CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217188Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 153517

MEETING MINUTES

Pfizer, Inc.
Attention: Karen Baker
Senior Director, Pfizer Global Regulatory Affairs
235 East 42nd Street
New York, NY 10017

Dear Ms. Baker:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Paxlovid (nirmatrelvir and ritonavir).

We also refer to the telecon between representatives of your firm and the FDA on May 24, 2022. The purpose of the meeting was to obtain the Agency's advice on the Chemistry, Manufacturing, and Controls (CMC) transition strategy for PAXLOVID from EUA 000105 to NDA 217188 and FDA feedback on CMC specific questions in preparation for NDA submission in June 2022.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact Erica Keafer, Regulatory Business Process Manager at erica.keafer@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

David Claffey, Ph.D.
Branch Chief
Division of New Drug Products I
Office of New Drug Products
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: B

Meeting Category: Pre-NDA

Meeting Date and Time: May 24, 2022, 12:00 PM – 1:00 PM

Meeting Location: Teleconference

Application Number: IND 153517

Product Name: Paxlovid (nirmatrelvir tablets and ritonavir tablets)

Indication: Treatment of patients with COVID-19 infection

Sponsor Name: Pfizer, Inc.

Regulatory Pathway: 505(b)(1)

Meeting Chair: David Claffey, Ph.D.

Meeting Recorder: Erica Keafer, M.S.

FDA ATTENDEES

Office of Pharmaceutical Quality (OPQ)

David Claffey, Ph.D.	Branch Chief, Division of New Drug Products 1 (DNDP I), Office of New Drug Products (ONDP)
Peter Guerrieri, Ph.D.	Senior Pharmaceutical Quality Assessor, DNDP I, ONDP
Shalini Anand, Ph.D.	Chemist, DNDP I, ONDP
Paresma Patel, Ph.D.	Branch Chief, Division of New Drugs API (DNDAPI) ONDP
Katherine Windsor, Ph.D.	Senior Pharmaceutical Quality Assessor, DNDAPI ONDP

Derek Smith, Ph.D.	Deputy Director, Office of Pharmaceutical Manufacturing (OPMA)
Hang Guo, Ph.D.	Senior Pharmaceutical Quality Assessor, Division of Pharmaceutical Manufacturing Assessment I (DPMAI) Office of Pharmaceutical Manufacturing (OPMA),
Abdollah Koolivand, Ph.D.	Visiting Associate, DPMAI, OPMA
Elsbeth Chikhale, Ph.D.	Senior Pharmaceutical Quality Assessor, Division of Biopharmaceutics (DB), ONDP
Gerlie Gieser, Ph.D.	Pharmacologist, DB, ONDP
David Lewis, Ph.D.	Branch Chief, Division of Post-Marketing Activities I (DPMAI), Office of Lifecycle Drug Products (OLDP)
Ramesh Gopalaswamy, Ph.D.	Chemist, DPMAI, OLDP
Erica Keafer, M.S.	Regulatory Business Process Manager, Office of Program and Regulatory Operations (OPRO)

Office of Compliance

Commander, Tara Gooen Bizjak	Director of Policy Staff, Office of Manufacturing Quality (OMQ)
Diane Bruce, PharmD, RAC	Senior Advisor to OMQ-Drug Shortages, OMQ

Office of New Drugs

Sarah Connelly, M.D.	Clinical Team Leader, Division of Antivirals (DAV), Office of Infectious Diseases (OID)
Stephanie Troy, M.D.	Clinical Reviewer, DAV, OID
Alicia Moruf, PharmD, MPH	Senior Health Regulatory Project Manager, Office of Regulatory Operations (ORO)

SPONSOR ATTENDEES

Lisa Skeens	Vice President, Global Regulatory Affairs Hospital Category
Karen Baker	Senior Director, Global Regulatory Affairs
William Dodge	Director, Regulatory CMC
Kara Follmann	Executive Director, Regulatory CMC
Beth Herman	Senior Manager, Regulatory CMC
Jared Piper	Director of Process Chemistry, Chemical R&D
Mike Coutant	Director, Analytical R&D
Daniel Arenson	Research Fellow, Pharmaceutical Sciences Team Lead
Olivier Dirat	Senior Director, CMC Advisory Office
Rodney (Matt) Weekly	Associate Research Fellow, Chemical Research and Development
Julia Wood	Senior Principal Scientist, Analytical R&D
Hugh Clarke	Senior Principal Scientist, Analytical R&D
Kimber Barnett	Research Fellow, Analytical R&D
Keith Masse	Senior Principal Scientist, Analytical R&D
Kazuko Sagawa	Research Fellow, Formulation Development
Patrick Daugherty	Senior Principle Scientist, Drug Product Design
Weili Yu	Associate Research Fellow, Drug Product Design
Timothy Graul	Director, Global CMC
Albert Pichieri	Director, Portfolio Lead – Drug Product, Launch Excellence, PGS
Glenn Schneider	Senior Director, PGS Design & Orchestration

Declan O'Shea	Operations Lead, External Supply API
Frances Barry	QA Compliance Lead, Pfizer Ringaskiddy
Ashley Collins	Director, Portfolio Lead – Packaging, Launch Excellence, PGS
Paul Meenan	Associate Research Fellow, Drug Product Design
Michael Neidig	Director, Quality Systems
Bharat Damle	Executive Director, Clinical Pharmacology
Donna Cox	Clinical Pharmacology Group Lead

1.0 BACKGROUND

On December 22, 2021, the FDA issued an Emergency Use Authorization (EUA) for emergency use of PAXLOVID for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, under section 564 of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. 360bbb-3). Paxlovid consists of nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir is a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor, and ritonavir, is an HIV-1 protease inhibitor and CYP3A inhibitor.

