POLICY AND PROCEDURES

OFFICE OF CLINICAL PHARMACOLOGY

Good Review Practices: Clinical Pharmacology Review of New Molecular Entity (NME) New Drug Applications (NDAs) and Original Biologics License Applications (BLAs)

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PURPOSE

- This MAPP and its attachments establish good review practices (GRPs) for Office of Clinical Pharmacology (OCP) reviews of NME NDAs and original BLAs.

- This MAPP is one in a series of MAPPs designed to document GRPs for review staff in accordance with MAPP 6025.1 *Good Review Practices*.

BACKGROUND

Clinical pharmacology is a multidisciplinary science. OCP reviews of NME NDAs and original BLAs are, therefore, expected to synthesize information from all relevant clinical pharmacology knowledge areas including *drug disposition*, *pharmacology and biomarkers*, *quantitative methods*, *drug safety*, *pharmacotherapy*, and *clinical trial methods* to inform regulatory decisions (e.g., approvability, labeling, post-approval requirements, and product lifecycle management).

The OCP review is issue-driven and assesses information in the applicant's[1] submission along with previously established knowledge to address issues of dose selection and optimization, therapeutic individualization, and benefit/risk balance (typically in subpopulations). The review also identifies any critical gaps in the understanding of conditions for optimal therapeutic use, and recommends studies that can practically address those gaps. OCP recommendations are guided by established and evolving regulatory policies and practices.

This MAPP contains:

(1) Guiding principles for performing OCP integrated reviews (Attachment 1).

(2) The general outline (Attachment 2) and specific template (Attachment 3) for integrated OCP reviews showing sections that should be included, order of content, and instructions.

(3) A guide for labeling issue identification (Attachment 4).

(4) A clinical pharmacology and pharmacokinetic (PK) summary table (Attachment 5).

POLICY

- The OCP review template in this MAPP is a guide to be used by all OCP reviewers to evaluate and document reviews of all NME NDAs and original BLAs. Use of this template is not required for non-NME submissions.

- Reviews should be issue-driven, and the template may be modified as needed to address specific issues in the review of a given application.

- Important findings and recommended regulatory actions must be clearly communicated in reviews.

[1] For the purpose of this MAPP, the term "applicant" includes any applicant or sponsor who has submitted an NDA or BLA for review.

- Reviews should be of sufficient length to support OCP-recommended regulatory actions.

- Conventions of the CDER Style Guide (Ref 1) are to be followed in completing the OCP review; coherent and concise writing is expected for all reviews.

- Elements from the review template may be used for non-NME NDA/BLA reviews, NDA/BLA amendments in response to an action letter, and labeling or efficacy supplements, as appropriate.

RESPONSIBILITIES

- All Review Team Members must meaningfully participate in the work represented in the review to take public responsibility for and sign off on the final version of the review (e.g., in the CDER review archival system). A review team must include an OCP Division/Unit Director or Deputy Director as a final signatory. Review Team Members must have participated in all of the following three ways to be listed as signatories:

  - Contributed to the conception and/or design of the review questions, approach to addressing the review questions, and/or analysis and interpretation of the data

  - Drafted the review or critically revised it for important content

  - Approved the final version of the review to be entered into the regulatory record (e.g., via the CDER review archival system)

  All members of the OCP review team should work collaboratively and are jointly responsible for the stated OCP positions and recommendations.

- Primary Reviewers are responsible for assessing information in the submission, analyzing and interpreting data, and completing individual study report reviews or integrated summaries of individual study reviews. The Primary Reviewers are primarily responsible for authoring the information contained in Section 4 of the integrated clinical pharmacology review. They interact and communicate with other review team members within and outside of OCP throughout the review process to comprehensively and collaboratively address review issues.

- The Lead Author is responsible for integrating information from primary reviews and authoring the majority of the OCP review (e.g., Sections 1-3) with input from other OCP Review Team Members. He/she is usually the main OCP representative attending multidisciplinary review team meetings.

