CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216482Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 140359

MEETING MINUTES

Alkem Laboratories Limited
c/o: Ascend Laboratories, LLC
Attention: Hindy Schiff
339 Jefferson Road
Parsippany, NJ 07054

Dear Ms. Schiff:

Please refer to your Pre-Investigational New Drug Application (PIND) file for mycophenolate mofetil oral suspension 200 mg/mL.

We also refer to the meeting, held in teleconference format, between representatives of your firm and the FDA on September 7, 2018. The purpose of the meeting was to discuss your plans to submit a New Drug Application via the 505(b)(2) regulatory pathway for mycophenolate mofetil oral suspension, 200mg/mL.

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

If you have any questions, call Derek Alberding, Regulatory Health Project Manager at (240) 402-0963.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-IND
Meeting Date and Time:	September 7, 2018, 10:00 a.m. – 11:00 a.m. ET
Meeting Location:	Teleconference
Application Number:	PIND 140359
Product Name:	mycophenolate mofetil oral suspension, 200 mg/mL
Indication:	Prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants
Sponsor Name:	Alkem Laboratories Limited
Meeting Chair:	Renata Albrecht, M.D.
Meeting Recorder:	Derek Alberding, PharmD

FDA ATTENDEES

Renata Albrecht, M.D.	Director, Division of Transplant and Ophthalmology Products (DTOP)
Ozlem Belen, M.D., M.P.H.	Deputy Director for Safety, DTOP
Ergun Velidedeoglu, M.D.	Medical Officer, DTOP
Marc Cavaillé-Coll, M.D.	Medical Officer, DTOP
Shukal Bala, Ph.D.	Clinical Microbiology/Immunology Reviewer, Division of Anti-Infective Products
Lori Kotch, Ph.D.	Pharmacology/Toxicology Supervisor, DTOP
Andrew McDougal, Ph.D.	Pharmacology/Toxicology Reviewer, DTOP
Philip Colangelo, PharmD, Ph.D.	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology IV (DCPIV)
Amit Somani, Ph.D.	Clinical Pharmacology Reviewer, OCP/DCPIV
Chunchun Zhang, Ph.D.	Product Quality Team Leader, Office of Pharmaceutical Quality (OPQ)/Office of New Drug Products (ONDP)
Peter Guerrieri, Ph.D.	Product Quality Reviewer, OPQ/ONDP
Judit Milstein, B.S.	Chief, Project Management Staff, DTOP
Derek Alberding, PharmD	Regulatory Health Project Manager, DTOP

ALKEM ATTENDEES

Hindy Schiff	US Agent for Alkem
Ujwal Chhabra	AVP, Regulatory Affairs
Dr. Akhilesh Sharma	President and Chief Medical Officer
Dr. Radha Krishna	V.P., Bioequivalence
[redacted] (b) (4)	

BACKGROUND

Alkem Laboratories Limited (Alkem) is developing a ready to use formulation of mycophenolate mofetil oral suspension. On July 10, 2018, Alkem requested a Pre-IND Type B meeting to discuss plans to submit a New Drug Application via the 505(b)(2) regulatory pathway for mycophenolate mofetil oral suspension, 200mg/mL. The teleconference was scheduled for September 7, 2018. FDA issued Preliminary Comments on August 29, 2018, in response to questions included in the July 10, 2018, Meeting Request.

DISCUSSION

For the purposes of this response, the questions submitted in the July 10, 2018, Meeting Request are re-numbered sequentially in **bold** font, our August 28, 2018, preliminary responses are in *italics* font, and the September 7, 2018, meeting discussions are in normal font.