With this meeting request, Pfizer is seeking to obtain the Agency's advice on the Chemistry, Manufacturing, and Controls (CMC) transition strategy for PAXLOVID from EUA 000105 to NDA 217188 and FDA feedback on CMC specific questions in preparation for NDA submission in June 2022.

FDA sent Preliminary Comments to Pfizer, Inc. on May 20, 2022.

2.0 DISCUSSION

The sponsor's questions are reproduced below. FDA's preliminary response to the questions, the sponsor's response to FDA's preliminary response, and the meeting discussion follow each question.

Question 1:
Pfizer will be including sites authorized in EUA 000105 in the initial NDA for PAXLOVID targeted for submission end of June 2022. For supply continuity, Pfizer will continue to add additional sites to the EUA following submission of the NDA and during the anticipated NDA review time period. A visual filing plan illustrating the upcoming site additions to the EUA or EUA/NDA is provided below.

Pfizer requests FDA concurrence with the strategy to align the CMC content in the EUA and NDA as needed and as soon as possible after the approval of the NDA.

Does FDA agree?

FDA Response to Question 1:

We encourage you to submit all changes that will impact commercial supply to the NDA – including additional drug substance and drug product manufacturing sites. You may choose to cross-reference the NDA in the EUA to align CMC content, as appropriate. If you choose to submit any changes concurrently to the EUA during the NDA review cycle, clearly outline any differences between the EUA and NDA submissions, along with justification for the differences.

This would appear to be a less regulatorily burdensome route and will aid in having more consistent product quality. However, if this is not possible, we would like to understand the rationale for your proposed approach – particularly for the proposed addition of the three sites in July 2022.

Further, we acknowledge the drug substance manufacturing sites you plan to add in Q4 2022: (b) (4) As you begin to obtain the CMC information (e.g., batch data) to support addition of these new sites, we encourage you to continue discussions with the Agency regarding the most suitable mechanism for each site addition. To help inform these discussions, we encourage you to communicate the following as you become aware: (1) more detailed estimated timelines for availability of the data to support each site (e.g., release data for the first three registration batches), and (2) any changes to the anticipated production schedule.

Additional recommendations:

For each drug substance manufacturing facility, the NDA should contain the following information:

- Release data for three batches of API manufactured to at least 10% of production scale and one drug product batch manufactured with API produced at the additional manufacturing site. The impurity profile and physical properties

(e.g., polymorphic form) of the API should be comparable to that of API produced at the current proposed manufacturer(s).

- Detailed description of any changes to the manufacturing process or equipment differences used at the new API manufacturer relative to that described in the NDA for nirmatrelvir API production. Also, confirm that there are no changes to specifications for starting materials and intermediates used to manufacture API at the alternate manufacturing site.

- Any available stability data for API manufactured at the newly proposed site. We recommend that stability studies be initiated on three batches of API (manufactured to at least 10% of production scale) produced at each additional manufacturing site.

For each drug product manufacturing facility, the NDA should contain the following information:

- Release data of three drug product batches manufactured to at least 10% of the production scale

- Side by side comparison of the manufacturing process, equipment, batch size excipients specifications, information about container closure system to manufacture (or package) drug product proposed for alternate site/area. Please note that any minor changes should be delineated, and a justification should be provided to support the change, in the NDA.

- Updated 3.2.P.3.4 section which should include the control of critical steps and intermediates, along with summary tables for comparison of in-process data among different drug product batches.

- Batch manufacturing and packaging records along with yield/reconciliation summary tables for three drug product batches manufactured to at least 10% of the production scale.

- Any available stability data for drug product manufactured at the newly proposed site. We recommend that stability studies should be initiated on three batches of the drug product produced at each additional manufacturing site.

We also request that in support of the addition of each proposed new drug substance or drug product manufacturing site, that you provide evidence of comparable in vitro dissolution profile data of the post-change and pre-change drug products in various pH media and using the proposed NDA dissolution method. We recommend including in the comparison the in vitro dissolution profile data of a pivotal clinical trial (or other clinical study) lot as (one of) the reference/pre-change drug product lot(s).

We also recommend that you include all manufacturing and testing sites related to both the drug substance and drug product in the initial NDA submission in 356h form as this would allow for a timely review of each facility to ensure that materials manufactured and tested at each site conforms to quality standards expected of GMP facilities.

Sponsor's response to FDA preliminary comments, Question 1:

Pfizer confirmed they would like to discuss this topic further at the May 24, 2022, meeting.

Discussion Question 1:

The sponsor indicated that at time of NDA submission, CMC data would not be available to support (b) (4) ritonavir tablet, (b) (4) nirmatrelvir tablet manufacturing site or the (b) (4) nirmatrelvir tablet testing site. However, data would be ready within one month of NDA submission – in July 2022. (b) (4) FDA stated that it would be acceptable to submit the information as amendments to the NDA within 30 days of NDA submission – and to reference this information in the NDA if amending the EUA. The sponsor agreed that they would take this approach. Regarding the submission of the three additional nirmatrelvir drug substance manufacturing sites, the sponsor stated that they would follow the FDA recommendation to communicate at a later time when more information is available about the proposals and their timelines. The sponsor thanked the FDA for their flexibility regarding this matter.

