CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213876Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 123322

MEETING MINUTES

Envigo, U.S. Agent for Diurnal Limited
Attention: Scott Wadsworth, Ph.D., PMP
Director, Program Management
100 Mettlers Road
East Millstone, NJ 08875-2360

Dear Dr. Wadsworth:

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

We also refer to the meeting between representatives of your firm and the FDA on February 6, 2019. The purpose of the meeting was to discuss available data package for a proposed literature-based 505(b)(2) New Drug Application (NDA) for this product for the treatment of pediatric adrenal insufficiency (AI).

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

If you have any questions, call Jennifer Johnson, Regulatory Health Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

William Chong, M.D.
Deputy Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
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:	Type C
Meeting Category:	Guidance
Meeting Date and Time:	Wednesday, February 6, 2019; 12:00 – 1:30 pm EST
Meeting Location:	White Oak Building 22, Conference Room 1309
Application Number:	IND 123322
Product Name:	hydrocortisone oral granules
Indication:	treatment of pediatric adrenal insufficiency (AI)
Sponsor Name:	Diurnal Limited
Meeting Chair:	William Chong, M.D.
Meeting Recorder:	Jennifer Johnson

FDA ATTENDEES

Office of Drug Evaluation II, Division of Metabolism and Endocrinology Products

William Chong, M.D.	Acting Deputy Director
Marina Zemskova, M.D.	Clinical Team Leader
Shannon Sullivan, M.D., PhD	Acting Clinical Team Leader
Diala El-Maouche, M.D.	Clinical Reviewer
Fred Alavi, Ph.D.	Pharmacology/Toxicology Reviewer
Pam Lucarelli	Chief, Project Management Staff
Jennifer Johnson	Regulatory Health Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology 2

Jaya Vaidyanathan, Ph.D.	Clinical Pharmacology Team Leader
Yunzhao Ren, Ph.D.	Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality, Office of New Drug Products

Danae Christodoulou, Ph.D.	Branch Chief, New Drug Product Division 2

Office of Biostatistics, Division of Biometrics 2

Sara Jimenez, Ph.D.	Acting Statistics Team Leader

Office of Surveillance and Epidemiology

Deveonne Hamilton-Stokes, RN, BSN, MA	Safety Regulatory Project Manager
Nichelle Rashid	Acting Chief, Safety Project Management Staff

Division of Medication Error Prevention Analysis

Susan Rimmel, Pharm.D.	Safety Evaluator
Teresa Mcmillan, Pharm.D.	Acting Team Leader

Sevan Kolejian, Pharm.D., MBA	Team Leader

Office of Drug Evaluation IV, Division of Pediatric and Maternal Health

Gettie Audain, MPH, BSN, RN	Senior Regulatory Health Project Manager
Ethan Hausman, M.D.	Medical Reviewer
Hari Cheryl Sachs, M.D.	Medical Team Lead

SPONSOR ATTENDEES

Representing Diurnal Limited

Dr. Martin Whitaker	Chief Executive Officer
Professor Richard Ross	Chief Scientific Officer
Dr. John Porter	Medical Director
Michael Bateman	Head of Regulatory
Michael Edwards	Regulatory Project Manager (via teleconference)

1.0 BACKGROUND

Diurnal Ltd (Diurnal) is developing a hydrocortisone multi-particulate granule formulation stored in capsules in which the multi-particulate capsule contents are to be administered directly into the child's mouth without consuming the capsule. This can be achieved by placing the granules onto a dry spoon which is then administered into the child's mouth, or by administering the granules directly onto the top and towards the back of the child's tongue, or for infants who have weaned and older children the granules can be sprinkled onto a spoonful of cold or room temperature yogurt or fruit puree (e.g., applesauce) immediately before administration. The granules can then be washed down with water, breast milk, formula milk or whole milk.

Currently marketed oral hydrocortisone products are solid tablet formulations that must be split or ground for use in pediatric patients. Diurnal proposes to submit a 505(b)(2) literature-based New Drug Application (NDA) for their product seeking an indication for treatment of pediatric adrenal insufficiency (AI).

