CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216986Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 123673

MEETING PRELIMINARY COMMENTS

Guerbet Group
Attention: Alpa Jain
Senior Regulatory Associate
821 Alexander Road, Suite 204
Princeton, NJ 08540

Dear Ms. Jain:

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

We also refer to your April 30, 2021, correspondence requesting a pre-NDA meeting to discuss the content and format of the upcoming NDA submission. Our preliminary responses to your meeting questions are enclosed.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting and will be limited to the discussion of this protocol.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, contact Sharon Thomas, Regulatory Project Manager, at 301-796-1994

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Imaging and Radiation Medicine
Office of Specialty Medicine
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	TBD
Application Number:	IND 123673
Product Name:	Gadopiclenol injection
Sponsor:	Guerbet Group
Proposed Indication:	Indicated in adults and children aged 2 years and older for contrast enhanced MRI to [redacted] (b) (4) lesions in: CNS, Body

SPONSOR's QUESTIONS and FDA's REPONSES:

REGULATORY

***Question 1*:** US FDA granted to Guerbet a pediatric study deferral for study of GADOPICLENOL in pediatric population of 0 years – 2 years old. The Clinical Development of GADOPICLENOL, which included all anatomical regions and all populations provided the appropriate evidence of safety and effectiveness necessary to support the below shown proposed labeling indication:

"GADOPICLENOL is indicated in adults and children aged 2 years and older for contrast-enhanced Magnetic Resonance Imaging (MRI) [redacted] (b) (4) lesions in:
- the Central Nervous System (brain, spine and [redacted] (b) (4) tissues),
- the body (head and neck, thorax [redacted] (b) (4), abdomen [redacted] (b) (4), pelvis [redacted] (b) (4) and musculo-skeletal system)."

Based on the safety and efficacy data for GADOPICLENOL presented in this pre-NDA Briefing Document, can the US FDA confirm that the proposed label indications shown above would be acceptable for NDA submission?

FDA Response to Question 1:

We note that [redacted] (b) (4) **Wording of the labeled indications will otherwise be determined after complete review of the submitted application. Submit your Amended Agreed iPSP with your marketing application.**

Question 2: There has been growing concern over the last years about potential long-term consequences of Gd deposition in various parts of human body, particularly in the brain, after repeated injections of GBCAs. On basis of the lower quantity of gadolinium (half-dose) administered compared to other contrast agents used in clinical practice, Guerbet plans to submit a Priority Review Request in its forthcoming GADOPICLENOL NDA. In fact, Guerbet is aware that the eligibility for the Priority Review Request will only be determined at the time of NDA submission (during the NDA filing review determination phase).

Does the FDA agree with Guerbet's intentions and proposed justification for the NDA Priority Review Request?

FDA Response to Question 2:

The determination of whether your NDA will be designated for priority review is made at the time of the application filing. Your priority review request should include a detailed justification of how the product would provide a significant improvement in safety or effectiveness, and should be supported by evidence from your drug development program. Additional information on this topic may be found in FDA Guidance for Industry: Expedited Programs for Serious Conditions - Drugs and Biologics.

Question 3: Guerbet plans to submit GADOPICLENOL drug product labeling for "Single use" and "Pharmacy Bulk Package" in the initial single NDA application. Therefore, Guerbet hopes that only one NDA PDUFA fee will be assessed.

Does the Agency agree with the proposed submission of GADOPICLENOL drug product labeling for "Single use" and "Pharmacy Bulk Package" in a single NDA, which would require only the single PDUFA NDA filing fee?

FDA Response to Question 3:

According to the Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees (the bundling guidance), different container sizes and configurations of one finished pharmaceutical product intended for the same route of administration for the same indication would be considered one application for purposes of assessing user fees. The proposed "Single use" and "Pharmacy Bulk Package" vial presentations of gadopiclenol are quantitatively and qualitatively identical in composition, are the same dosage form, and are intended for the same route of administration for the same indication. Therefore, the proposed "Single use and "Pharmacy Bulk Package" vial presentations can be bundled and submitted in one

application, which would be assessed one application fee. Please note the final determination regarding the number of applications and/or user fees will be determined once the submission is received by the FDA in its entirety.