Regulatory Pathway Agreement

1. **The sponsor plans to submit an NDA for Mycophenolate Oral Suspension, 200mg/ml via the 505(b)(2) regulatory pathway. Mycophenolate Oral Suspension, 200mg/ml is intended to be a new, ready-to-use liquid formulation of Mycophenolate. The sponsor intends to seek the same label as the Listed Drug, CELLCEPT (NDA 050759), which will be prescribed at the same doses and dosing regimens as CELLCEPT. The Sponsor proposes to rely on the following information to support product approval:**

   - **The FDA's previous findings of safety (nonclinical and clinical) and efficacy of Mycophenolate mofetil as reflected in the approved labeling for the Listed Drug;**
   - [redacted] (b) (4) **and**
   - **Findings from a sponsor-conducted nonclinical pharmacology study and a nonclinical toxicity study to satisfy safety requirements of the NDAs.**

   a. **Does the Agency agree that the 505(b)(2) regulatory pathway is appropriate for submission of the proposed Mycophenolate mofetil Oral Suspension, 200mg/mL NDA?**

FDA Response:
Yes, we agree and refer you to the Additional FDA Comments regarding the 505(b)(2) REGULATORY PATHWAY, located later in this document.

Meeting Discussion: None.

b. Does the Agency agree that CELLCEPT (NDA 050759) is the appropriate Listed Drug?

FDA Response:
Yes, we agree.

Meeting Discussion: None.

2. The Pediatric Research Equity Act (PREA) requires NDAs for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the application has obtained a waiver or deferral.

Sponsor intends to seek the same labeling as Cellcept powder for oral suspension for its Mycophenolate mofetil oral suspension. Cellcept powder for oral suspension is indicated for use in pediatric patients, therefore, sponsor requests for full waiver for pediatric study plan as the RLD is currently approved in pediatrics.

a. Does the Division agree that the proposed full waiver for pediatric subjects is reasonable?

b. Does the Division require a pediatric assessment for use in those subjects for the new product?

FDA Response:
Regarding PREA, the sponsor is expected to submit an initial pediatric study plan (iPSP) within 60 days of holding an end-of-Phase 2 meeting with the FDA. Part of the pediatric study plan can be to address the available pediatric information for the indications approved in adults, or request a waiver, if applicable. We also refer you to the Additional FDA Comments regarding PREA REQUIREMENTS, located later in this document.

Meeting Discussion:
The Sponsor stated that the proposed drug product contains established inactive ingredients, and the same active ingredient and route of administration as the proposed RLD (CellCept). The Sponsor acknowledged that CellCept is approved for kidney, liver and heart transplantation in adults, but approved only for kidney transplantation in pediatric patients. The Sponsor confirmed plans to seek the same labeling as the RLD.

CellCept, "mycophenolate mofetil for oral suspension" is marketed in powder form and reconstituted with water prior to dispensing to the patient. However, the current proposed product, "mycophenolate mofetil oral suspension" is intended to be marketed as a ready-to-use liquid formulation of mycophenolate mofetil.

The Division noted during the teleconference that "oral suspension" and "for oral suspension" are considered different dosage forms, and this was confirmed with staff from the Office of Pharmaceutical Quality (OPQ) following the meeting; therefore, PREA will apply to this 505(b)(2) application. The Division recommended that the Sponsor submit an initial Pediatric Study Plan (iPSP) and include a rationale to support their request for a waiver from PREA requirements as soon as possible.

Clinical Pharmacology Questions

3. **In order to support this application, as per the Agency's product specific guidance published on Oct 2017 for mycophenolate mofetil for oral suspension; we intend to conduct the in-vivo bioequivalence study under Fast and Fed conditions along with the** (b) (4) **on newly developed Mycophenolate Oral suspension of Sponsor's product and CellCept Oral Suspension (mycophenolate mofetil for oral suspension) 200mg/mL distributed by Roche Laboratories Inc, Nutley, New Jersey, USA.**

   The proposed protocols for in-vivo bioequivalence study under Fast and Fed conditions are provided along with this meeting request as Exhibit-1 and II respectively for Agency's review and comments, if any.

   Does the agency agree with the design of the studies proposed in the protocols appended along with meeting request package?

