "post-action meetings requested within three months following an FDA regulatory action other than an approval." Refer to "Formal Meetings Between the FDA and Sponsors or Applicant of PDUFA Products" for a complete list of Type A meetings.

Type B meetings are pre-IND, End of Phase (EOP) 1, and EOP2/pre-phase three milestone meetings. Other Type B meetings include those occurring outside the context of a marketing application to discuss REMS or post-marketing requirements. Meetings other than Type A, B, D, or INTERACT are considered Type C.

CMC and Quality Enhancements

By: Margaret Studzinska, Associate Director, CMC and Nonclinical Writing and Nancy Hsu, Regulatory Affairs Associate

FDA establishes numerous enhancements in PDUFA VII to facilitate timely access to safe, effective, and innovative new medicines for patients, including:

- Product quality reviews;
- CMC readiness for products submitted under accelerated pathways;
- Advancing utilization of innovative manufacturing technologies;
- Performance goals for review of original manufacturing supplements.

Enhancing Product Quality Reviews

The primary focus of PDUFA VII is improving communications during drug development and application review.

FDA will utilize the "Four-Part Harmony" approach for CMC information request (IR) to promote an efficient and effective application review process and enhance communication between FDA and Sponsors at appropriate time points within the review cycle and product life cycle.

The Four-Part Harmony approach includes the four essential components of CMC IR, which will communicate the FDA's position on the following:

- Acknowledge **what** was provided and where;
- Identify **what** the issue or deficiency is;
- Identify **what** information is needed to achieve resolution and make a regulatory decision;
- Justify **why** it is needed to achieve resolution and make a regulatory decision.

FDA has further committed to update and conduct training on the CDER Manual of Policies & Procedures (MAPPs) and the CBER Standard Operating Procedures and Policies (SOPPs) on product quality IRs by the end of the fiscal year 2023 to promote FDA reviewers' use of Four-Part Harmony.

In addition, FDA will enhance communication related to pre-license and pre-approval inspections, which will help the sponsors with inspection readiness preparation.

Under PDUFA VII, FDA is targeting to communicate its intent to inspect a manufacturing facility for BLA pre-license inspections and NDA pre-approval inspections at least 60 days in advance and no later than the mid-review cycle. Although, per PDUFA VII, FDA maintains the right to inspect manufacturing facilities at any time during the review cycle.

Lastly, the COVID-19 public health emergency has

triggered a need for FDA to expand the use of alternative tools to assess facilities named in the application.

Based on recently gained experience, FDA will develop and issue guidance documents and policies discussing the best practices for using alternative tools, including:

- Requesting existing inspection reports from other trusted foreign regulatory partners
- Requesting information from applicants
- Requesting records and other information directly from facilities and other inspected entities
- Utilizing new or existing technology platforms to assess manufacturing facilities.

FDA is targeting September 30, 2023, to issue a draft guidance.

CMC Readiness for Products Submitted under Accelerated Pathways

As accelerated clinical development programs often face challenges in expediting and aligning CMC development activities, PDUFA VII outlines FDA goals to enhance CMC readiness for accelerated-track products.

FDA will develop a new MAPP on approaches to address challenges in expediting and aligning CMC development activities for CDER-regulated products with accelerated clinical development timelines.

The MAPP will describe FDA's early engagement with Sponsors, including science- and risk-based approaches, modern pharmaceutical principles, and modern regulatory tools detailed in ICH Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management.

Beginning in the fiscal year 2023, FDA will conduct a CMC Development and Readiness Pilot (CDRP) to accelerate the CMC development of products under an IND application.

Sponsors participating in the CDRP will benefit from two additional CMC-focused Type B meetings and other CMC-focused discussions based on readiness and defined CMC milestones.

By December 31, 2022, the FDA will publish a Federal Register Notice (FRN) announcing the pilot and outlining the eligibility criteria and process for submitting a request to participate.

FDA also announced that starting April 1, 2023, they will accept requests to participate in the CDRP program and select no more than nine proposals, with approximately two-thirds being CBER-regulated products and one-third CDER-regulated products.

The FDA will issue a new Federal Register notice to announce pilot programs for the three following fiscal years.

For more details, visit Federal Register :: Chemistry, Manufacturing, and Controls Development and Readiness Pilot Program; Program Announcement.

FDA will also conduct a public workshop by July 31, 2025, to focus on CMC aspects of expedited development (i.e., case studies, lessons learned, and stakeholder input on the CMC Development and Readiness Pilot) and create a strategy document on how to proceed with developing or revising other policies and on proposed time frames for the specific actions.

Advancing Utilization of Innovative Manufacturing Technologies

Another key PDUFA VII provision is the FDA's commitment to conduct a public workshop by the fiscal year 2025 to focus on utilizing innovative manufacturing technologies for CDER- and CBER-regulated products. The workshop will include best practices, lessons learned, case studies, barriers to adoption, and regulatory strategies for advanced manufacturing technologies.

Following the close of the public comment period for the public workshop, FDA will draft a strategy document.