Provide a justification for the fill volume in the multidose container (Pharmacy Bulk Package" and relate dosing information to the fill volume.

Question 4: The proposed Table of Contents for the forthcoming NDA submission is included in Appendix 1 of the pre-NDA Briefing Document.

Does the FDA agree with the proposed Table of Contents for the forthcoming NDA submission?

FDA Response to Question 4:

Yes, we agree. For Module 5, please also include the electronic data with define files, the statistical analysis programs, and the statistical analysis plans for the two phase 3 studies.

Include the final reports, associated data, and datasets of all clinical pharmacology studies in the original NDA submission. FDA expects the NDA submission to be complete at the time of original NDA submission. See Clinical Pharmacology Additional Comments 1 to 3 below. In addition, include population PK analysis, dose-response or exposure-response analyses for efficacy and safety, and sub-group analyses of safety and efficacy data for the renal impairment (RI) categories. Provide evidence to support the lack of metabolism of gadopiclenol.

Question 5: A common NDA Package Insert will be proposed for both commercial presentations; single dose presentation in vials or pre-filled syringes (PFS) and pharmacy bulk package in vials.

Does the FDA agree that this regulatory approach is acceptable?

FDA Response to Question 5:

We recommend separate Prescribing Information for the single dose presentation and the pharmacy bulk package.

Question 6: Guerbet has completed the clinical development of GADOPICLENOL drug product. The safety and efficacy data are presented in this pre-NDA Briefing Document show that the clinical development met its primary and secondary objectives for GADOPICLENOL drug product.

Based on the presented safety and efficacy data, does the FDA agree that the presented safety and efficacy data support the filing of NDA dossier for GADOPICLENOL drug product?

FDA Response to Question 6:

The presented safety and efficacy data appear to support your plan to submit a New Drug Application. The determination of whether the application can be filed will be subject to review once the application is received.

CMC

Question7: Concerning the excipient "Tetraxetan/DOTA" used in the formulation of GADOPICLENOL, we propose to use the United States Adopted Name (USAN) "Tetraxetan" in the USPI. However, in the documents of the Module 3, the used term is "Tetraxetan (DOTA)" to make the link with our internal documentation (i.e. Certificates of analysis).

Tetraxetan (DOTA) is part of the active substance of the registered contrast agent Dotarem, "DOTA" is the term used in the USPI of Dotarem and is the historical name of this compound; this is also the term commonly used by the manufacturers of the substance.

Does the Agency Agree that Guerbet can use the United States Adopted Name (USAN) "Tetraxetan" in the USPI, that is included in the pre-NDA Submission Document?

FDA Response to Question 7:

You may use Tetraxetan (DOTA) in the USPI.

Question 8: The sterility testing of GADOPICLENOL, drug product, is done as per the compendial test method (USP <71>), which will be submitted with the initial NDA application.

(b) (4)

Does the FDA agree with this proposed regulatory approach?

FDA Response to Question 8:

The Division of Microbiology Assessment agrees with the submission of a comparability protocol detailing (b) (4) **that can be reviewed within the new drug application (NDA). The final reporting category will be determined upon review of the comparability protocol submitted in the NDA. Also, for additional information, we recommend** (b) (4) **.**

Question 9: Concerning analytical procedure description and validation for both Drug Substance and Drug Product, some representative chromatograms will be included in Sections 3.2.S.4 Control of drug substance and 3.2.P.5 Control of drug product. No additional raw data (chromatograms, copy of notebook) will be included in Section 3.2.R Regional Information.

Does the FDA consider this acceptable knowing that those additional data will be available upon request during the NDA review and/or during a site inspection?

FDA Response to Question 9:

We strongly recommend that you include raw chromatograms as supporting data for method validation in the application with your assignments and explanations depicting e.g., isomers, isomeric ratio(s), etc. Copies of notebooks need not be included in the application, but should be available at the manufacturing site during inspectional assessment.

Question 10: Drug substance: As agreed during the type B meeting held with the FDA on July 10, 2017, the supportive CMC registration data for the batches manufactured at two different Guerbet sites: pilot scale at one site and the first industrial batch at another site, will be included in NDA submission.