   FDA Response:
   We note that you cite the Agency's product specific guidance published on October 2017; please note this is a guidance intended for Generic Drug Development: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM217148.pdf

   However, since you are proposing to submit your product as part of a 505(b)(2) New Drug Application (NDA), we have the following specific advice for your drug development:

   Yes, the design of the proposed in vivo fed and fasted bioequivalence (BE) studies are generally acceptable, based on the protocols you have provided in Exhibits I and II. However, we have the following comments for the submitted protocols:

   - *Provide Annexure III that is cited in Section 11.2 of the fed BE protocol. This breakfast needs to be the same as that recommended in the Guidance for Industry Food-Effect Bioavailability and Fed Bioequivalence Studies Document (December 2002)*

- *Reconcile the discrepancy* (b) (4) (b) (4)

Please note that you plan to submit a 505(b)(2) NDA. Therefore, for pharmacokinetic (PK) bridging, it is not necessary to establish strict BE between your proposed drug product, i.e., mycophenolate mofetil (MMF) ready to use liquid for oral suspension, and the RLD, CellCept Oral Suspension. But rather, it is important to demonstrate that your proposed product shows comparable bioavailability (BA) in terms of both MMF and mycophenolic acid (MPA) plasma concentrations. However, if you can demonstrate that it is not possible to measure MMF concentrations in plasma accurately and reliably, then evaluate the comparative BA of MPA only, using the confidence interval approach.

Also, note that the proposed two studies in healthy subjects alone may not be adequate to support submission of a future 505(b)(2) NDA, and depending on the results of the proposed BE studies in healthy adult subjects, you may also need to conduct additional clinical safety and/or efficacy studies in transplant patients. See also the response to Question 4.

Meeting Discussion:
The Sponsor acknowledged the discrepancy noted in the BE protocol, and stated that amended protocols will be submitted.

The Division stated that the Sponsor is not required to establish strict BE between the proposed drug product and the Listed Drug, however the Division recommended the Sponsor apply the BE criteria of 80 to 125%. The Division stated that if the Sponsor is not able to accurately and reliably measure MMF plasma concentrations, it is acceptable to measure MPA only and apply the aforementioned BE criteria for MPA Cmax and AUC.

4. **Sponsor proposes that the BE between the proposed product and Cellcept is the basis for the scientific bridge to the FDA's findings of clinical safety and efficacy for Mycophenolate mofetil as reflected in the approved labeling (NDA 050759). Sponsor intends to rely on this information for the approval of the proposed product.**

   Does the Agency agree that if BE is established between the proposed product and the Listed Drug (Cellcept), no additional clinical efficacy and safety studies will be required to support the submission and approval of the 505(b)(2) application?

   FDA Response:
   It is premature to provide a definitive answer at this time. We agree with your proposal to conduct the proposed bioavailability studies in healthy adult subjects. However, depending on the results of these two studies in healthy adult subjects, you may also need to conduct additional clinical safety and/or efficacy studies in transplant patients to adequately support a future 505(b)(2) NDA submission for your proposed MMF oral suspension drug product. Without PK information from healthy subjects, it is not currently possible to determine the types (or numbers) of clinical studies that may be needed.

Meeting Discussion:
The Division clarified that additional clinical safety and/or efficacy studies in transplant patients may not be required if the BA/BE studies conclusively establish comparable systemic exposure to MPA and/or MMF, in terms of both Cmax and AUC, between the proposed product and the Listed Drug.

The Division stated that the results of the BA/BE studies need to be reviewed before determining the types (or numbers) of clinical studies that may be needed.

Non-Clinical Questions

5. **Sponsor proposes that the BE between the proposed product and Cellcept is the basis for the scientific bridge to the FDA's findings of nonclinical safety for Mycophenolate mofetil as reflected in the approved labelling (NDA 050759).**

   Does the Agency agree that the proposed nonclinical pharmacokinetic and toxicity studies supported by the Agency's previous findings of nonclinical safety of Mycophenolate mofetil and approval of the proposed 505(b)(2) submission will be sufficient for submission?

   FDA Response:
   We concur with your approach. Please be aware that nonclinical studies may be warranted to qualify impurities, to qualify changes to the formulation, or if the BE study is not sufficient for bridging.

   Meeting Discussion:
   The Sponsor acknowledged the Division's comments and plans to qualify impurities.

Chemistry, Manufacturing and Control Questions

6. **Qualitative and Quantitative Composition along with functions and limit as per the IID data base is being provided as follows - [*see meeting request*]**

   Does the above proposal of inactive ingredients with quantities acceptable to the Agency?