- The Team Lead and Secondary Reviewers provide scientific and regulatory input to Primary Reviewers, ensure appropriate discussion of key review issues, manage review quality, and interact and communicate with relevant parties within and outside of OCP. The OCP review team should appoint one Team Lead for the application to be responsible for oversight of the integrated review process in terms of assuring overall quality and consistency. Team Lead and Secondary Reviewers are also responsible for assuring that the summary of OCP's findings and regulatory recommendations are comprehensive and clear.

- The Division/Unit Director or Deputy Director is the final review signatory and is responsible for communicating the official OCP position on review issues (e.g., approvability, dosing, labeling, post-approval requirements) and ensuring that OCP positions are clearly stated in the review. He/she is responsible for ensuring reviews are comprehensive and clearly written. He/she promotes consistency in the review, ensures transparency in the decision-making process, and guides review teams on complicated or precedent-setting review issues that may have policy implications. He/she interacts with OCP senior management, the OCP Director, and other Center staff on timely issue identification and resolution as needed.

  The signatory Division or Unit Director also adjudicates and reconciles differences in opinions, if any, among reviewers before finalizing the OCP review.

  A separate Division Director's memo should generally be written when: (1) major disagreements occur within the OCP review team; (2) the Division Director does not agree with the final recommendations of the review team; (3) OCP is taking a precedential or controversial review position; or, (4) the complexity of the review issues necessitates further written communication.

- The Office Director or designee may write an Office Director's memo on highly controversial and/or precedent-setting issues to provide an independent assessment and recommendation. He/she may adjudicate and reconcile differences in opinions among reviewers and Division/Unit Directors when disagreements cannot be resolved at the Divisional level.

PROCEDURES

1. Reviewers in OCP will use the attached review template as a guide when documenting their reviews. The template is annotated to provide additional explanations of the content for each heading and subheading.

2. Prior to writing reviews, appropriate review planning should occur in accordance with CDER MAPP 5100.5, titled "An Integrated Genomics, Pharmacometrics, and Clinical Pharmacology Review Process" (Ref 2) and the OCP Internal

Quality Procedure (IQP) 2002, titled "Office of Clinical Pharmacology Scoping Meeting: Policies and Procedures" (Ref 3).

REFERENCES

1. CDER Style Guide-Style and Formatting for CDER Documents, http://inside.fda.gov:9003/downloads/programsinitiatives/drugs/documentpreparationandclearance/ucm039859.pdf.

2. CDER MAPP 5100.5 An Integrated Genomics, Pharmacometrics, and Clinical Pharmacology Review Process 6/16/2010.

3. CDER OCP Intranet, http://inside.fda.gov:9003/CDER/OfficeofTranslationalSciences/OfficeofClinicalPharmacology/ucm355932.htm.

EFFECTIVE DATE

This MAPP is effective upon date of publication.

CHANGE CONTROL TABLE

Effective Date	Revision Number	Revisions
09/23/2016	N/A	
1/30/23	Rev. 1	Revised to be in alignment the integrated review processes described in MAPP 5100.5. Specifies the template is required for NME NDAs or original BLAs. For other NDA or BLA applications, use of the template is optional. Clarified staff responsibilities. Section 3 of the previous review template, "Detailed Labeling Recommendations", is removed. High-level labeling recommendations are included in Section 2.4. Review structure is now arranged in four sections:1 – Executive Summary; 2 – Summary of Clinical Pharmacology Assessment; 3 – Comprehensive Clinical Pharmacology Review; 4 – Appendices.
2/7/25	N/A	Administrative edit to ensure compliance with EO 14161.

ATTACHMENT 1

OCP NME NDA AND ORIGINAL BLA INTEGRATED REVIEW: GUIDING PRINCIPLES

The integrated clinical pharmacology review is based on five principles:

(1) The review should lead the reader logically through the thought process used in identifying and addressing scientific, clinical, and regulatory questions and issues.

(2) Key review highlights and conclusions should consider and support the needs of other members of the CDER review team who are not clinical pharmacologists.

(3) Reviews should be issue-driven, and staff should focus on important issues and good management of the review process to maximize efficiency.

(4) Reviewers should utilize the most contemporary scientific and regulatory knowledge to assure the highest quality reviews.