The sponsor wanted to clarify if manufacture of one batch of drug product was necessary to support new drug substance manufacturing sites for the NDA. The sponsor noted that submission of drug product data has not been a requirement for the EUA submission. The FDA clarified that the regulatory standards between an EUA and NDA are different.

FDA generally considers the principles of the Postapproval Changes to Drug Substances Guidance for Industry when considering addition of new drug substance sources for an NDA. FDA confirmed that at least one batch of drug product (manufactured with drug substance from a new site) should be submitted to support comparability of drug substance and addition of a new drug substance manufacture site. The sponsor asked the FDA if it would be possible to meet this requirement by submitting drug product batch information as an amendment during NDA review or as a post approval commitment. FDA agreed with submission of the supportive drug product batch data to support new drug substance manufacture sites as amendments during NDA review. FDA also confirmed that if the data would not be available during NDA review, that we may consider post-approval commitments based on the timelines for drug product manufacture. The sponsor asked for

confirmation that only one batch of drug product (manufactured at one drug product site) needed to be submitted to support any additional drug substance site, and FDA confirmed that would be sufficient. The sponsor thanked the FDA for their feedback and no further discussion occurred.

Question 2:

(b) (4)

FDA endorsed methods and specifications may vary between the EUA and NDA. EUA and/or NDA lots will be released in accordance with the respective methods and specifications approved at the time of testing.

Does FDA agree?

FDA Response to Question 2:

As noted in our response to Question 1, we encourage you to submit all changes that will impact commercial supply to the NDA. You may choose to cross-reference the NDA in the EUA to align CMC content, as appropriate.

If you choose to submit any changes concurrently to the EUA during the NDA review cycle, clearly outline any differences between the EUA and NDA submissions, along with justification for the differences as appropriate.

FDA is unable to comment (b) (4) FDA will continue to work with you to ensure continued supply of your product at the time of NDA approval.

Sponsor's response to FDA preliminary comments, Question 2:

Pfizer confirmed they would like to discuss this topic further at the May 24, 2022, meeting.

Discussion Question 2:

(b) (4)

and acknowledged the FDAs feedback of not being able to comment at this time. The sponsor asked the FDA if they had any further feedback for Question 2. The FDA stated they had nothing additional to add and stated they will work closely with the sponsor during the NDA review period to ensure that the supply of the drug product is not interrupted. The sponsor thanked the FDA for their feedback and no further discussion occurred.

Question 3:

To meet projected demand, (b) (4)

via a Comparability Protocol to be included in the initial NDA.

Additional detail for each site in tabular format as requested in FDA's feedback in the pre-NDA Written Responses dated 13-Apr-2022 is provided in section 12.

(b) (4)

Does FDA agree?

FDA Response to Question 3:

Refer to the Agency's response to Question 1 regarding information that should be provided to support any (b) (4)

The adequacy of the information provided to support (b) (4) – as well as any proposed comparability protocol – will be evaluated during NDA review.

All facilities involved in the disposition of a commercial drug product, including those used for storing commercial drug product under quarantine prior to a disposition decision should be included in the NDA. Refer to *"Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers Guidance for Industry".*

Sponsor's response to FDA preliminary comments, Question 3:
The Sponsor accepted FDA's response; no discussion occurred.

Discussion Question 3:
The Sponsor accepted FDA's response; no discussion occurred.

Question 4:
Does FDA agree with submission of the 3 month data for (b) (4) during validation and that the totality of the data will allow for a (b) (4) retest period?

FDA Response to Question 4:

Yes, your proposal to submit 3-month long-term and accelerated stability data for (b) (4) drug substance before mid-July appears acceptable.

The determination of the drug substance retest period will be made at the time of NDA review and will consider the totality of the data provided in the NDA, including supporting stability data for drug substance manufactured (b) (4) . We encourage you to provide any updated drug substance stability data that may become available during the NDA review.

Sponsor's response to FDA preliminary comments, Question 4:
The Sponsor accepted FDA's response; no discussion occurred.

Discussion Question 4:
The Sponsor accepted FDA's response; no discussion occurred.

Question 5:
Does FDA agree with the submission of the 9 month data in June and the 12 month data in mid-September to support the 24 month shelf life?

FDA Response to Question 5:

Generally, we expect that at least 12 months of long-term stability data and 6 months of accelerated stability data for three primary drug product batches be included in the initial NDA submission per the recommendations in ICH Q1A(R2). However, f*or a product being developed to address an unmet medical need, we are willing to accept less stability data for the primary batches in the initial NDA submission.* Therefore, your proposal to submit 9-month data at the time of NDA submission and 12-month data in mid-September appears acceptable.

The determination of the drug product expiry period will be made during NDA review and will be based upon the totality of the submitted data. Please submit all the available supporting data (e.g., developmental batches data) and additional data which may become available during NDA review.

Further, we request that you provide all available direct and supportive stability data and risk assessments for ritonavir tablets from each of the sources in the proposed blisters to support the proposed drug product expiry period.