   FDA Response:
   The excipients proposed to be used in the formulation seem reasonable.

   Meeting Discussion: None.

7. **Quality Target Product Profile**

   The Critical Quality Attributes that are evaluated during development of the proposed product are tabulated [*see meeting request*]:

In addition to the above, parameters such as physical stability, palatability assessment, dosing accuracy, elemental impurities, leachable and extractable will be carried out on the product or adequate justifications will be provided in the NDA package submission.

Does the Agency agree that the identified Critical Quality Attributes of the proposed product are suitable to guide product development?

FDA Response:
The identified critical quality attributes appear to be reasonable to adequately guide product development. Assessment of the overall control strategy to address critical quality attributes will be a review issue. Please indicate if the suspension has any settling issues; an evaluation of physical stability should include re-dispersibility.

Meeting Discussion:
The Sponsor acknowledged the Division comments, and stated that they would perform re-dispersibility studies and evaluate the need for a re-dispersibility test in the drug product specifications.

8. Impurity Justification

As per above table, all the critical quality attributes specified for the drug product were found satisfactory at 25°C and 40% RH. (b) (4) Specified unidentified impurity at (b) (4) will be identified and qualified by toxicity studies in animals for higher limits up to (b) (4) as per ICH Q3B in drug product. Thus, Mycophenolate mofetil oral suspension 200mg/mL developed in the lab and evaluated for critical physico-chemical attributes is found complying with CQAs for the drug product. From the data, it is recommended to store the product at not more than 25°C for the storage and transportation.
Does agency agree that the justification provided for (b) (4) and specified unknown impurity at (b) (4) level is reasonable for the proposed product?

FDA Response:
The approach to establish limits for (b) (4) and the specified unknown impurity at (b) (4) appears to be reasonable. Final assessment of drug product release and stability specification limits for impurities will be a review issue. Justification for the limit for total impurities should also be provided with your submission.

Meeting Discussion:
The Division acknowledged the Sponsor's plan to identify the impurity at (b) (4) and qualify it with an animal toxicological study, and stated that the Sponsor should also include a justification for the limit for total impurities.

Miscellaneous/Administrative Questions

9. Considering the above proposed plan of 505(b)(2) submission for a new dosage form, will the applicant be eligible for a 3 years exclusivity period?

FDA Response:
A 505(b)(2) application may be granted 3 years of Waxman-Hatch exclusivity if one or more of the clinical investigations, other than Bioavailability/Bioequivalence (BA/BE) studies, was essential to approval of the application and was conducted or sponsored by the applicant (21 CFR 314.50(j); 314.108(b)(4) and (5)).

Please be advised that the Agency does not make exclusivity determinations until after approval of an NDA. As described at 314.50(j), an applicant should include in its NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will consider the applicant's assertions regarding exclusivity in the review of the application.

Meeting Discussion: None.

10. As per the Prescription Drug User Fee Act (PDUFA), an application fee (without clinical data) of USD 1,210,748 would only be applicable. The program fee will not be applicable. Does the Agency agree with the applicants understanding?

FDA Response:
According to section 736(a)(1)(A)(ii) of the Act "A fee established under subsection (c)(5) for a human drug application for which clinical data (other than BA/BE studies) with respect to safety or effectiveness are not required for approval, such fee shall be half of the amount of the fee established under clause (i)." The fee required by subparagraph (A) shall be due upon submission of the application.

You have indicated that you will be relying on the following information to support product approval of mycophenolate mofetil oral suspension:

a. The FDA's previous findings of safety (nonclinical and clinical) and efficacy of mycophenolate mofetil.
b. Findings from a sponsor-conducted nonclinical pharmacology study and a nonclinical toxicity study to satisfy safety requirements of the NDAs.

(b) (4)

(b) (4)

(b) (4) *The final determination regarding user fees will be made when the application is submitted in its entirety.*

The Prescription Drug Program fee is assessed after a product gains approval.

Meeting Discussion: None.

Additional FDA Comments

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to

justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR

314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. 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: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the

availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the

CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

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/

RENATA ALBRECHT
09/19/2018