(5) Review recommendations and decisions should be clinically relevant, pragmatic, and placed in the specific therapeutic context (e.g., nature of disease, size of population, unmet medical need, and available treatments). A risk-based approach that utilizes the totality of evidence is desirable.

The purpose of the review template (Attachment 3) is to consistently ensure that critical information is presented by OCP review teams in a prioritized, issue-driven, and logical manner. The template also provides standardization and consistency in the format and content of clinical pharmacology reviews and ensures that critical presentations and analyses will not be inadvertently omitted. The standardized structure also enables readers to readily locate specific information. As such, headings and subheadings should be named, numbered, and ordered as stipulated in the template unless there is a compelling reason not to for a specific application.

The template may be modified by OCP review teams if deemed necessary to ensure clarity and cohesion for a given application; this, however, is expected to be a rare occurrence.

Information should generally not be repeated within the review. Reviewers may refer the reader to relevant sections and use hypertext links wherever necessary. Text, tables, and figures may be used to summarize information, but there should not be redundancy in the information presented. The approach that best ensures clarity and understanding should be used. Proper attribution regarding data sources and analyses is expected. Reviews should be clear as to which assertions, conclusions, and recommendations are those of the applicant and those of the review team. Coherent and concise writing is expected for all draft and final reviews.

ATTACHMENT 2

OVERVIEW OF OCP INTEGRATED REVIEW STRUCTURE

The OCP integrated review consists of four sections. An overview of these four sections with description of their intended targeted audiences is provided in **Table 1**.

- **Section 1. Executive Summary**: Summarizes OCP's position and final recommendations on key regulatory actions (e.g., approvability, dosing, labeling, need for PMR/PMC).

- **Section 2. Summary of Clinical Pharmacology Assessment**: Summarizes major clinical pharmacology information and analyses used to address issue-specific review questions.

- **Section 3. Comprehensive Clinical Pharmacology Review**: Contains more detailed information and explains the thought process for clinical pharmacology questions that are relevant to the application.

- **Section 4. Appendices**: Includes individual study report reviews or integrated summary of individual study reviews, and/or analyses on various clinical pharmacology areas that inform key regulatory actions.

All four sections will be entered in the CDER review archival system as a complete clinical pharmacology review.

Table 1. Overall Structure and Intended Audience for Integrated Clinical Pharmacology Reviews

OCP Integrated Review Section	Targeted Audience
Section 1 - Executive Summary	OCP, OND, and CDER Senior Leadership
Section 2 - Summary of Clinical Pharmacology Assessment	OCP, OND, and CDER Senior Leadership
Section 3 - Comprehensive Clinical Pharmacology Review	OCP staff and multidisciplinary review team members
Section 4 – Appendices	OCP staff, multidisciplinary review team members, and regulatory scientists

ATTACHMENT 3

OCP INTEGRATED REVIEW TEMPLATE

Office of Clinical Pharmacology Review	
NDA or BLA Number	
Link to EDR	
Submission Date	
Submission Type	*[Indicate priority or standard review]*
Brand Name	
Generic Name	
Dosage Form and Strength	
Route of Administration	
Proposed Dosing	
Proposed Indication	
Applicant	
Associated INDs	*[INDs associated with EOP2, Pre-NDA, and/or Pediatric Study Plan]*
OCP Review Team	*[List lead author first]*
OCP Final Signatory	*[Include name and title]*

Table of Contents

3.3.1. To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

3.3.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

3.3.3. Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

3.3.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

4 Appendices

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1. Executive Summary

Very briefly highlight the drug development program, intended place in therapy, or other relevant orienting information. Note any novel, precedential, or controversial issues and how they were addressed. Highlight major review issues addressed, and provide OCP review team's positions/recommendations.

1.1. Recommendations

- Explicitly state OCP's position on approvability and the following key issues as appropriate: adequacy of dosing information, adequacy of risk management (if necessary), and adequacy of labeling and health communication.

- The OCP review team should recommend a complete response (CR) if there are major clinical pharmacology deficiencies that preclude safe and effective use and cannot be addressed by labeling, risk management options beyond labeling, or by conducting postmarketing requirements (PMRs).