Performance Goals for Review of Original Manufacturing Supplements

The performance goals for reviewing original manufacturing supplements set in PDUFA VII remain the same as previously outlined in PDUFA VI.

FDA targets to review or act on 90% of prior approval supplements (PAS) within four months of the receipt date and 90% of all other manufacturing supplements within six months of receipt.

Updates to Drug Safety

By: Aaron Pyle, Regulatory Affairs Associate and Dr. Amanda Beaster, Associate Director of Regulatory Strategy

Patient safety remains at the forefront of the FDA's intentions to continue/enhance existing programs and develop new programs under PDUFA VII.

Commitment to Enhanced Communication on Risk Management Activities During Review

Some of the planned enhancements under PDUFA VII, like the switch to standard approaches for the review of NME NDAs and original BLAs, may reveal a shift in focus for the FDA to managing and evaluating risk in the post-market setting.

In addition to indicating that REMS will be included in discussions at pre-submission meetings, FDA has indicated that risk management will be a focus of the mid-cycle communication. FDA notes that these will also be included as discussion topics for the FDA review team at the late-cycle meeting. The mid-cycle communication is an update from the Review Planning and Monitoring (RPM) meeting (generally within two weeks of the mid-cycle review meetings).

It will continue to summarize significant review issues and provide preliminary thoughts/rationale on the following:

- What additional studies may be required post-marketing, such as Post Market Requirements (PMRS) or Post Marketing Study Commitments (PMCs)
- The ability to provide sufficient risk information using adverse event (AE) reporting and FDA's Active Risk Identification and Analysis (ARIA) system under the Sentinel Initiative.
- Risk management and REMS

The earlier notification of the potential for additional work on the Sponsor's part will be very valuable for planning, circulating ideas and strategies, and getting approval before committing to the FDA. For example, knowing a PMR or PMC is likely required allows for more time for the Sponsor to begin planning these studies and having critical discussions about study design and feasibility.

The additional consistency and predictability around when this will be shared will also be helpful for both FDA and Sponsors. In the case of PMRs, depending on the status of an application's review, FDA is committing to communicating details of anticipated PMRs six (priority review) to eight (standard review) weeks before the PDUFA action date.

FDA has also built time frames and goals for responding to requests for post-approval review for release from existing PMRs.

ARIA and Sentinel

The FDA has also committed to drafting additional processes and procedures for ARIA sufficiency determination.

ARIA was mandated under the FDA Amendments Act (FDAAA) in 2007. It is intended to allow FDA to gain access to data from disparate sources and develop and validate methods to establish a system that links these together and analyzes the resulting safety data.

In 2008, the Sentinel Initiative Pilot was launched to conduct medical product safety surveillance, and the full system was officially released in 2016. The Sentinel structure, data sources, and databases have gained traction over time and are now mentioned extensively in the PDUFA VII goal letter.

Modernization and Improvement of REMS Assessments

In addition to targeted discussions of REMS during the planning stage, as mentioned above, PDUFA VII also indicates many actions the FDA will take to improve assessments of existing REMS.

The first is that assessment planning will be built into REMS by design. FDA plans to issue additional recommendations on this early in 2024. These should include additional identification of key metrics and recommendations for design, assessment, and data quality.

At the same time, the FDA plans to clarify REMS performance evaluation methods and determine if further modifications or revisions to the REMS assessment plan are needed. New guidance on the content and format of the REMS assessment report is also planned for 2026 - 2027.

Optimization of the Sentinel Initiative

As mentioned above, the Sentinel initiative will continue to expand and integrate into FDA drug safety activities under PDUFA VII. This will include communicating with Sponsors and the public, maintaining Sentinels' source data, transparency of study information via web presence, and maintaining the FDA Sentinel training program.

The FDA also has new initiatives which will be completed in the coming years. By the end of the fiscal year 2025, the FDA will publish an update concerning access to Sentinel's data via its website. In the same year, it will analyze and report how effectively Sentinel is being utilized for regulatory purposes. Then during the fiscal years of 2023-2027, there will be an update to the PDUFA Financial Report addressing its obligations for updated PDUFA VI commitments on the PDUFA VII Sentinel initiative.

The FDA will take two steps to advance the capabilities of Sentinel:

- Further exploring RWE for study effectiveness and product safety.
- Developing a robust post-marketing approach for assessing drug safety during pregnancy using electronic healthcare data and pregnancy registries.

Pregnancy Safety PMRs and PMCs

FDA adds pregnancy safety PMRs and PMCs at the time of marketing authorization to help inform the Pregnancy and Lactation Labeling Rule (PLLR) on the safety of use in pregnancy and to detect or evaluate safety signals.