Sponsor's response to FDA preliminary comments, Question 5:

Pfizer confirmed they would like to discuss this topic further at the May 24, 2022, meeting.

Discussion Question 5:

The sponsor thanked the FDA for their feedback regarding their stability plans. The sponsor stated (b) (4) They also reiterated that they would submit drug product stability updates to the NDA in September 2022.

The FDA asked about the extent of available stability data for the ritonavir tablets from the proposed (b) (4) sources in the commercial blister packaging. The sponsor indicated that three months stability would be available for the AbbVie product and release data would be available for the Hetero product. The FDA acknowledged that drug product stability data were available for ritonavir tablets in other packaging configurations, but that the limited data in the proposed commercial blister packaging would require extensive justification. FDA encouraged the sponsor to include all available justification to support the ritonavir tablet expiry period. The sponsor confirmed their understanding and indicated that they have a modeling approach to justify shelf life together with stability data from AbbVie and Hetero. The

FDA reiterated that they should provide all available data to justify the ritonavir tablet expiry period in the commercial blister packaging.

Question 6:

The Pfizer NDA will cross-reference the suppliers' ANDA/NDA for ritonavir drug substance and bulk drug product supported by Letters of Authorization as was done in the EUA. To ensure projected supply, multiple suppliers for Ritonavir bulk tablets will be needed in the NDA, similar to the EUA. Current plans include AbbVie Inc (NDA 022417), Hetero Labs LTD Unit III (ANDA 204587) (b) (4)

Does FDA agree with the approach?

FDA Response to Question 6:

Your proposal to cross-reference the suppliers' ANDA/NDA for ritonavir drug substance and bulk drug product, supported by Letters of Authorization, appears reasonable. We recommend that you include all facilities (testing and manufacturing) involved with suppliers' ANDA/NDA for ritonavir drug substance and bulk drug product and the corresponding DMFs (as applicable) in the NDA.

As you propose to include multiple suppliers of ritonavir tablets (b) (4) in the finished drug product is critical for its performance, we recommend that you include a control (b) (4) in the release and stability specifications for ritonavir tablets.

Sponsor's response to FDA preliminary comments, Question 6:

Pfizer confirmed they would like to discuss this topic further at the May 24, 2022, meeting.

Discussion Question 6:

The sponsor stated the NDA will cross reference the suppliers for ANDA ritonavir sources and acknowledges the FDA agrees with this approach. The sponsor requested clarification on the need for polymorphic form testing based on AbbVie and Hetero data indicating no change (b) (4) over time. The sponsor proposed to include the rationale as to why testing was not needed. The FDA recommended that the sponsor test batches at release and on stability, as this is a critical quality attribute known to impact bioavailability, and use of (b) (4) different ritonavir tablets from different suppliers/processes is proposed. These testing data

may be used to justify reduction of this testing at a future date. The sponsor stated they would discuss this matter internally and no other discussion occurred.

ADDITIONAL COMMENTS

1. We remind you to address all recommendations in the 16-DEC-2021 comments from the Agency provided under EUA 105 outlining updated nirmatrelvir drug substance information to be provided in any future NDA submission. For example, provide details of your control strategy for particle size distribution, including justification (e.g., results from your bioavailability studies) for any proposed particle size controls.

2. Regarding your 21-DEC-2021 Response to Comment #11 on environmental impacts, please include a similar analysis under the NDA (b) (4)

3. In the NDA submission, provide sufficient justification for any proposed exclusion of tests that were included in the nirmatrelvir drug substance specification at the time of emergency use authorization of PAXLOVID.

Sponsor's response to FDA preliminary comments, Additional Comments 1 - 3:

The Sponsor accepted FDA's response; no discussion occurred.

ADDITIONAL COMMENTS

4. FDA understands that for the NDA you plan to (b) (4) The acceptability of these proposals will be determined during NDA review when the supporting data/information become available for FDA evaluation.

(b) (4)

(b) (4)

Sponsor's response to FDA preliminary comments, Additional Comment 4:

Pfizer confirmed they would provide an update for Additional Comment 4 at the May 24, 2022, meeting.

Discussion, Additional Comment 4:

(b) (4)

Other Discussion: The sponsor asked about OPQ/sponsor communication during the NDA review. The FDA indicated that given the complexity and unusual interrelated nature of the NDA/EUA issues, that OPQ is open to scheduling regular (e.g., monthly) meetings with the sponsor during NDA review to discuss CMC issues.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DAVID J CLAFFEY
05/26/2022 03:10:55 PM

IND 153517

MEETING REQUEST-
WRITTEN RESPONSES

Pfizer Inc.
Attention: Karen Baker
Senior Director, Global Regulatory Affairs
235 East 42nd Street
New York, NY 10017

Dear Ms. Baker:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act Paxlovid (nirmatrelvir and ritonavir).

We also refer to your submission dated February 15, 2022, containing a meeting request. The purpose of the requested meeting was to obtain the Agency's advice regarding your planned new drug application (NDA) for the use of this drug in the treatment of mild-to-moderate COVID-19 in adults (b) (4) who are at high risk for progression to severe COVID 19, including hospitalization or death.

Further reference is made to our Meeting Granted letter dated March 2, 2022, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your February 15, 2022, background package.