- Use the table below to summarize OCP's recommendations and comments on key review issues.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness[†]	
General dosing instructions	
Dosing in patient subgroups (intrinsic and extrinsic factors)	
Labeling	

Bridge between the to-be-marketed and clinical trial formulations	
Other (specify)	

† See Section 3.3.1 of the MAPP.

1.2. Post-Marketing Requirements and Commitments

If there is no PMR or PMC, state that in this section.

Otherwise, describe the need for requested PMRs and PMCs. Describe the issues to be addressed, the justification for the PMR and/or PMC, and the experimental/methodological approaches recommended using the table below (repeat rows as needed). If a definitive title for the PMR/PMC is finalized at the time of the review, then it may be appropriate to include the study title as part of this section.

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
☐ PMC ☐ PMR			

2. Summary of Clinical Pharmacology Assessment

This section provides an integrated synopsis of the major clinical pharmacology issues dealt with in the course of a typical OCP review of an NME NDA or original BLA. Only topline information should be presented in this section. Additional details are expected to be included in Section 3, "Comprehensive Clinical Pharmacology Review."

The information in this Section should be organized into Subsections 2.1-2.4 to address the following topics:

- Brief description of findings and conclusions in support of OCP recommendations
- Appropriateness of proposed dosing for the indication sought
- Appropriateness of dose and/or treatment in relevant patient subsets (e.g., molecularly-defined, segmented by degrees of organ impairment, etc.)
- Presence or likelihood of clinically significant food-drug or drug-drug interactions (DDIs) and their clinical management strategies

- Other clinical pharmacology issues germane to the optimal use of the drug in populations or individuals

- Areas of uncertainty in the review (e.g., where assumptions were critical in filling information gaps)

- Important omissions from the application

- High-level labeling recommendations

Subsections 2.1-2.4 are described below:

2.1 Pharmacology and Clinical Pharmacokinetics

Provide topline information on the pharmacologic and PK (e.g., absorption, distribution, metabolism and excretion (ADME)) properties of the drug.

No detailed description is necessary for clinical PK studies (e.g., single and multiple ascending doses, specific populations, drug interactions, relative bioavailability, and other studies).

2.2 Dosing and Therapeutic Individualization

2.2.1 General Dosing

Summarize the assessment and final recommended dosing guidelines for the general patient population for which the indication is being sought.

2.2.2 Therapeutic Individualization

Summarize the assessment and final recommendations on the dosing regimen(s) and/or the appropriateness of treatment in relevant patient subsets based on various intrinsic (e.g., organ impairment, genotype) or extrinsic (e.g., food, drug interactions) factors.

2.3 Outstanding Issues

Describe areas of uncertainty in the review and important omissions from the application. Describe high-level recommendations on preferred approaches to resolving these outstanding issues (e.g., PMR/PMC). Also note if the submission did not adequately address important biopharmaceutics and bioanalytical issues. State "None" if there are no outstanding issues.

2.4 Summary of Labeling Recommendations

Describe labeling recommendations at a high level, including areas of concurrence/disagreement. The information should be captured in a narrative description

of the labeling issues. Inclusion of extensive red line/strike outs of the applicant's proposed labeling in this section is not appropriate. Attachment 4 could be used as a guide for labeling issue identification.

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3. Comprehensive Clinical Pharmacology Review

In subsequent subsections, integrate information across studies to address review questions that are most relevant to the application. Organize information under broad categories of questions in this section where appropriate.

OCP reviewers are referred to OCP online resources[2] for an extensive list of sample questions and review guides that can serve as aids in completing Section 3, "Comprehensive Clinical Pharmacology Review." The review team should consider which questions are most relevant to support overall clinical pharmacology conclusions and recommendations.

State the answer to key review questions up front and provide details to support the conclusion. Regulatory recommendations, including the rationale for particular labeling recommendations, should be clearly stated in the appropriate section.