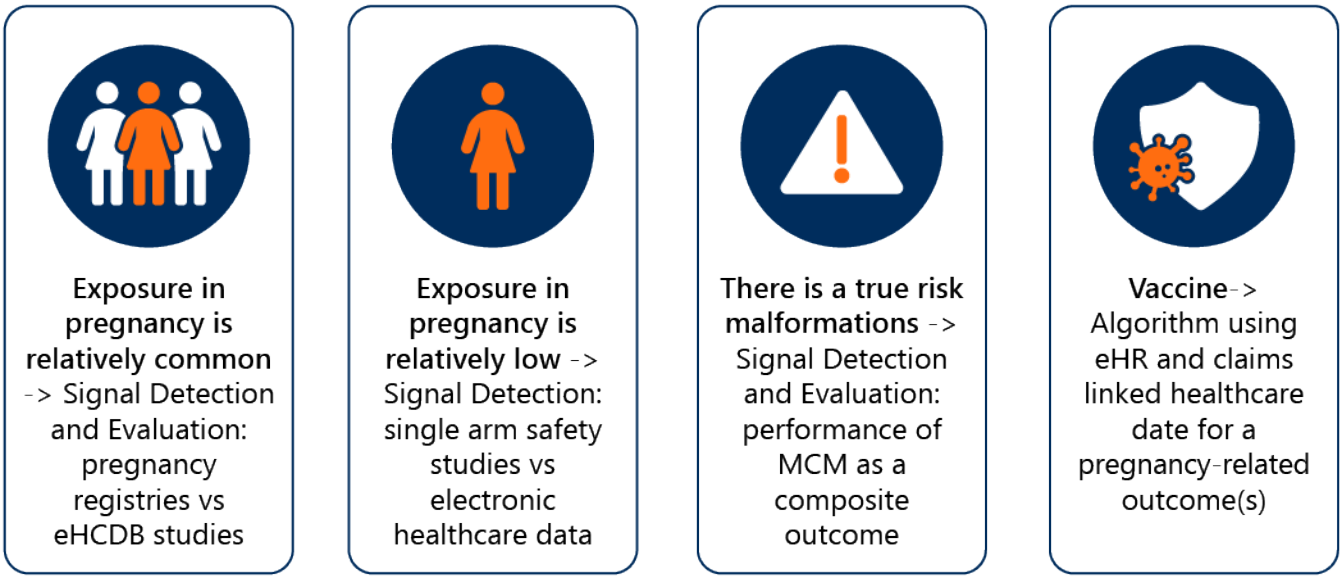
Under PDUFA VII, FDA intends to develop a framework to convey the optimal uses of data from different types of post-market pregnancy safety studies. This will incorporate data from different studies used in this context in the past and identify gaps in this data to be filled by "demonstration projects."

FDA plans to conduct five such demonstration projects to collect data on the performance characteristics of different study designs. The demonstration projects that FDA is currently planning (although they may be modified) are summarized in *Figure 1*.

The data from these demonstrations will be used to update the framework and create a process for pregnancy post-marketing studies (guidance, MAPP, or SOPP).

FDA will also review published literature and post-market pregnancy data that have been included in

Figure 1. Planned Demonstration Projects For Pregnancy Safety Framework



eHCDB= electronic healthcare database; eHR = electronic health record; MCM =major congenital malformations (MCM)
Note: pregnancy-related outcomes include spontaneous abortion, stillbirth, congenital malformations, etc.

pregnancy labeling. The framework will take into account the following:

- Purpose of study
- Types of post-market studies
- Anticipated exposure in females of reproductive potential (FRP) and pregnant women
- Potential toxicity of the drug and proposed risk mitigation
- Benefits of the drug
- Magnitude and type of risk to be detected.

In addition, this framework will specifically address the use of pregnancy registries as well as Sentinel and other sources of electronic healthcare data.

By late 2023, FDA intends to hold a workshop to help determine the ideal post-market study design(s) for collecting pregnancy safety information. It hopes that the framework will also allow for some decision tree that allows for some predictability in determining the likely necessity and type of pregnancy post-marketing studies to be required.

Exploring the use of Real-World Evidence in Regulatory Decision Making

By: Supriya Perambakam, Global Regulatory Affairs Manager

The PDUFA VII Commitment Letter builds on the programs supporting the use of Real-World Evidence (RWE) in regulatory decision-making begun under PDUFA VI. Specifically, the following initiatives incorporating RWE have been incorporated into PDUFA VII:

- Pilot Advancing RWE Program
- Use of RWE negative controls
- Use of RWE for capturing post-approval safety and efficacy data for cell and gene therapy (CGT) products

Pilot Advancing RWE Program

In a Federal Register notice released on October 20, 2022, the FDA has announced that it is committed to establishing an "Advancing RWE Program."

Per FDA, the purpose of this program is to "seek to improve the quality and acceptability of RWE-based approaches in support of new intended labeling claims, including approval of new indications of approved medical products or to satisfy post-approval study requirements."

Given the high cost and administrative burden of randomized clinical trials (the current standard for regulatory decision-making), this announcement has garnered much interest.

In the PDUFA Commitment letter, FDA commits to running this pilot intended to identify and characterize and build consistent RWE approaches that could potentially support labeling claims for the efficacy of the drug or that could be used to meet further study requirements implemented at the time of marketing approval, such as PMRs.

To do this, FDA intends to discuss study designs under consideration in public forums. These discussions will focus on data, design, and regulatory issues for studies that have the potential to generate RWE in support of a proposed regulatory decision.