Diurnal's clinical development plan has consisted of completion of four phase 1 studies in dexamethasone-suppressed healthy adults (Infacort studies 001, 002, 006 and 007) and two phase 3 studies (Infacort studies 003 and 004) in pediatric patients with adrenal insufficiency. All studies were conducted within the EU. Study 003 is a single pivotal open-label study to evaluate the efficacy of Infacort in the target patient population; Study 004 is an open-label follow-up study for patients who have satisfactorily completed Study 003 and wished to continue receiving treatment.

An orphan drug application for Infacort for the treatment of pediatric AI (0 through 16 years of age) was granted by the FDA in May 2015.

The proposed proprietary name, Infacort, has not yet been reviewed. However, because this proposed proprietary name is used throughout the briefing package, this proposed proprietary name is used in this document solely for convenience.

The sponsor requested this meeting on October 17, 2018, to discuss the data package for their proposed NDA. A Meeting Granted letter was issued on November 7, 2018. On December 5, 2018, the sponsor submitted a meeting background package.

FDA sent Preliminary Comments to Diurnal on February 1, 2019.

2. DISCUSSION

The sponsor's questions are repeated below in regular text, followed by the FDA response (bolded) and meeting discussion (bolded/italicized).

Question 1: Following the Agency's review of the Infacort IND, and regarding the overall clinical study program, does the Agency agree that the clinical data package (studies Infacort 001-004, Infacort 006, and Infacort 007) is adequate to support a literature-based 505(b)(2) application for Infacort to treat pediatric AI?

FDA Response to Question 1: Based on the information submitted in your briefing package, the completed clinical studies may be sufficient to support filing of your NDA. However, whether the data from clinical studies will support the proposed indication will be a review issue.

Please clarify the following:

1. **You state that you plan to submit a literature-based 505(b)(2) application to treat pediatric AI. You also conducted PK studies evaluating bioequivalence between your drug and other hydrocortisone formulations (e.g., Infacort 001, 002). Thus, it remains unclear whether you plan to rely on the FDA's previous findings of safety and effectiveness for one or more listed drugs (e.g., Cortef) and on information from the literature pertaining to hydrocortisone or to rely solely on published studies to establish safety and efficacy of your drug. Please clarify.**

   We remind you that if you plan to submit an NDA for Infacort under 505(b)(2) of the Food, Drugs, and Cosmetics Act that relies on the FDA's previous findings on safety and/or effectiveness for one or more listed drugs and/or on information from the literature pertaining to listed drug(s) you need to identify each of those listed drug(s). As with all 505(b)(2) applications, you should establish a "bridge" between the active ingredients in your product and each of the listed drug (s) upon which you propose to rely to demonstrate that such reliance is scientifically justified, and must submit data necessary to support any aspects of the proposed drug product that differ from the listed drug(s) relied upon.

   Please note that if you seek 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 is scientifically appropriate. Whether or not the scientific justification for reliance is appropriate and whether or not information from the studies you propose to rely on, provides sufficient evidence

to establish that your drug is safe and effective for the indication you seek will be a review issue.

2. **Clarify the intended population and/or specific age group you intend to indicate your drug for (e.g., all pediatric patients 0-16 years old, children < 6 years old). Clarify why you do not plan to develop/indicate your drug for use in adults with AI.**

Discussion during FDA meeting:
Refer to slide 8 of sponsor presentation in Section 6.0. The sponsor stated that they plan to rely on the RLD Cortef, as bioequivalence to their proposed product has been demonstrated. FDA asked if the source of the comparator was a U.S. product. The sponsor said that for Infacort studies 001 and 002, the source of the comparator was a UK product. However, a U.S. product was used in subsequent studies submitted to the IND and conducted in the UK. FDA said that this should be acceptable but would still be a review issue. FDA reminded the sponsor that the Cortef product has a wide range of does (20-140 mg), so they will need to provide evidence to support their proposed doses.