[1]We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, call me, at (301) 960-9339 or the Division's mainline at, (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Talia Lindheimer
Regulatory Project Manager
Antivirals Group
Division of Regulatory Operations for Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Written Responses
- Bioanalytical Method Performance Template
- Clinical Pharmacology In Vitro and In Vivo Study Table Template

U.S. FOOD & DRUG ADMINISTRATION

WRITTEN RESPONSES

Meeting Type: Type B
Meeting Category: Pre-NDA

Application Number: 153517

Product Name: Paxlovid (nirmatrelvir and ritonavir)

Indication: Treatment of adult COVID-19 patients (b) (4)

Sponsor Name: Pfizer, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

1.0 BACKGROUND

An Emergency Use Authorization (EUA) for the use of Paxlovid for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death was initially authorized on December 22, 2021, under section 564 of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. 360bbb-3). Paxlovid consists of nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir is a SARS-CoV-2 main protease (Mpro: also referred to as 3CLpro or nsp5 protease) inhibitor, and ritonavir, is an HIV-1 protease inhibitor and CYP3A inhibitor.

Pfizer is pursuing a marketing application for Paxlovid for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults (b) (4) who are at high risk for progression to severe COVID-19, including hospitalization or death.

With this meeting request, Pfizer is seeking the Agency's feedback on the structure, format, and data plan for their future NDA submission including:

1. Sufficiency of nonclinical toxicology safety studies,

2. Nonclinical antiviral resistance assessments,

3. Planned integration of safety data (Studies 1005 (EPIC-HR) and 1002 (EPIC-SR)) from PAXLOVID clinical trials and proposed format, standards, and structure of the datasets to be submitted,

4. Viral sequencing reports, and

5. Format and criteria of safety narratives.

2.0 QUESTIONS AND RESPONSES

General FDA Comments:

After a complete review of your Pre-NDA meeting request and briefing document, and as described in both the cover letter as well as in the Executive Summary of the briefing document, the information implies you plan to submit a new drug application (NDA) by the end of June 2022 for the following indication:

- the treatment of mild-to-moderate COVID-19 in adults (b) (4) who are at high risk for progression to severe COVID-19, including hospitalization or death.

We also note in section **4.2 Proposed Indication** of your background package you state,

Supportive studies to be included in the nirmatrelvir/ritonavir dossier are 2 ongoing pivotal clinical Studies (1002 [EPIC-SR], 1006 [EPIC-PEP]) (b) (4) *at the time of submission of the NDA. These pivotal trials will support licensure for the following indications:*

- *For the treatment of adult patients* (b) (4) *who are at* (b) (4) *risk of progressing to severe disease (Study 1002).*

(b) (4)

It is not clear if you plan to include the following indications in your planned original NDA submission:

1. For individuals at [redacted] risk for progression to severe COVID-19, [redacted]

Please clarify the indication/claims that will be submitted at the time of your original NDA submission. Please note that a major amendment to an unapproved NDA may not include data to support an indication or claim that was not included in the original NDA submission, but it may include data to support a minor modification of the indication or claim that was included in the original NDA submission (21 CFR 314.60(b)(6)).

Please refer to the below comments regarding recommended content to be included with the original NDA.

2.1. Non-Clinical

Question 1: Does the Agency agree that the nonclinical safety studies undertaken, as outlined below, are sufficient to support NDA 217188? All components of the nonclinical safety package have been submitted to the IND with exception of the ongoing PPND study in rats. The sponsor intends to submit the PPND study report in April 2022. Upon completion and submission of the PPND study, the sponsor considers the nonclinical safety package complete for the NDA submission of PAXLOVID.

FDA Response to Question 1: Yes, we agree that nonclinical safety studies undertaken are sufficient to support NDA 217188. We also remind you that, besides the final report of the ongoing pre- and postnatal development (PPND) study in rats, you have only submitted unaudited draft reports of the 1-month repeat-dose toxicity studies in rats (#21GR122) and monkeys (#21GR125) (on November 24, 2021, to support EUA 105). It's unclear whether you plan to include the final reports of the 1-month repeat-dose toxicity studies in the NDA submission. Please comment on when you plan to submit the final reports for these studies.

Question 2: Does the Agency agree that the nonclinical virology antiviral resistance studies undertaken or planned, as outlined below in Table 3, are sufficient to support NDA 217188? Upon completion of the studies, the sponsor considers the nonclinical virology antiviral resistance package complete for the NDA submission of PAXLOVID and will have data to update the relevant section of the label.

FDA Response to Question 2: We do not fully agree. While we agree that nonclinical resistance studies using SARS-CoV-2 are more likely to be relevant than those using MHV, and results will be interpreted accordingly, we still request the MHV selection study report PF-07321332_12Oct21_035634 be included in the NDA as this study could still be supportive for identifying potentially important nirmatrelvir resistance pathways. For example, nirmatrelvir selection of MHV resulted in the emergence of the Mpro S144A substitution (as well as other substitutions), which, when engineered into a recombinant SARS-CoV-2 Mpro enzyme, reduced nirmatrelvir susceptibility by 92-fold

in a biochemical assay. The MHV selection study confirmed that this substitution could emerge during viral replication in the presence of nirmatrelvir selective pressure.