FDA has committed to report "aggregate and anonymized information" on the RWE submissions at least annually starting in June of 2024, if not earlier.

Subsequently, a discussion will be held in a public forum to discuss RWE case studies, and the focus will be on RWE approaches to support regulatory decision-making.

Finally, RWE-related guidance documents will be updated or drafted to contain FDA recommendations built on the experience gained from this pilot.

Use of RWE Negative Controls

As part of PDUFA VII, FDA has committed to the optimization of the Sentinel Initiative and has stated that one of their goals is to build a methodology to allow for causal inference in Sentinel/BEST that may allow for product safety questions to be addressed and thus further advance FDA's understanding of using RWE for determining effectiveness.

First, the FDA is planning to hold a public workshop and then intends to kick off two projects to develop methods to automate the process and build negative controls. FDA plans to release a report of their findings in 2027.

CGT and RWE

FDA has also committed to continuing to work on novel approaches to development, specifically within the field of cell and gene therapy.

This innovative field has been at the forefront of ground-breaking approvals in recent years, including those for rare diseases, so, understandably, FDA will continue to develop its capabilities to make recommendations and understand the complexities unique to these programs.

Under this initiative, FDA has committed to convening a public meeting on complex CGT products by the end of the fiscal year 2024 and has indicated that the use of RWE and registries for capturing post-approval safety and efficacy data will be discussed. Updated or new guidance on this topic will subsequently be issued.

Clinical Trial Information System Updates: Cross-Functional Teams are Needed for Success

By: Swathi Pandhiti, Associate Director of Regulatory Operations

The Clinical Trials Information System (CTIS) is a single portal for European Union (EU) competent authority and ethics submissions for clinical trial applications (CTAs) across EU member states. The system represents the actualization of the EU Clinical Trials Regulation (CTR), which harmonizes the assessment and supervision of clinical trials in the EU.

Logistically, this fully integrated portal represents an advancement over previous attempts at coordinated reviews, such as the voluntary harmonization procedure (VHP). However, while the VHP was optional, allowing Sponsors to make filing decisions based on the clinical trial's scale across regions, using CTIS will soon be a mandatory requirement.

Starting in January of 2023, the older Clinical Trials Directive approach to filing will no longer be an option for new clinical trials. Many professionals experienced with CTAs will face an unfamiliar portal and workstream.

In addition to the technical and IT challenges inherent in setting up and establishing permissions and roles within a portal while juggling clinical trials startup activities, Sponsors must be forward-thinking in their preparations for the public accessibility of submission components uploaded to the portal.

Integrated working models involving close coordination between Regulatory Strategy, Regulatory Operations, Medical Writing, and Transparency will be critical in preventing delays and unanticipated consequences within the new system.

Embracing the Change

2023 will be a very important year for clinical trial applications submitted in European Union. Although the regulation went into effect on January 31, 2022, there has been a slow but steady uptick in the number of clinical trials submitted in CTIS. Sponsors must be on time, as all new clinical trials must be submitted in CTIS beginning January 31, 2023.

CTR is a harmonized dossier in a centralized system with standardized competitive timelines for all parties. It allows for a smoother work-sharing arrangement between Reporting Member State (RMS) and other concerned member states (MSCs), which culminates in a single decision for the trial. The process is fully electronic with a primary objective of increased transparency in the publication and sharing of clinical trial data and documents.

The first year of CTR implementation has been the year of learnings and adjustments for Sponsors and regulators such as National Competent Authorities (NCAs) and Ethics Committees (ECs). EMA continues to enhance and develop operations and IT for training and support with CTIS.

If you still need to prepare, you must develop robust processes, procedures, training, and documentation of

all CTIS-related activities within the organization.

Sponsors should deploy a team of experts from all functional lines to be part of their internal CTIS steering committee and update processes as they adjust to the regulatory, compliance, and transparent environment of CTIS and CTR.

The Dream Team

Integration between Regulatory, Medical Writing, and Transparency teams will be essential for clinical trial applications in CTIS.

While working or transitioning to new submission portals is not uncommon for regulatory teams, CTIS is a next-level portal with a broader purpose in actualizing the EU CTR, necessitating an all-hands-on-deck approach.

Attention to detail and documentation are necessary when setting up user access as there are 18 specified user roles in the system, each with different levels of editing, viewing, and submission accesses.

Experienced Regulatory Operations teams with strong knowledge of CTR and CTIS (preferably with hands-on experience with the CTIS Sandbox) are required to ensure proper naming conventions, version controls, and awareness of best practices for structured data and documents within CTIS fields.

Transparency Is Built into Every Step of CTR

With increased transparency comes higher consequences for mistakes. For example, accidentally uploading a quality document that is part of Request For Information (RFI) responses to incorrect sections could inadvertently lead to releasing commercially confidential information (CCI).

Anonymizing the data can be easier if clinical trial documents are authored with disclosure in mind.