Refer to slide 9 of sponsor presentation in Section 6.0. FDA noted that Cortef is approved for several indications and asked the sponsor if they are only seeking the pediatric adrenal insufficiency indication; the sponsor confirmed that this is the only indication they are seeking at this time.

Question 2: Does the Agency agree that, given the small number of clinical studies which would be submitted in support of an NDA for Infacort, and the small size of the study population overall, sections 2.7.3, Summary of Clinical Efficacy, and 2.7.4, Summary of Clinical Safety, would be sufficiently detailed to serve as the Integrated Summaries of Effectiveness and Safety, respectively?

FDA Response to Question 2: Yes, we agree.

However, we request that you include in your NDA specific information to indicate what kind of information is contained in these publications so that we can assess whether the data included in these publications can be reasonably expected to support filing an NDA. You should submit in tabular format a summary of the information that you propose to submit for the clinical efficacy and safety section of the NDA. For instance, for efficacy, the table should describe the publication, the number of patients and the nature of the clinical trial design (including strengths and limitations), endpoints evaluated, type of efficacy analyses conducted, treatment effect, dose regimens evaluated, durations of metyrapone exposure, general conclusions that can be drawn on the basis of each specific publication. A similar approach should be followed for case-series, and case reports. Individual case reports for efficacy can be summarized as a group, if feasible.

At the time of NDA submission, you should indicate clearly where in the NDA one can find the specific source of information submitted in support of each label claim. In doing so, we encourage you to be as specific as possible.

Discussion during FDA meeting:
Refer to slides 10-12 of sponsor presentation in Section 6.0. The sponsor agreed to provide in the NDA submission summary tabulations as suggested, as well as detailed clinical summaries and tabulations in Module 2.7.3 and 2.7.4 and a clinical overview and tabulations in Module 2.5. The summaries and tabulations will be filed to the IND as well.

The sponsor also asked if it would be necessary to request a pre-NDA meeting to discuss the nature of the tabulations, or if draft tabulations could be submitted for comment and suitability by written correspondence. FDA said that a written feedback may be sufficient to address the tabulations. The sponsor estimated an NDA submission by the end of August if all goes smoothly and asked for clarification regarding the timeline for Pre-NDA meeting written response feedback. FDA stated that written feedback would be sent to the sponsor within 60 days of receipt of a meeting request, assuming that a meeting background package is submitted at least one month prior to the due date for issuing written responses.

The sponsor said that they will provide in the NDA submission an annotated label including hyperlinks to information supporting each labeling claim. FDA stated that this appears reasonable.

FDA asked if the sponsor expected to have a different dosage range for neonates, infants, toddlers, etc. The sponsor said that they plan to use the Endocrine Society dosing guidelines for treatment of AI in children. FDA said that the sponsor needs to clearly provide evidence for their proposed dose ranges.

Additional FDA Comments:

According to your submission, the granules are provided in hard capsules as the storage medium and the capsule itself is not intended for consumption. We are concerned the design of your product may lead to users swallowing the capsule whole due to negative transfer. A capsule can be suggestive of one method of administration (swallowing whole) even though it is not intended, and this would not match the user's expectation of how to use the product.

Postmarketing experience with similarly packaged marketed products (e.g., Spiriva and Aciphex Sprinkles) show that despite labeling and administration instructions, users still swallow the capsule whole. For example, despite graphical depiction and labeling instruction indicating Spiriva capsules are not to be swallowed, we are aware of many cases describing the error of patients swallowing the capsule.[1] Additionally, we have identified cases where "DO NOT crush or chew, SWALLOW WHOLE" auxiliary labels were automatically printed on pharmacy labels for Aciphex Sprinkle because the capsule

[1] Institute for Safe Medication Practices. Health Alerts. ISMP Med Saf Alert Community/Ambulatory Care. 2008. 7 (3): 3.

content is not intended to be crushed or chewed.[2] This has led to confusion and increased risk of incorrect administration.