Please also continue to phenotypically characterize specific amino acid changes potentially associated with reduced nirmatrelvir susceptibility. This includes analyses of recombinant viruses encoding the substitutions of interest as described under EUA Condition "O1" (letter March 17, 2022), as well as cell culture and/or biochemical phenotypic analyses of other potential nirmatrelvir resistance-associated substitutions identified in nonclinical and clinical studies (e.g., treatment-emergent substitutions identified in Study 1005). Include a current report with cumulative data from these studies in the NDA. In the report include a summary of phenotypic analyses that are ongoing and planned at the time of NDA submission.

Please also plan to include all other supporting nonclinical virology-related study reports (e.g., mechanism of action; biochemical and cell culture antiviral activity; combination antiviral activity with ritonavir, remdesivir or other antiviral agents; cytotoxicity).

Please evaluate in cell culture assays the effect of nirmatrelvir/ritonavir on the anti-influenza virus activity of (a) oseltamivir and (b) baloxavir, and conversely the effect of (a) oseltamivir and (b) baloxavir on the anti-SARS-CoV-2 activity of nirmatrelvir/ritonavir. Completion of these studies would not be required for the initial NDA, but we recommend the studies are at least ongoing at the time of NDA submission, so data are available in a timely manner to inform the potential use of these agents in individuals co-infected with SARS-CoV-2 and influenza virus.

Please include a summary of virology studies in NDA Module 2.

2.2. Clinical

Question 3: For the NDA, the sponsor is planning to pool available safety data from ongoing clinical studies for PAXLOVID and summarize in the SCS. The integrated safety data will include data from Study 1005 PCD CSR, and Study 1002. (b) (4) Safety data from Study 1006 (expected to be completed at the time of submission for the NDA), following 5 or 10-day dosing regimen of PAXLOVID, will be provided in the SCS and would not be pooled with Studies 1005 and 1002. Does the Agency agree with (b) (4) presentation of separate pediatric (Study 1026) and EPIC-PEP (Study 1006) safety data for evaluating the overall safety of PAXLOVID in COVID-19 patients? Also, does the Agency agree with the analyses outlined in the iSAP?

FDA Response to Question 3: As noted in our opening General FDA Comments, please clarify the proposed original NDA indication(s). You indicate in your background package (b) (4)

[redacted] Based on this understanding, we provide the below comments regarding Question 3:

1. Please provide timelines on the expected safety and efficacy data locks for EPIC-PEP and EPIC-SR and timelines for these trial clinical study reports.

2. We strongly recommend that the original NDA incorporates complete efficacy and safety results from EPIC-HR along with at least EPIC-PEP and preferably both EPIC-PEP and EPIC-SR. Our recommendation is based on the following:

   a. [redacted] As mentioned in the General FDA comments, any additional claims that are not included in the initial NDA would be reviewed under a new NDA review clock or as efficacy supplements; [redacted].

   b. As stated in the FDA Guidance for Industry, *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019), FDA will consider a number of factors when determining whether to rely on a single adequate and well-controlled clinical investigation to support an NDA. These factors may include the persuasiveness of the single trial, the robustness of the confirmatory evidence, the seriousness of the disease and whether there is an unmet medical need, the size of the patient population, and whether it is ethical and practicable to conduct more than one adequate and well-controlled clinical investigation.

      While we acknowledge the robustness of the results for EPIC-HR, and the nonclinical supportive data, we believe additional data from EPIC-PEP and/or EPIC-SR trials could support effectiveness and provide broader information about the drug's effectiveness. Because EPIC-PEP should be complete and EPIC-SR should be within 3 months of completion at the time you currently plan to submit your NDA, we strongly encourage you to

include either or both of these Phase 2/3 trials with the submission of the original NDA.

c. We note that even under a rolling review, application sections are expected to be complete at the time of submission (e.g., we would expect submission of a complete clinical section at the time of submission). You will need to submit a request for rolling review if a rolling review is desired.

We would be willing to have an additional meeting to discuss the proposed contents of an original NDA that include EPIC-PEP efficacy data or EPIC-PEP and EPIC-SR efficacy data. Please review the FDA guidance, *"Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry"* (December 2017)[2], to ensure you submit the appropriate meeting request type. This will facilitate the Agency's alignment of resources to provide an efficient and timely response to your meeting request.

3. (b) (4)

4. While the pooling strategy for the safety data does not seem unreasonable, we do not agree with the quantity of data being proposed to support this NDA as outlined above and recommend inclusion of EPIC-PEP and/or EPIC-SR efficacy data with an original NDA submission.

[2] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-sponsors-or-applicants-pdufa-products-guidance-industry

2.3. Clinical Virology

Question 4: Does the Agency agree that submission of in vitro infectivity/phenotypic data from Study 1005 breakthrough cases and the final viral sequencing report including raw sequencing data is sufficient to support NDA approval?

FDA Response to Question 4:
We do not fully agree. As noted above (Question 2: Antiviral Resistance Assessments), and in addition to your planned analyses of samples from "breakthrough" cases, please also continue to phenotypically characterize specific amino acid changes potentially associated with reduced nirmatrelvir susceptibility in nonclinical or clinical studies. These analyses should include nirmatrelvir treatment-emergent substitutions identified in Study 1005 regardless of whether they were detected in samples from "breakthrough" cases. Include a current report with cumulative data from these studies in the NDA. In the report include a summary of phenotypic analyses that are ongoing and planned at the time of NDA submission.