Sponsors can prepare for this by:

- developing and implementing lead-authored templates
- avoiding the inclusion of personal and confidential data when possible (for example: cross-referencing to other sections/documents that are not subject to publication)
- using consistent Personal Protected Data (PPD) terminology
- early identification of CCI information that can be harmonized across all sections or documents

Communication and good process will be crucial to document handoffs from authoring to translation to anonymization (and vice-versa) and ultimately through submission in CTIS.

Communication and process continue after submission and will also be essential during the monitoring stages. With no automated notifications in CTIS, there is a need for additional resources to monitor system alerts, notices, RFIs, etc.

Functional teams must be brought together to develop a governance strategy to prevent delays or lapses in the application. During this time, regulators, sponsors, and CROs may continue to change processes, so it's time to roll up your sleeves, buckle up, and embrace the ride.

Understanding Regulatory Information Management System (RIMS): Risk Management Considerations for Sponsors

By: Swathi Pandhiti, Associate Director of Regulatory Operations, Nomakhwezi Mvumvu, Associate Manager of Regulatory Operations, and Vidyasagar Chowdary Vadde, Team Lead, Regulatory Operations

Regulatory Information Management System/ Software (RIMS) are centralized platforms designed to

support and streamline Regulatory Affairs teams and operations.

RIMS helps in the creation, organization, submission, and archival of regulatory information in regulated formats.

The process is designed to manage and store information in a traceable fashion to the specified local markets and ICH Guidelines pertinent to the registration and approval of a product. It enables end-to-end tracking, managing regulatory activities and objects, and archiving respective product dossiers or data for future use.

RIMS' existence dates back to the medicinal products regulations' inception. However, the standardization of the current processes that harmonize regulatory submission in different geographic areas was formulated by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) in collaboration with the FDA, the EMA, and other ICH members in the year 2000.

A common set of documentation known as the Common Technical Document (CTD) for approval submissions was then created to ease regulatory information complexities.

What Is the Role of RIMS in Regulatory Compliance?

Regulatory compliance is an ongoing process; thus, mismanagement of regulatory information can be detrimental to an organization's growth and innovation, derailing the product to market access and consequently implicating the organization's market share.

The traditional approach of multiple spreadsheets, disintegrated systems, and SharePoint, silo working teams and can no longer accommodate the dynamic and evolving global regulatory submission requirements.

Clinical trials and product registration regulations are becoming more complex; successful teams must be harmonized and have clear, transparent workflows and integrated systems to achieve compliance, positive regulatory audits, and successful product development.

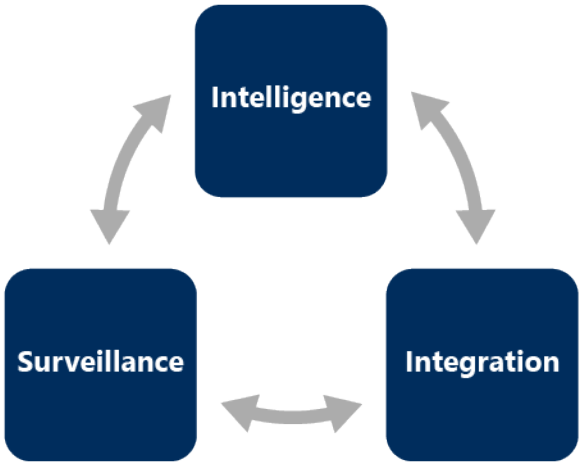
An information system that provides data integrity and continuity, plans, manages, tracks, and archives regulatory submissions and Health Authority (HA) correspondences, is the first step in managing the risk associated with evolving health authorities' laws.

Integration of RIMS with other systems, such as publishing tools, document management systems, quality management systems, etc., is of paramount importance.

Furthermore, regulatory affairs teams must adequately develop processes and best practices for data/document management to optimize the use of RIMS and reduce any potential business risks.

The Core Functions of RIMS

RIM core operations can be divided into three main functions:



Intelligence

1. Facilitates regulatory strategic planning, Authoring, Dossier Creation, Dispatch archiving, tracking of submissions, HA interactions
2. Product development analysis and global market access

Integration

1. Creation of wokflow to facilitate streamlined approach for cross functional teams
2. Interface with other business systems to provides transparency and a centralized approach

Surveillance

1. Generating and monitoring reports and dashboards
2. Safety reports, risk management, and mitigation process monitoring

Why Are Sponsors Required to Use RIMS?

Most organizations are multinational companies, and their data collation, processing, and organization can be tedious. A RIM system can tremendously impact all organizational functions by centralizing information, automating, and streamlining submission activities that can also be easily backtracked.

The below few points are observed for organizational support:

1. An efficient RIM system fast-tracks the product-to-market process for Sponsors, thereby providing a competitive edge.
2. Standardizes & simplifies lifecycle management of products or documents from clinical trials to post-market authorization ensuring regional regulatory requirements and laws are met.
3. Information is seamlessly tracked, approved, and archived, reducing silo working within an organization.
4. Streamlines global regulatory compliance.
5. Provides transparency during the auditing of a Sponsor's multinational regulatory activities and operations.