We are concerned that the proposed presentation (granules packed in capsule) and intended mode of administration (capsule to be opened and granules to be sprinkled on back of tongue or on soft food or yogurt) may be associated with a potential safety issue of choking; infants and young children (the intended population) are even at greater risk.

In addition, the systemic exposure of hydrocortisone following the accidental swallow of the capsule has not been studied, which may raise efficacy concerns.

Please provide your rationale for why a different packaging configuration (b) (4) was not chosen. Please provide your rationale for why your proposed presentation is appropriate for this product. In addition, please note any safety/efficacy concerns and risks you have identified with users potentially swallowing the proposed dosage form and how these concerns/risks have been appropriately addressed.

Additionally, we note that you propose several strengths (0.5 mg, 1 mg, 2 mg, and 5 mg) in order to cover the total daily dosage ranges for the intended patient population. However, the exact dosage may not be achievable in some cases. For example, if a calculated total daily dosage of 13.2 mg (BSA is 1.32 for a 12-year-old girl) is required, we are unclear how healthcare professionals will determine and select the appropriate strength(s) for achieving the calculated dosage. We are also unclear whether users will understand and can safely prepare dosages requiring multiple strengths. In addition, we are unclear if users will need to divide the capsule contents (i.e., the granules inside the capsule) to achieve the calculated dosages. Please provide your mitigation strategies to ensure users understand how to select the appropriate strength and administer the appropriate dose required to achieve the recommended dosing for Infacort and also explain how you validated your mitigation strategies.

If you consider an alternate commercial configuration of your drug product, (b) (4) , you must generate and submit to the NDA application 12-month stability data under normal storage and 6-month stability data under accelerated storage for at least three batches of your drug product. You may propose bracketing of the different strengths. You will need also to assess the ability to sprinkle the drug product out of the lowest strength from (b) (4) This can be demonstrated in an *in-vitro* study, where the product is sprinkled in a solution and by assay determination you verify how much product is sprinkled.

Discussion during FDA meeting:
Refer to slides 13-16 of sponsor slide presentation in Section 6.0. The sponsor noted that the European Medicines Agency (EMA) also raised the concern of accidental swallowing prior to submission of their application. The sponsor brought sample capsules to demonstrate that

[2] Institute for Safe Medication Practices. Safety briefs: Patients should not swallow AcipHex Sprinkle capsules. ISMP Med Saf Alert Community/Ambulatory Care. 2017. 16 (12). 2-3.

Infacort capsules are significantly larger than FDA's cited examples (e.g., Spiriva and Aciphex Sprinkles), (b) (4)

<u>Choking Risk:</u>
FDA pointed out that the capsules being significantly larger is not necessarily a safety enhancement if placed in the child's mouth or accidentally ingested; despite clear labeling there have been reports of people accidentally swallowing capsules not intended for direct administration and choking is more likely with a large capsule. The sponsor said that they understand FDA's concerns and explained that the capsule presentation was chosen because parents and caregivers are accustomed to administering capsules to children, (b) (4) ***The sponsor also addressed FDA's concern about choking in young children (see slide 17), noting that Infacort has been studied in pediatric phase 3 trials for up to two years and has been marketed in Europe since May 2018 with no reports of choking. FDA asked the sponsor to confirm that there were no reports of choking since the product has been marketed in Europe. The sponsor said that was correct, that the first six-month periodic safety update report has been submitted, and the next one will be submitted this month. The sponsor has also developed a risk management plan which is undergoing review and would flag any incidents of choking (or other adverse events). FDA asked that available postmarketing data be provided in the NDA.***

<u>Drug Delivery:</u>
FDA noted there is also a concern about drug delivery if the capsule is swallowed whole, as opposed to being sprinkled, noting several FDA-approved capsules are also intended to be swallowed whole. Thus, FDA asked about the possibility of correct dosing in the case of swallowing (that is, would the proposed capsule interfere with the bioavailability of hydrocortisone). The sponsor replied that they will provide the in vitro dissolution profile to justify that the capsule product behaves as an immediate-release product. FDA commented that the acceptability of the in vitro dissolution results and the need for a clinical study to address this issue will be a review issue. FDA reminded the sponsor to include this result in the NDA submission for the biopharmaceutics team to review.