3.1 Overview of the Product and Regulatory Background

Only relevant product information and regulatory history/activities (including key milestone discussions) that contribute to the clinical pharmacology assessment should be described.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Include a general overview of the drug's non-clinical and clinical pharmacology information to provide a context for specific OCP recommendations. Briefly include information on the drug substance [3], drug product, and bioanalytical method if relevant to an important aspect of the review. Key information may be summarized in a table format (see Attachment 5 for an example).

3.3 Clinical Pharmacology Review Questions

This section addresses a series of clinical pharmacology questions that are relevant to the safe and effective use of all drugs. These questions should be answered explicitly and up front.

3.3.1. To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

[2] CDER OCP Intranet (http://sharepoint.fda.gov/orgs/CDER-OCP/SitePages/Home.aspx).
[3] For BLAs, drug or drug substance means the therapeutic protein. They can be used interchangeably.

Clinical pharmacology information often provides pivotal support for evidence of effectiveness in situations that involve extrapolation of findings of an approved product to a new population (e.g., adult to pediatric), or a different dose, dosing regimen, or dosage form.[4]

There are also situations in which compelling clinical pharmacology information can be used to provide additional evidence of effectiveness for an NME NDA or original BLA. These situations include, but may not be limited to:

- As one of two adequate and well controlled trials (e.g., randomized phase 2 dose-finding studies).
- As mechanistically supportive of a single adequate and well controlled trial (e.g., because of a strong effect on a physiologically relevant pharmacodynamic (PD) biomarker).
- To identify subsets of patients with notably large treatment effects or favorable risk/benefit balance for a drug with significant toxicity or otherwise marginal average treatment effects.
- To provide exposure-response information in support of drug activity in the intended population.
- To determine the individual contributions of components of a combination therapy (e.g., in the absence of a full factorial clinical trial).

This question should address the above bulleted or similar issues encountered in the review.

In general, safety of the drug should be discussed in Section 3.3.2 as part of the risk-benefit assessment of the proposed dosing regimen for the general population. However, in rare instances, if there is a mechanistic basis for a significant safety concern that may outweigh the benefit of the drug's intended pharmacologic effect, a brief statement of the risk in this section may be appropriate to provide proper context.

3.3.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Provide an assessment of and final recommended dosing guidelines for the general patient population for which the indication is being sought. If necessary, this section should include revised dosing recommendations to be incorporated into labeling or

[4] See Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (1998).

proposal for further studies to resolve any unresolved issues related to dosing for the indication sought.

Information needed to address this question may include (but is not limited to):

- Exposure-response analyses for safety and/or efficacy.
- Therapeutic index of the drug if known.
- Applicant's rationale to support dosing or labeling claims.
- Additional analyses if OCP's conclusion is different from that of the applicant.

3.3.3. Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Provide an assessment of and final recommendations on dosing regimen(s) and/or the appropriateness of treatment in relevant patient subsets based on various intrinsic factors. Intrinsic factors include age, sex, race/ethnicity, genetics, body weight, organ impairment, etc.

If necessary, this section should include revised dosing recommendations to be incorporated into labeling or proposals for further studies to resolve any unresolved issues related to dosing in specific populations. The basis for alternative dosing recommendations in these populations should be explicitly described (e.g., average exposure matching, interpolation or extrapolation based on exposure-response analyses, etc.).

This section can provide information on:

- Intrinsic factors that influence exposure (PK of parent and/or relevant metabolites) and/or PD of the drug.
- Whether dosing adjustment is warranted for a particular subpopulation and the nature of the data that support those conclusions.
- Applicant-proposed management strategies (if any).
- Review team-proposed management strategies (if different from the applicant).
- Rationale to support proposed management strategies (e.g., based on empirical results from dedicated standalone or nested studies, modeling, simulation, or theoretical concerns).
- The review should explicitly state whether intrinsic factors were adequately assessed and if such information is pertinent to safe and effective use of the drug.

- Intrinsic factors that were evaluated or considered but that do not influence exposure should be discussed. The adequacy of the data to support a negative finding should be discussed.