Outsourcing RIM Functional Deliverables

Some Sponsors need more resources or RA experts who can dedicate their time to follow and meet the requirements for RIMS within the given timelines or ongoing basis. Skilled professionals are needed to understand, manage, and control submission tracking and archival of health authority correspondences and commitments.

Leveraging a CRO with expertise in this space will ensure that a dedicated team is assigned to manage RIMS activities and supplemental support to their RA teams.

Some organizations just beginning to transition into a RIM system may need experts to advise on setting up processes, assist with non-compliance, and create an effective and efficient RIMS process right from the start. Organizations with comparatively huge portfolios can also look for external expertise within RIMS to continuously improve processes and pioneer themselves within industry trends.

Diversity Focus in 2023: PDUFA VII and Beyond

By: Dr. Amanda Beaster, Associate Director of Regulatory Strategy, Dr. Christine Clarke, Senior Global Regulatory Affairs Manager, Dr. Erin Booth, Associate Director of Regulatory and Medical Writing

Historically, Sponsors have struggled to generate sufficient data on the safety and efficacy of medical products within diverse racial and ethnic populations. This year (2022), FDA has held true to its promise to implement further actions to ensure greater diversity in clinical trials.

In April, FDA released its draft guidance titled, Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials. In addition, there is a brief but important mention in the PDUFA VII commitment letter, and FDA's Center for Devices and Radiological Health (CDRH) has also recently (October 21, 2022) issued a draft on Select Updates for the Breakthrough Devices Program Guidance: Reducing Disparities in Health and Health Care.

Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials

This guidance has garnered a lot of attention from the industry, but it joins several older recommendations

the FDA has issued to improve clinical trial diversity, including:

- FDASIA Section 907: Inclusion of Demographic Subgroups in Clinical Trials;
- Older guidances for the industry, such as the Action Plan to Enhance the Collection and Availability of Demographic Subgroup Data
- Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs (November 2020);
- Collection of Race and Ethnicity Data in Clinical Trials (October 2016);
- Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies (September 2017)

The focus of this new guidance is the Race and Ethnicity Diversity Plan, which provides information on when a race and ethnicity diversity plan is recommended, the timelines and process for submitting it, and the recommended content.

Diversity Plans are recommended for both drugs and devices, and FDA recommends that they are submitted to the IND or investigational device exemption (IDE) "as soon as practicable during drug development."

Per FDA, the overall emphasis of the Diversity Plan should be the enrollment of representative numbers of participants from underrepresented and diverse racial and ethnic populations early and throughout the medical product's development.

The expectations and details outlined in the guidance will give Sponsors greater clarity and confidence in developing and implementing diversity plans.

For Sponsors currently approaching Phase 3 development and planning marketing authorization applications, FDA feedback at the EOP2 meeting is critical to the design, planning, and implementation of their pivotal Phase 3 studies.

As Sponsors engage in EOP2 milestone meetings to discuss important EOP2 Plan-specific questions, FDA feedback will provide greater insight into the FDA's expectations on enrollment goals and action plans for enrolling and retaining diverse participants.

Discussions with the FDA will enable Sponsors to develop robust and realistic Plans, successfully execute them, and ultimately meet their diversity goals.

Diversity Plan Content and eCTD Submission

FDA has laid out several content recommendations, including five categories for content and the associated recommendations for scope. These five categories include:

1. Overview of the disease/condition
2. Scope of the development program
3. Goals for enrollment of underrepresented racial and ethnic participants
4. Specific action plan to enroll and retain diverse participants
5. The status of meeting enrollment goals (applicable for updates to initial plans)

For drug products, the initial Diversity Plan may be submitted to the IND as a stand-alone submission or as a part of a milestone meeting package (Module 1.6.2). FDA also specified that it should not be submitted any later than when feedback is being sought on pivotal trials, which is "often at the EOP2 meeting." Sponsors may obtain feedback on the Plan by including Plan-specific questions in the formal milestone meeting request. In addition, FDA advises that the Diversity Plan be included in Module 5 of the marketing application.

For devices, Sponsors are to submit their Diversity Plan as part of the IDE application's investigational Plan. Before submitting the Diversity Plan to the IDE, should a Sponsor wish to obtain FDA feedback, request a meeting, discuss clinical studies that are not conducted under an IDE, or their planned enrollment strategy with the FDA, then the FDA recommends that the Q-submission process be followed.

Diversity Plan Implementation Summaries and Periodic Updates

In addition to including the Diversity Plan in the marketing application for the medical product, Sponsors should include a description of the successes and challenges in implementing the Diversity Plan. These "implementation summaries" should contain clinical trial data and be included in Module 5.

FDA has clarified that reports of individual study data may be included in the study tagging file (STF) and

tagged as "demographic data" but still recommends consultation with the review division on placement.

Periodic updates should be made to the initial Diversity Plan, whenever applicable, and should emphasize and discuss the status of meeting the goals for diverse participant enrollment outlined in the initial Plan.

If a Sponsor, despite their best efforts, cannot achieve their planned enrollment goals during their study, FDA recommends that Sponsors provide justification and develop a plan for collecting these data during post-marketing studies.