FDA asked if the product is approved in Europe for all ages or only for children under the age of six. The sponsor stated that their product is approved up to age 18 years per advice from the EMA. Even though studies were done in younger children, the product could be beneficial for children who cannot swallow, or if the practitioner is concerned about dose accuracy.

<u>Selecting Dose:</u>
The sponsor then addressed FDA's comments regarding safe and exact dosage delivery in children, as well as mitigation strategies for selecting the appropriate strength. See slides 18-26, which include instructions to prescribers and patients in the UK product (Alkindi) labeling, as well as a link to a multi-lingual dosing video for prescribers. FDA asked how the sponsor determined frequency of dosing, as recommendations differ depending on which resource is consulted. The sponsor said that they incorporated the Endocrine Society dosing guidelines of 3-4 times daily with the exact dosing regimen to be determined by the prescribing endocrinologist.

FDA asked if there are multiple doses and all capsules are the same size, how do you differentiate between doses, especially if capsules are mixed up at home? Are the capsules labeled? The sponsor replied that yes, there is a different printed color for each dose on the capsules. FDA asked if there are different colors on the labeling and labels; the sponsor confirmed that there are. (b) (4)

FDA asked if the sponsor intends the product only for oral administration or if there is consideration for administration via gastric tubes or other types of feeding tubes. The sponsor said that they do not intend the product to be administered via feeding tube (b) (4)

Additional Post-Meeting Comments

We refer to your meeting slides titled "Infacort IND 123322 Type C Meeting Presentation v1.0 05-Feb-2019.pdf." You have not adequately addressed or alleviated our safety concerns that are described in our Preliminary Meeting Comments. The table below outlines our previously communicated questions/concerns, your reply, and our assessment of your reply. Our additional post-meeting comments are provided following the table.

FDA Preliminary Meeting Comments	Diurnal's Reply	FDA Comments to Diurnal's Reply
Please provide your rationale for why a different packaging configuration (b) (4) *) was not chosen.*	(b) (4)	(b) (4) . However, we are unclear if you have thoroughly considered and explored other alternative packaging options that may be suitable for Infacort and are less vulnerable to the risk for medication errors to occur. We continue to have concerns with the proposed presentation for this product.
Please provide your rationale for why your	Capsules were identified as optimal presentation during pharmaceutical development	While we acknowledge there can be some benefits to the proposed capsule presentation, we note

FDA Preliminary Meeting Comments	Diurnal's Reply	FDA Comments to Diurnal's Reply
proposed presentation is appropriate for this product.	• Highly accurate & reproducible fill weight • Ease of opening & administration • Familiar dosage form for patients/caregivers (compounded crushed tablets in capsules) where available	you have not provided any additional data to support your rationale that the 'capsule' dosage form is the most appropriate presentation for the proposed product. In addition, you have not provided any additional data (e.g., human factors data) to support that the proposed product user interface supports the safe and effective use as you intend for this product, nor have you validated any proposed risk mitigation strategies to address potential use-related errors. Thus, we continue to have concerns with the proposed presentation for this product.
Please note any safety/efficacy concerns and risks you have identified with users potentially swallowing the proposed dosage form and how these concerns/risks have been	• Infacort capsules are significantly larger than examples cited by FDA (see image below). The size of the capsule is such that swallowing would be unlikely. (b) (4) [redacted]	We acknowledge that the capsule size for the examples cited (e.g., Spiriva and Aciphex Sprinkles) are smaller than the proposed capsule size for Infacort (b) (4) [redacted]. However, we note that there are currently marketed products that utilize larger capsule sizes (e.g., Suprax [cefixime] capsule 400 mg is contained in a 000 [26 mm] size capsule) and are intended for swallowing.[3] Thus, we disagree