2.4. Narrative Strategy

Question 5: The sponsor is planning to continue to write hybrid narratives for safety events using the same format as submitted in the PAXLOVID EUA and Study 1005 CSRs. The sponsor does not plan to provide completed CRFs for participants with safety narratives. Does the Agency agree with the proposed safety narrative strategy for NDA 217188?

FDA Response to Question 5: We request that you include safety narratives for subjects with Grade 3 or higher AEs, significant hypersensitivity reactions, and subjects who meet DILI criteria. Otherwise, the proposed safety narrative strategy appears reasonable.

2.5. Data Standards

Question 6: Does the Agency agree, as outlined below, with the proposed format, standards and structure of the datasets that are planned to be submitted with the NDA?

FDA Response to Question 6: Your overall proposed plan appears reasonable. In regard to the Clinical Virology datasets, we generally agree with your plans for the submission of viral sequencing data as previously conducted for Study 1005. More specifically, please include available, cumulative raw NGS fastq data files along with an associated cumulative amino acid frequency table following the same formats as previously done for Study 1005 for the EUA. In the frequency table, please include an additional column flagging all data rows that are updated or new relative to the latest table/dataset submitted to the EUA (i.e., latest EUA submission by the date of

NDA submission). Note that if it helps to streamline the virology datasets included in the NDA, it is not necessary to assemble and submit the more comprehensive analysis ready datasets (e.g., ADVIRG and CMBVIRG).

2.6. Regulatory

Question 7: The sponsor is planning to submit a separate CMC specific briefing document ahead of the NDA submission. In the meantime, the sponsor would like to understand whether it is acceptable to discuss certain CMC questions related to the NDA preparation following the accelerated communication pathways agreed for the EUA. For example, if the sponsor requires clarification, seeks guidance, or likes to provide an update on the commitments made in the EUA that impact the NDA, eg, to revise the dissolution method, would the Agency agree to communication or meetings under the umbrella of the EUA to ensure alignment between the Agency and the sponsor?

FDA Response to Question 7: We encourage you to request a pre-NDA CMC-specific meeting. In order to facilitate your NDA submission, we will make every effort to address other requests for clarification, guidance or comments regarding dissolution related or other CMC information in a timely manner, as resources permit.

Question 8: In consideration that an Advisory Committee meeting was not convened prior to the issuance of the EUA 000105 for PAXLOVID, can the Agency confirm that an Advisory Committee meeting is not expected to be convened prior to approval of the NDA?

FDA Response to Question 8: The Agency's decision to hold an Advisory Committee meeting for a new molecular entity or new chemical entity will be made at the time FDA filing (i.e., 60 days after receipt of the original NDA).

Question 9: The sponsor submitted a request for Fast Track Designation for PAXLOVID to IND 153517 on 28 January 2022. Can the Agency confirm that relevant criteria are met such that PAXLOVID is also eligible for Priority Review?

FDA Response to Question 9: Qualifying criteria for priority review designation can be found within the FDA Guidance, *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014)[3]. The Agency will determine at the time of NDA filing whether the proposed product would be a significant improvement in safety or effectiveness of the treatment, prevention, or diagnosis of a serious condition. Pfizer may submit a request for priority review with the original NDA submission if they believe they meet the qualifying criteria for Priority Review.

[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics

Question 10: The sponsor plans [redacted] (b) (4) [redacted]. The sponsor proposes to also submit the available data sets to the NDA for consideration. Does the agency agree that these data sets can be submitted to the NDA for review?

FDA Response to Question 10: As noted in our response to Question 3, we strongly recommend that you do not submit your NDA until you can incorporate, at a minimum, complete safety and efficacy results from at least EPIC-PEP. We also remind you that application sections are expected to be complete at the time of NDA submission [redacted] (b) (4) [redacted] Please refer to the General FDA Comments for additional information.

2.7. Additional Comments

1. To facilitate efficient review of your clinical pharmacology information, please submit the following summary documents with your NDA 1) the provided method validation template for each respective clinical pharmacology study and 2) the attached in vitro ADME and in vivo PK study table template as a MS Word document file (.doc or .docx). A pdf copy of the template for each summary document is included at the end of this Written Response.

2. Please plan to provide a comprehensive review of post-authorization safety events with PAXLOVID in your NDA submission, including reports of events that may have occurred as a result of drug-drug interactions. This review should also include an assessment of post-authorization events related to the warnings and precautions in Norvir labeling, such as hypersensitivity reactions and pancreatitis.

3. The design of the Paxlovid 150 mg;100 mg packaging configuration is not optimized [redacted] (b) (4) [redacted], despite labeling mitigations. To minimize confusion and potential sources of medication error, we recommend you explore and develop a more optimal packaging configuration for NDA submission [redacted] (b) (4) [redacted] and is consistent with dosing.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed in this document.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- At this time, a preliminary discussion was not held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

4.0 INCLUSION OF MINORITIES IN CLINICAL TRIALS

The Agency encourages the inclusion of a diverse population in all phases of drug development. This inclusion helps to ensure that medical products are safe and effective for everyone. We strongly encourage the enrollment of populations most affected by COVID-19, specifically racial and ethnic minorities. Please incorporate strategies to ensure that a diverse population is included in your current and future COVID-19 clinical trials.