The guidance does not indicate how the FDA plans to use the Sponsors' information submitted in the marketing application describing the successes and challenges encountered during the implementation of the Diversity Plan. It is hoped that FDA plans to share learnings from programs with successful enrollment across underserved populations.

Select Updates for the Breakthrough Devices Program Guidance: Reducing Disparities in Health and Health Care

CDRH also recently (October 21, 2022) issued a draft on Select Updates for the Breakthrough Devices Program Guidance: Reducing Disparities in Health and Health Care (i.e., an update to the much older Breakthrough Devices Program guidance [December 18, 2018]).

These updates to the Introduction and Section III of the original guidance aim to clarify how this program could be applied to devices that benefit populations impacted by "health or healthcare disparities." Some key changes further describe CDRH's intention to assign a designation to devices that meet the existing statutory criteria for designation and benefit populations impacted by health or healthcare disparities.

For the purposes of this guidance, the FDA has adopted the World Health Organization's definition of Health Equity as "the absence of unfair, avoidable, and remediable differences in health status among groups of people." It also acknowledges that such disparities exist in many dimensions, including race and ethnicity (as addressed in CDER's guidance), but also based on socioeconomic status, age, sex, disability status, sexual orientation, gender identity, language, and location, among others.

The guidance also distinguishes the line between "accessibility" (i.e., "an individual or group's capacity to benefit from a medical device or procedure") and "access" ("refers to commercial availability of a medical device following marketing authorization").

Through the release of this update, the FDA indicates its intention to consider technologies and device features that allow for improved accessibility when determining whether a device provides for "more effective" treatment or diagnosis.

In addition, FDA intends to publicly disclose Breakthrough Device Designation status once a designated Breakthrough Device obtains marketing authorization for the designated indication for use. This additional transparency could allow FDA to make statements about the approved device's potential for use in underserved populations.

PDUFA VII: Digital Health Technologies to Increase Diverse Patient Populations in Clinical Trials

Although not the focus of the commitment letter, the FDA intends to continue developing strategies to reach populations impacted by health or healthcare disparities. As part of their goal to enhance the use of digital health technologies (DHTs) to support drug development and review, FDA has committed to convene the first of a series of five public meetings or workshops with key stakeholders, including patients, biopharmaceutical companies, DHT companies, and academia to gather input into issues related to the use of DHTs in regulatory decision-making.

One of the objectives of the meetings and workshops will be to understand priorities for developing DHTs to support clinical trials, including the potential for DHTs to increase diverse patient populations in clinical trials.

Putting Words into Action

The code of federal regulations (21 CFR 312. 20) and ICH E5 describe the basic tenet of FDA market approvals—i.e., to ensure the validity of clinical trial results, clinical study populations must represent the populations for which the medical product is intended.

The FDA's adherence to these tenets, its commitment to the inclusion of underrepresented populations, and

patient equity in clinical trials are demonstrated in its guidelines and regulatory decisions.

FDA has noted a lack of diversity as part of their rationale in a recent decision not to authorize the marketing of a product developed solely in trials conducted outside of the US. FDA indicated that the trial population was not reflective of the racial and ethnic diversity of the US population—particularly that of underrepresented populations—and did not account for differences in intrinsic and extrinsic factors. As such, the study did not align with the FDA's commitment and initiative across the pharmaceutical industry for equitable representation of racially and ethnically diverse populations in clinical trials.

SENDing Successful Nonclinical Submissions through Validation, Review, and Beyond

By: Ben Kaspar, Director of Regulatory Affairs, Swathi Pandhiti, Associate Director of Regulatory Operations

This white paper continues the theme of preparation for 2023 by concluding with a quick refresher on a topic that we have received many questions about throughout the year: the CDISC Standard for the Exchange of Nonclinical Data (SEND) requirements for US INDs, NDAs, and BLAs.

These requirements, designed to improve the ease of nonclinical data review at the FDA, should be considered in the context of improved efficiency. In planning a study startup or filing an application for approval, time spent understanding SEND invariably saves time downstream and results in a more predictable submission.

The relevant study start date cutoffs and expectations for specific study types requiring SEND datasets differ by center and application type, as shown in *Table 1*.

While both CBER and the CDER strongly encourage IND Sponsors and NDA applicants to consider implementing and using these study data standards as early as possible in the product development life cycle, SEND data is currently only required for nonclinical reports filed to CDER. Depending on the study start date, Sponsors may be required to submit a simplified Trial Summary (TS) file, full TS file, or full SEND datasets. TS files contain information about each study used by the eCTD validator to determine if SEND data is needed. Thus, some form of TS file is, at minimum, required for all eCTD submissions to CDER shown below.

Sponsors filing applications to CDER can check their study type against the study start date to determine which files are required and whether failure to include a simplified TS file, full TS file, or full SEND data will result in a technical rejection.

A submission that receives a technical rejection fails eCTD validation. Thus, rejection occurs before the submission goes through the gateway, a potentially costly error for which there may be limited recourse beyond adding the appropriate file to the submission.