3.3.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Provide assessment of and final recommendations on dosing regimen(s) and/or therapeutic management strategies needed to address important food-drug (including beverage-drug) or drug-drug interactions (DDIs). If necessary, this section should include revised management strategies to be incorporated into the labeling or proposals for further studies to resolve such clinically relevant interactions. The basis for alternative dosing recommendations under these conditions should be explicitly described (e.g., average exposure matching, interpolation or extrapolation based on exposure/response analyses, etc.).

This section provides information on:

- Influence of food/diet, alcohol use, herbal supplements, and concomitant drugs on the exposure (PK of parent and/or relevant metabolites) and/or PD of the new drug.

- The new drug's effect on the exposure and/or PD of concomitant drugs.

- Whether a dosing adjustment is warranted and the nature of the data that supports those conclusions.

- Applicant-proposed management strategies (if any).

- Review team-proposed management strategies (if different from the applicant).

- Rationale to support proposed management strategies (e.g., based on empirical results from dedicated standalone or nested studies, modeling, simulation, or theoretical concerns).

- The review should explicitly state whether the impact of food/diet, alcohol use, and DDIs were adequately assessed and if such information is pertinent to safe and effective use of the drug.

- Interactions that were evaluated or considered but that do not influence exposure should also be discussed. The adequacy of the data to support a negative finding needs to be discussed.

4. Appendices

This section is organized to include key individual study report reviews or integrated summaries of individual study reviews and analyses on various clinical pharmacology areas that inform major decisions and recommendations. Subsections should be divided into informative topical subheaders.

Reviewers should take into account whether pivotal clinical pharmacology studies are fit for their intended purposes based on study design, data quality, and the appropriateness of the data analysis. Reviews may include independent OCP data analyses. This section, as with other sections of the review, should not include non-essential information. The review team should exercise judgment on the breadth and depth of information to be included in this section.

Examples of subheaders for this Section are provided below:

4.1 Summary of Bioanalytical Method Validation and Performance

4.2 Clinical PK and/or PD Assessments

4.3 Population PK and/or PD Analyses

4.4 Exposure-Response Analyses

4.5 Enrichment, Stratification, and/or Biomarker-based Assessment

4.6 Mechanistic Safety Assessment

ATTACHMENT 4

A GUIDE FOR LABELING ISSUE IDENTIFICATION†

Section/heading	Acceptable to OCP?			Comment
	A	AWE	U	
Highlights/DDI	☐	☐	☒	• Revised to include dose modification with concurrent strong CYP3A4 inhibitors, avoidance of foods that inhibit CYP3A4. • Revised to include avoidance of concurrent use with sensitive CYP2D6 substrates or CYP2D6 substrates that have a narrow therapeutic index.
Highlights/Specific Population	☐	☐	☒	Revised to include dose modification for mild and moderate hepatic impairment and avoidance in severe impairment.
Section 1/ Indications and Usage	☐	☒	☐	Revised to exclude patients with wild-type BRAF mutations for a lack of in vitro and clinical responses.
Section 2.1/ Recommended Dosing	☐	☒	☐	Added cross reference to Section 12.3 (PK) to food recommendation.
Section 2.2/ Dose Mod HI	☐	☐	☒	Dose modification for mild and moderate hepatic impairment and avoidance in severe impairment.
Section 2.3/ Dose Mod CYP3A4 INH	☐	☐	☒	Added dose modification with concurrent strong CYP3A4 inhibitor use.
Section 5.2/QTc Interval Prolongation	☐	☒	☐	Added subsection, information regarding the QTc change observed in studies 1 & 2 and a risk mitigation strategy to conduct periodic monitoring with ECGs and electrolytes in vulnerable populations and to permanently discontinue Drug X in patients who develop QTc interval prolongation with signs/symptoms of life threatening arrhythmia.
Section 5.6/Hepatotoxicity	☐	☒	☐	Revised “dose adjustments may be considered” to “dose modifications are recommended.”
Section 7	☐	☒	☐	Revised general statement regarding metabolic and transporter systems that affect and are affected by Drug X.
Section 7.1/Agents that increase Drug X concentrations	☐	☐	☒	Revised to include the expected exposure change, dose modification with concurrent strong CYP3A4 inhibitor and CYP3A4 inhibitor examples consistent with the revised FDA DDI guidance. Non-actionable information moved to section 12.
Section 7.2/Agents that decrease Drug X concentrations	☐	☐	☒	Revised to include lack of clinical information, the expected exposure change from PBPK simulations, avoidance language with concurrent strong CYP3A4 inhibitor use, and CYP3A4 inducer examples consistent with the revised FDA DDI guidance. Non-actionable information moved to section 12.
Section 7.3/Agents whose Plasma Concentrations may be Increased by Drug X	☐	☐	☒	Revised to include the range expected exposure change in CYP2D6 substrates, avoidance language for concurrent use with sensitive CYP2D6 substrates or CYP2D6 substrates that have with a narrow therapeutic index, and CYP2D6 inhibitor examples consistent with the revised FDA DDI guidance. Non-actionable information moved to section 12.
Section 8.6/Hepatic Impairment	☐	☐	☒	Non-actionable information removed, dose modification for mild and moderate hepatic impairment and avoidance in severe impairment. Added more actionable monitoring recommendations.
Section 8.7/Renal Impairment	☐	☐	☒	Non-actionable information removed and a sentence that the dialyzability of Drug X is unknown was added.
Section 12.1/MOA	☐	☒	☐	Removed reference to MOA that misleadingly implies an