[3] Suprax Prescribing Information for Suprax. DailyMed U.S. National Library of Medicine. March 2018. Cited 2019 FEB 13. Available from:

FDA Preliminary Meeting Comments	Diurnal's Reply	FDA Comments to Diurnal's Reply
appropriately addressed.	• Comprehensive guidance, including dosing diagram, will be given in patient information (see images and labeling below). (b) (4) [redacted]	with your statement that "the size of the capsule is such that swallowing would be unlikely." Please refer back to the concern we raised about the potential for administering the capsule whole to the upper age range of the intended patient population (e.g., adolescents that are 16 years old). We acknowledge that you are proposing to mitigate the risk of swallowing the capsule whole through labeling strategies; however, you did not explain how you validated your proposed labeling strategies. In addition, you did not provide adequate data to support that the residual risk of swallowing the capsule whole is acceptable (i.e., the clinical impact would not be concerning). Thus, you have not adequately addressed our safety concerns regarding the risks of swallowing the capsule whole.

https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d0fd45bd-7d52-4fa6-a5f7-f46d5651ffa2.

FDA Preliminary Meeting Comments	Diurnal's Reply	FDA Comments to Diurnal's Reply
	(b) (4)	
Please provide your mitigation strategies to ensure users understand how to select the appropriate strength and administer the	*Recommended Dosing* • Pediatric endocrinologists are aware of the limitations of current dosage forms of hydrocortisone • When calculating a dose, prescribers would normally round up or down to the nearest 1 mg or 0.5 mg	We acknowledge that you are proposing to mitigate the risk of improper dose errors through labeling strategies; however, you did not explain how you validated your proposed labeling strategies. Thus, you have not alleviated our concerns that users will not understand how to administer the

FDA Preliminary Meeting Comments	Diurnal's Reply	FDA Comments to Diurnal's Reply
appropriate dose required to achieve the recommended dosing for Infacort and also explain how you validated your mitigation strategies.	• Current compounded forms do not allow for accurate reproduction of 0.5 mg dose increments • BSA is used more in young children, in adolescents most prescribers would alter dosing to fit with expected adult dosing (e.g., in 5 mg increments). *Mitigation Strategies* (b) (4)	appropriate strength(s) to achieve the prescribed dosage.

We recommend that you conduct a comprehensive use-related risk analysis for your product, taking into account the safety concerns we have raised and considering the use and

administration of Infacort in the real-world use by the intended user groups (e.g., patients, caregivers, and healthcare professionals).

The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures.

Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable.

Based on this risk analysis, you will need to determine whether you need to submit the results of a human factors (HF) validation study conducted under simulated use conditions with representative users performing necessary tasks to demonstrate safe and effective use of the product.

If you determine that you do need to submit a HF validation study for your product, the risk analysis can be used to inform the design of a human factors validation study protocol for your product. We recommend you submit your study protocol for feedback from the Agency before commencing your study. Please note we will need 60 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly. Note that submission of a protocol for review is not a requirement. If you decide not to submit a protocol, this approach carries some risk to you because prospective Agency review is not possible, but this is a decision for your company.

Please refer to our draft guidance titled "Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications" for the content of a human factors validation study protocol submission. The guidance is available online at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621902.pdf

The requested information should be submitted to the IND. Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in:
Applying Human Factors and Usability Engineering to Medical Devices, available online at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf.

Guidance on Safety Considerations for Product Design to Minimize Medication Errors and can be found online at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf.

Note that we recently published two draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development and can be found online at:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf.

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors and can be found online at:
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf.

3.0 ADDITIONAL INFORMATION

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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.pd

f), 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 started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started 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 started on or 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.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

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

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).

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.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the Guidance for Industry, Collection of Race and Ethnicity Data in Clinical Trials (available at: https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf) and for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items that were identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

- Diurnal PowerPoint presentation

37 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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/

WILLIAM H CHONG
03/08/2019 11:57:38 AM