Sponsors with plans to submit NDAs, BLAs, and Abbreviated New Drug Applications (ANDA) to CDER should note that the study start date requirements for submitting SEND data to these applications are generally a year earlier than the IND requirements. Thus, it is possible Sponsors would have to file SEND to an NDA/BLA/NDA even if not required for the IND.

To ensure sufficient preparation time, Sponsors of biologics should note that requirements for CBER, which will go into effect for single-dose toxicology, repeat-dose toxicology, and carcinogenicity studies, started after March 15, 2023. Therefore, understanding the requirements will be essential to avoid rejection for INDs starting as early as the second quarter of 2023.

Sponsors should also note that SEND datasets are

typically required for both interim and final reports. It's important to consider the overarching rationale for SEND: to increase the efficiency with which nonclinical data required for specific regulatory decisions can be evaluated. Consistent with this objective, the SEND data should be filed concurrently with the decision that is being made.

Because these rules are relatively new and variable, it is recommended that Sponsors use a Study Data Standardization Plan (SDSP) during development to communicate the intent to submit SEND datasets or to explain further the intended use of simplified or full TS files.

For INDs, an SDSP should be submitted in the General Investigational Plan of the Initial IND. For NDAs and BLAs, an SDSP should be provided with pre-NDA and pre-BLA meetings (appended to BD or cross-referenced).

Table 1. SEND Data Requirements for CDER and CBER

Center	Application	Study Type & Location	Study Start Date	Expectation	SEND Implementation Guide	Status	Rejection Criteria
CDER	NDA, BLA, ANDA	single-dose toxicology (4.2.3.1), repeat-dose toxicology (4.2.3.2), and carcinogenicity studies (4.2.3.4)	On or prior to 2016-12-17	Submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)	NA	Requirement	Applied
CDER	IND	single-dose toxicology (4.2.3.1), repeat-dose toxicology (4.2.3.2), and carcinogenicity studies (4.2.3.4)	On or prior to 2017-12-17	Submit a simplified TS whether or not the study contains an xpt dataset (other than the ts.xpt)	NA	Requirement	Applied
CDER	NDA, BLA, ANDA	single-dose toxicology (4.2.3.1), repeat-dose toxicology (4.2.3.2), and carcinogenicity studies (4.2.3.4)	After December 17, 2016	Submit a Full TS	SENDIG v3.0	Requirement	Applied
CDER	IND	single-dose toxicology (4.2.3.1), repeat-dose toxicology (4.2.3.2), and carcinogenicity studies (4.2.3.4)	After December 17, 2017	Submit a Full TS	SENDIG v3.0	Requirement	Applied
CDER	NDA, BLA, ANDA	single-dose toxicology (4.2.3.1), repeat-dose toxicology (4.2.3.2), and carcinogenicity studies (4.2.3.4)	After March 15, 2019	SEND (Full ts.xpt)	SENDIG v3.1	Requirement	Applied
CDER	IND	single-dose toxicology (4.2.3.1), repeat-dose toxicology (4.2.3.2), and carcinogenicity studies (4.2.3.4)	After March 15, 2020	SEND (Full ts.xpt)	SENDIG v3.1	Requirement	Applied
CDER	NDA, BLA, ANDA	Cardiovascular and Respiratory Safety Pharmacology Studies (4.2.1.3)	After March 15, 2019	SEND (Full ts.xpt)	SENDIG v3.1	Requirement	Not Applied
CDER	IND	Cardiovascular and Respiratory Safety Pharmacology Studies (4.2.1.3)	After March 15, 2020	SEND (Full ts.xpt)	SENDIG v3.1	Requirement	Not Applied

Center	Application	Study Type & Location	Study Start Date	Expectation	SEND Implementation Guide	Status	Rejection Criteria
CDER	NDA, BLA, ANDA	Animal Rule Natural History and Efficacy Studies (4.2.1.1)	After March 15, 2022	SEND (Full ts.xpt)	SENDIG AR v1.0	Requirement	Not Applied
CDER	IND	Animal Rule Natural History and Efficacy Studies (4.2.1.1)	On or prior to 2017-12-17	SEND (Full ts.xpt)	SENDIG AR v1.0	Future Requirement	Not Applied
CBER	NDA, BLA, ANDA	single-dose toxicology (4.2.3.1), repeat-dose toxicology (4.2.3.2), and carcinogenicity studies (4.2.3.4)	After March 15, 2023	SEND (Full ts.xpt)	SENDIG v3.0	Future Requirement	Applied
CBER	IND	single-dose toxicology (4.2.3.1), repeat-dose toxicology (4.2.3.2), and carcinogenicity studies (4.2.3.4)	After March 15, 2023	SEND (Full ts.xpt)	SENDIG v3.0	Future Requirement	Applied

Additional Resources:

- Study Data Technical Conformance Guide (Oct 2021): Technical Specifications Document (fda.gov)
- Study Data Standards Resources | FDA
- Providing Regulatory Submissions in Electronic Format – Standardized Study Data Guidance for Industry (fda.gov)
- Creating Simplified TS.XPT Files
  - Technical specifications document (fda.gov)
  - Creating a simplified ts.xpt using R

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