				unapproved indication.
Section 12.2/PD	☐	☒	☐	Extraneous preclinical information was removed.
Section 12.2/PD	☐	☒	☐	Per 21 CFR 201.57(c)(13)(i)(B) added "The exposure-response relationship for Drug X is unknown."
Section 12.2/PD	☐	☒	☐	Revised to include the following contextual information regarding the central tendency analysis of the QTcF data and pharmacokinetic/pharmacodynamic analysis in Study 2.
12.3/General	☐	☒	☐	Additional information regarding accumulation added.
12.3/Absorption	☐	☒	☐	• Bioavailability, T_{max}, and dose proportionality information was condensed and revised to create a more logical flow, and extraneous information was removed. • Additional study context for the food effect trial was added. • Additional context was added for pH based solubility and DDI potential.
12.3/Distribution	☐	☒	☐	Distribution subsection was condensed, and additional information regarding P-gp substrate effects was added.
12.3/Elimination	☐	☒	☐	Oral clearance, half-life, and variability information from the pop-PK analysis were added.
12.3/Metabolism	☐	☒	☐	• Additional context regarding the metabolism of Drug X was added. • Non-actionable information regarding metabolites was removed. The contribution of UGT systems was added.
12.3/Excretion	☒	☐	☐	
12.3/Specific Populations	☐	☒	☐	The specific populations subsections were revised to include information regarding sex and age from the pop-PK analysis. Additional clinical trial context to support hepatic and renal impairment information in section 8 was added.
12.3/DDI	☐	☒	☐	In vitro DDI findings and additional clinical trial context to support information in section 7 was added.
12.5/Pharmacogenomics	☒	☐	☐	

A = Acceptable; AWE=Acceptable with minor edits; U=Unacceptable/substantive disagreement (must provide comment);

† This guide is pre-populated with an illustrative example.