5.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric*

Study Plans and Amended Pediatric Study Plans.[4] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[5]

6.0 PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[6] and Pregnancy and Lactation Labeling Final Rule[7] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the

[4] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[5] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[6] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[7] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

7.0 DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start/end of trial period (i.e., method of assignment of study events to a specific study

period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

8.0 MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[8] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[9]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

9.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the

[8] https://www.fda.gov/media/84223/download
[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[10]

[10] https://www.fda.gov/media/85061/download

BioAnalytical method validation summary

Regarding NDA 217188, please complete the bioanalytical method performance summary table below for for each clinical pharmacology study. Do not delete any rows from the tables. Include any other additional bioanalytical information in a separate table that might be relevant for review in your NDA submission. We recommend you submit these tables in eCTD Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods as pdf and docx formats.

Table 1. Summary method performance of a bioanalytical method to measure [analyte] in [matrix]

Bioanalytical method validation report name, amendments, and hyperlinks			
Method description			
Materials used for calibration curve & concentration			
Validated assay range			
Material used for QCs & concentration			
Minimum required dilutions (MRDs)			
Source & lot of reagents (LBA)			
Regression model & weighting			
Validation parameters	**Method validation summary**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	x	Eg. Table 1 of report # 123
	Cumulative accuracy (%bias) from LLOQ to ULOQ Product A Product B and/or C [Applicable for bioanalytical method in 351(k). Delete for other applications]	 x to y% x to y%	Table y of 2 report #123
	Cumulative precision (%CV) from LLOQ to ULOQ Product A Product B and/or C [Applicable for bioanalytical method in 351(k). Delete for other applications]	 ≤ x% ≤ x%	Table 4 of report #123
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 5 QCs** QCs: Product A Product B and/or C	 x to y% x to y%	Table 5 of report #123
	Inter-batch %CV QCs: Product A Product B and/or C	 ≤ x% ≤ x%	Table 6 of report #123
	Total Error (TE) QCs: Product A Product B and/or C	 ≤ x% ≤ x%	Table 7 of report #123
Selectivity & matrix	Number of total lots tested. Range of observed bias. State any issue		

effect		
Interference & specificity	Number of total lots tested. Range of observed bias. State any issue	
Hemolysis effect	Number of total lots tested. Range of observed bias. State any issue	
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue	
Dilution linearity & hook effect	Highest concentration tested and number of dilution factors. Range of observed bias	
Bench-top/process stability	Describe summary data here Product A Product B/C	
Freeze-Thaw stability	Describe summary data here Product A Product B/C	
Long-term storage	Describe summary data here Product A Product B/C	
Parallelism	Describe summary data here.	
Carry over	Describe summary data here	
Method performance in study number (In addition to the report name, also provide hyperlink to the report)		
Assay passing rate	(including incurred sample reanalysis (ISR))	
Standard curve performance	• Cumulative bias range: x to y% • Cumulative precision: ≤ x% CV	
QC performance	• Cumulative bias range: x to y% • Cumulative precision: ≤ x% CV • TE: ≤ x% (LBA only)	
Method reproducibility	Incurred sample reanalysis was performed in x% of study samples and x % of samples met the pre-specified criteria	
Study sample analysis/ stability	Describe the length of storage stability for standard/QCs and study samples and the coverage	

If the method above was modified, describe the modification(s) and cross-validation results, with any additional information in Table 2 below.

Table 2. Summary of method [x] modification(s) and cross-validation results

Bioanalytical method validation report name and hyperlink		
Changes in method		
New validated assay range if any		
Validation parameters	**Cross-validation performance**	**Source location (hyperlinked)**

Standard calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	x to y%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ x%	
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	x to y%	
	Inter-batch %CV	≤ x%	
	Percent total error (TE)	≤ x%	
Cross-validation	Numbers of spiked or incurred samples analyzed and result		
List other parameters			

Clinical Pharmacology In Vitro and In Vivo Study Table Template

For the following clinical pharmacology study types, please provide the below requested information in MS Word format:

In Vitro ADME Studies

Report Title	
Study Type	
Positive control(s) and concentrations	
Negative control(s) and concentration	
Report Number (with hyperlink to the full report)	
Study System (for example whole blood, plasma, recombinant enzymes, transfected cells, cryopreserved hepatocytes etc.)	
Method	Note: Include a very brief description of the methods. For drug interaction studies, please use cutoff criteria recommended in FDA drug interaction guidance.
Results	Note: Include a brief description of the major findings of the study. Also include the results of the positive control when applicable.
Discussion/Conclusion	Provide a succinct discussion of the results and their clinical relevance. Please indicate if a follow up in vivo trial was conducted to confirm the in vitro findings. If yes, please include the hyperlink to the complete study report. If not, please indicate why a follow up in vivo trial was not conducted.

In Vivo PK Studies

Location	Study # with hyperlink
Title	
Brief Description of Trial Design	
PK sample collection times	
Results	For each analyte, please include a table with PK parameters (for example, AUC, Cmax, Ctrough (if applicable), t1/2). For each comparison of PK parameters between groups, include a table of statistical comparisons (if applicable) of the PK parameters, including (GLSMs, GLSM ratio, 90% CI)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUZANNE K STRAYHORN
04/13/2022 09:35:03 AM