POLICY AND PROCEDURES

Office of Clinical Pharmacology

OCP Prioritization, Triage, and Review Process for INDs and Pre-INDs

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PURPOSE

This Manual of Policies and Procedures (MAPP) provides review staff within the Office of Clinical Pharmacology (OCP) with good review management principles and practices for submissions during the investigational new drug application (IND) phase of drug development, promotes excellence in scientific reviews, and provides a consistent approach to the conduct of the IND review process in conjunction with the policies of the Office of New Drugs (OND) and other stakeholders within the Center for Drug Evaluation and Research (CDER).

The scope of this MAPP is OCP's policy and procedures for:

- Prioritization of IND submissions for review
- Conduct of a consistent and high-quality review
- Documentation of review findings (clear, concise, and transparent decision making)

BACKGROUND

The IND phase of drug development spans the time from submission of an initial IND-related request, including a pre-IND meeting request or an original IND, to the

submission of a marketing application. It may extend beyond initial approval or licensure to include additional trials relevant to the drug's development and labeling. There are several relevant regulations, MAPPs, and guidance documents that address procedures for submitting an IND, types of submissions, review timelines, and responsibilities of CDER staff that can be viewed at: https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application.

FDA has a critical role in increasing the efficiency of the drug development process by improving the quality of drug development during the IND phase. From this perspective, OCP can enhance drug development from initial planning of clinical trials to regulatory action by actively documenting and implementing good review practices (GRPs). The fundamental values for all GRPs are: Priority, Quality, Clarity, Transparency, Consistency, and Efficiency.[1]

From an OCP standpoint, the expectations for the fundamental values of GRPs can be defined as follows:

- **Priority**: Prioritization of submissions is based on the expected value added to the development program by OCP. The order of priority reflects OCP prioritization and is complementary to existing Agency prioritization and practices in a specific therapeutic area.

- **Quality**: The clinical pharmacology review of IND submission documents OCP review findings, feedback, and rationale on specific scientific and/or regulatory questions raised by the sponsor and aspects that could impact the design and conduct of future studies or the development program. OCP provides scientifically rigorous advice and recommendations on fulfilling regulatory requirements when necessary, even in the absence of a specific question from the sponsor.

- **Clarity**: Review conclusions, recommendations, and responses to sponsor's questions provided by OCP are substantiated by a clearly articulated rationale. The rationale should be clearly specified in the review document and take into account current developments in science, guidance documents, and/or regulations.

[1] See the FDA guidance for industry and review staff entitled *Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications* for more information. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm. When final, this guidance will represent the Agency's current thinking on this topic.

- **Transparency**: OCP's views and recommendations are shared internally and with sponsors in a timely manner. Any changes to OCP's advice and recommendations based on these interactions should be documented and archived in accordance with CDER's records management policies.

- **Consistency**: OCP strives for consistent advice on similar issues. As the science of clinical pharmacology evolves, standard practices could be modified accordingly, and new precedents established. The review document captures the scientific and regulatory basis and rationale for this evolution.

- **Efficiency**: Efficient review is achieved by standardizing the approach for prioritization of submissions, depth of review, as well as the practices for documenting the review process and conclusions. Efficient review process and documentation are achieved by use of standardized approaches/templates that are appropriate for the type of the submission and the therapeutic area.

POLICY

The following are considered high-priority submissions for OCP, and the consistent review and documentation practices outlined in this MAPP should be followed across all OCP review divisions:

- Meeting packages with clinical pharmacology issues (e.g., dose-finding and optimization, drug-drug interactions, specific populations, bioavailability/bioequivalence issues, clinical trial design elements related to clinical pharmacology, such as endpoints, inclusion/exclusion criteria, and pharmacokinetic sampling).

- Original INDs as appropriate and consistent with an individual Division's practices (both commercial and research).

- Special Protocol Assessments.

- High-priority clinical pharmacology protocols (i.e., protocols that require specific clinical pharmacology input). These include dose-finding, pivotal relative bioavailability, pediatric protocols, protocols associated with postmarketing requirements/postmarketing commitments with a clinical pharmacology focus or components, Animal Rule protocols and any other protocol deemed appropriate by the Division's leadership and in line with the Division's practices.

Depending on how drug development proceeds in different disease areas, the types of submissions may vary; however, the fundamental values of OCP-GRPs as described in the previous section should be maintained.

RESPONSIBILITIES

The Director of OCP or designee will:

- Coordinate with CDER's OND and other stakeholders within CDER to determine and develop policies, responsibilities, and procedures described in this MAPP and ensure appropriate implementation.

- Ensure that OCP's scientific review management and staff understand the policies, responsibilities, and procedures described in this MAPP.

- Ensure that this MAPP is reviewed periodically and updated as necessary to reflect current policies and operating procedures.

OCP Division and Staff Management will:

- Implement this MAPP at the Division and Staff level.

- Coordinate with OND and OCP Management when needed to facilitate the implementation of this MAPP.