ATTACHMENT 5

AN ILLUSTRATIVE EXAMPLE OF SUMMARY OF GENERAL CLINICAL PHARMACOLOGY AND PHARMACOKINETICS†

<table>
<tr><th colspan="4">Pharmacology</th></tr>
<tr><td>Mechanism of Action</td><td colspan="3">Include the mechanism of action and key in vitro findings such as IC_{50}. Add any other relevant mechanistic information related to effect/safety.</td></tr>
<tr><td>Active Moieties</td><td colspan="3">Provide details on the active moieties and their relative contribution to the overall effect.</td></tr>
<tr><td>QT Prolongation</td><td colspan="3">Specify the drug's ability to block the hERG channel (IC_{50}). Provide results of a thorough QT trial and/or key findings of concentration-QT analysis.</td></tr>
<tr><th colspan="4">General Information</th></tr>
<tr><td>Bioanalysis</td><td colspan="3">Describe the bioanalytical method used and topline method validation and performance information. Refer to the Appendix for details.</td></tr>
<tr><td>Healthy vs. Patients</td><td colspan="3">Provide a comparison of the PK between healthy subjects and the target patient population.</td></tr>
<tr><td>Drug Exposure at Steady State Following the Therapeutic Dosing Regimen</td><td colspan="3">Include the dosing regimen and exposure metrics (including measure of central tendency and variation) and specify whether data are from healthy subjects or patients.</td></tr>
<tr><td>Range of Effective Dose or Exposure</td><td colspan="3">Provide the drug's range of effective dose or exposure (if known, include minimally effective dose, lowest maximally effective dose, etc.)</td></tr>
<tr><td>Maximally Tolerated Dose or Exposure</td><td colspan="3">Provide the drug's maximally tolerated dose or exposure (if relevant and known).</td></tr>
<tr><td>Dose Proportionality</td><td colspan="3">Describe the relationship between the drug dose and exposure (e.g., increases in the drug dose yield proportional increases in plasma concentration over the dose range of X mg/day (ratio to approved dosage) to Y mg/day (ratio to approved dosage)).</td></tr>
<tr><td>Accumulation</td><td colspan="3">Provide the fold accumulation of the drug at steady-state following the dosing regimen.</td></tr>
<tr><td>Variability</td><td colspan="3">Describe the between-subject and within-subject variability in key exposure metrics.</td></tr>
<tr><th colspan="4">Absorption</th></tr>
<tr><td>Bioavailability</td><td colspan="3">Provide information on absolute bioavailability and/or pertinent relative bioavailability. Specify the route of administration and the formulation of interest.</td></tr>
<tr><td>T_{max}</td><td colspan="3">Provide the median T_{max} and range in hours</td></tr>
<tr><td rowspan="3">Food effect (Fed/fasted)</td><td>$AUC_{0-\infty}$</td><td>C_{max}</td><td>T_{max}</td></tr>
<tr><td>Provide this metric as the follows: Geometric Mean Ratio [90% CI]</td><td>Provide this metric as follows: Geometric Mean Ratio [90% CI]</td><td>Provide this metric as follows: Effect on time to reach C_{max} [Δ mean Tmax (Fed-Fast)]</td></tr>
<tr><td colspan="3">Include the experimental conditions that provided the above metrics (e.g., Following a high fat meal[b])</td></tr>
<tr><th colspan="4">Distribution</th></tr>
</table>

Volume of Distribution	Include the Vd or Vd/F. If information is available based on compartmental modeling, specify the volume of distribution in specific physiologic space.
Plasma Protein Binding	Include the percent of drug binding, the type of proteins involved in binding, and whether the binding is concentration-independent over relevant clinical exposures.
As Substrate of Transporters	Provide information on drug as substrate for various transporters that have been assessed.
Elimination	
Terminal Elimination Half-Life	Provide the mean and range for the terminal elimination half-life for the relevant dose range.
Effective Elimination Half-Life	Provide the effective elimination half-life, if it is different from the terminal half-life.
Metabolism	
Fraction Metabolized (% dose)	Express how much of the drug is metabolized as a percent of the dose.
Primary Metabolic Pathway(s)	Describe the major metabolic pathways and the enzymes for the drug and the specific contributions for the pathways if available (e.g., oxidation, conjugation).
Excretion	
Primary Excretion Pathways (% dose) ±SD	Provide information on the excretion pathways as described below: --Feces: % (approximate % unchanged Drug X) --Urine: % (approximate % unchanged Drug X)
Interaction liability (Drug as perpetrator)	
Inhibition/Induction of Metabolism	Describe the potential for the drug to act as a perpetrator in the inhibition or induction of metabolic enzymes.
Inhibition/Induction of Transporter Systems	Describe the potential for the drug to act as a perpetrator for the inhibition or induction of transporter systems.

a= PK parameters are presented as mean ±standard deviation (SD) or median (minimum to maximum) unless otherwise noted; b= Approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively.

† This table is an illustrative example. The table content can be modified to include most relevant information for a particular product.