- Guide and train team leaders and reviewers on the triage and prioritization process for IND submissions within the division or group. This includes identifying high priority clinical pharmacology situations that warrant a stand-alone documentation of the clinical pharmacology team's recommendation and rationale irrespective of expectations set by other related CDER/OCP guidance or MAPPs.

OCP Team Leaders will:

- Implement this MAPP within their team by ensuring that OCP reviewers are familiar with and comply with this MAPP.

- Train reviewers to provide input on drug development plans and specific study protocols using the concept of added value.

- Brief reviewers on the OCP IND prioritization, triage, and review process described in this MAPP.

- Monitor pre-IND and IND submissions to ensure appropriate assignment and timely referral of IND submissions to OCP staff and consult with their OCP Division Director as appropriate.

- Conduct secondary reviews of primary IND submission reviews and clear/sign those reviews in CDER's IT System of Record as appropriate.

- Monitor the OCP process described in this MAPP and evaluate it for continued improvement.

- Identify and recommend to Division Management and reviewers the best review practices and ways to further improve OCP's review processes during the IND phase to ensure reaching OCP's goals of documenting and implementing GRPs.

OCP Reviewers will:

- Become familiar with this MAPP, follow the recommendations and training given by the team leader, and carry out the policies and procedures of the process.

- Conduct scientific and regulatory reviews and provide input into the sponsor's development of an integrated plan to obtain efficiently derived clinical pharmacology data.

- Focus attention on priority IND submissions as described in this MAPP and overall development plans based on added value criteria.

- Identify and communicate to team leaders ways to improve our processes to make application review and drug development more complete with respect to clinical pharmacology information.

- Document primary IND submission reviews in CDER's IT System of Record.

OCP Project Managers will:

- Evaluate the process for improvements as needed and facilitate the implementation of any improvements.

PROCEDURES

1. The assigned OCP team leader(s) and reviewer(s) will determine the level of documentation of the clinical pharmacology review for the IND submission based on submission type, priority ranking, therapeutic area considerations, and workload. This determination is based on the priorities and practices outlined by the Division/Staff management. The OCP review team will use the most efficient and effective method available to communicate recommendations and comments to the multi-disciplinary review team and sponsors when completing IND reviews. In general, OCP's review documentation provides the rationale behind the decisions supporting recommendations and comments from a clinical pharmacology perspective. Archiving past decisions to ensure continuity (e.g., as people leave, cross-team assignment) and to maintain consistency in recommendations is also an essential function of review documentation. Examples of review documentation include full reviews, abbreviated reviews, memos to file, meeting minutes, and no action indicated (NAI).

   Regardless of level and format, IND review documentation should: 1) be issue-driven; 2) be concise and informative; 3) integrate review findings of general clinical pharmacology, pharmacometrics, genomics, translational and precision medicine, and applied regulatory science, as appropriate; and 4) provide the rationale in support of recommendations.

2. As the IND review process continues to evolve at CDER, other review templates not listed in this document could become available. Staff are advised to consult all relevant available templates at the time of finalization of their review. Current templates can be found at: https://fda.sharepoint.com/sites/CDER-OND-SpecialPrograms/IND%20Protocols%20and%20Amendments/SitePages/Home.aspx.

In general, a full review should be conducted for the high priority submissions listed above (i.e., meeting packages with clinical pharmacology issues, original INDs, Special Protocol Assessments, and high-priority clinical pharmacology protocols).

For Original INDs, refer to options (e.g., No Action Intended (NAI)), timelines, and expectations of the integrated review template specified within CDER's IT System of Record with flexibility to attach a clinical pharmacology review template. The need for a full review of original research INDs is determined based on specific therapeutic area practices and the unique clinical pharmacology focus of the submission (e.g., pediatric protocols).

For IND meeting packages, *FDA-Issued Meeting Preliminary Comments* should clearly and succinctly document the clinical pharmacology rationale for responses, and *FDA-issued Meeting Minutes* should capture discussions around clinical pharmacology responses. In some cases, an IND meeting package may warrant a separate review (e.g., if a complete documentation of the clinical pharmacology rationale for responses is not included in the *FDA-Issued Meeting Preliminary Comments*).

OCP reviews for study reports submitted to FDA during the IND phase should only be performed if results of the study are deemed to inform future trial designs (e.g., food effect); otherwise, study reports should be NAI with a review performed after submission of the New Drug Application/Biologics License Application (NDA/BLA).

USEFUL LINKS

- CDER NEXUS: https://cdernexus.fda.gov/
- CDER NEXUS Resources: https://fda.sharepoint.com/sites/CDER-Cross-Office/SitePages/CDER-NEXUS-Resources.aspx#access-cder-nexus-here-https-cdernexus.fda.gov
- Review Templates: https://fda.sharepoint.com/sites/CDER-OND-SpecialPrograms/IND%20Protocols%20and%20Amendments/SitePages/Home.aspx

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
5/26/2006	N/A	Initial
4/3/2023	1	• Removed 'MAPP' from title

		• Added clarity on defining the expectations for the fundamental values of GRPs • Removed redundant prioritization sentence under Policy • Clarity on OCP goals under OCP Team Leader • Revised references to internal record management archiving to a general/broader language • Spelled out NDA and BLA