Drug substance pilot scale site: Guerbet manufacturing site located in Aulnay-sous-Bois, France.
Drug substance commercial scale site: Guerbet manufacturing site located in Lanester, France.
The validation batches and the commercial batches of the Drug Substance will be manufactured in Guerbet manufacturing site located in Lanester.

Guerbet proposes to submit the CMC information in the following sections:
- Release data for validation batches at pilot scale in Section 3.2.S.4.4 Batch Analyses,
- Release data of the first industrial validation batch in Section 3.2.S.4.4 Batch Analyses,
- Batch record of the first industrial validation batch in Section 3.2.R Regional Information.

Does the FDA consider this CMC submission information approach acceptable?

FDA Response to Question 10:

Your approach is reasonable.

Question 11: Drug product: As agreed during the Type B meeting on July 10, 2017, NDA will include the supportive CMC registration data that were derived from the pilot scale at one Guerbet site and from the first industrial batch at another Guerbet site for both presentations (vial, pre-filled syringe):

Drug product pilot scale site: Guerbet manufacturing site located in Aulnay-sous-Bois, France.
Drug product commercial scale site: Liebel-Flarsheim LLC manufacturing site located in Raleigh, USA.

The validation batches and the commercial batches of the Drug Product will be manufactured in Liebel-Flarsheim LLC manufacturing site located in Raleigh, USA.

Guerbet proposes to submit the CMC information in the following sections:

- Process validation at pilot scale in Section 3.2.P.3.5 Process Validation and/or Evaluation,

- Sterilization validation for Liebel-Flarsheim LLC site in Section 3.2.P.3.5 Process Validation and/or Evaluation,
- Release data of the pilot batches and the first industrial validation batch in Section 3.2.P.5.4 Batch Analyses,
- Batch record of the first industrial validation batch in Section 3.2.R Regional Information.

Does the FDA consider this regulatory submission approach acceptable?

FDA Response to Question 11:

Your approach is reasonable.

The Division of Microbiology Assessment agrees that the sterilization validation information for the Liebel-Flarsheim LLC site be included in Section 3.2.P.3.5. Also, please ensure that a description of the manufacturing process and (b) (4) for this manufacturing location are included in section 3.2.P.3.3. The depyrogenation information for the vials, stoppers and syringes that are used for manufacturing at this location should also be included. For additional information on the type of information recommended for validation of sterile manufacturing process, refer to the November 1994 Guidance document "Submission Documentation for sterilization process validation in applications for human and veterinary drug products". https://www.fda.gov/media/71442/download. For information on the correct placement of product quality information please refer to the August 2001 "Guidance for Industry M4Q: The CTD – Quality". https://www.fda.gov/media/71581/download.

Question 12: Guerbet would like to confirm the interpretation of the guideline "Control of (b) (4) Impurities in Human Drugs (b) (4)" with the FDA. If the risks of (b) (4) are identified, risk assessment should be submitted with the initial NDA application. If no risks of (b) (4) are identified, the risk assessment will not be submitted for FDA's review. Guerbet would like to confirm with the FDA whether the proposed Guerbet's approach is in-line with the current FDA's expectations. Concerning (b) (4) impurities, a risk assessment for GADOPICLENOL product is on-going.

Does the FDA agree that the (b) (4) Risk Assessment Report can be included (if necessary) in Section 3.2.P.5.5 of the eCTD?

FDA Response to Question 12:

You may submit to the application the rationale and conclusion of your risk assessment for absence of (b) (4) impurities.

QUALITY

Question 13: Considering the existing Mutual Recognition Agreement for good manufacturing practice (GMP) inspections and batch certification between European Union and USA, will the

US FDA conduct Pre-approval inspection of the Guerbet's Drug Substance (DS) manufacturing site located at Lanester, France)?

FDA Response to Question 13:

We cannot comment at this time regarding the need for any inspection or alternative to inspection. An assessment will be made once the NDA is submitted. As noted in FDA's Guidance for Industry updated in January 2021, "Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency - Questions and Answers", the Agency continues to use alternate tools and approaches where possible, including requesting existing inspection reports from other trusted foreign regulatory partners through mutual recognition agreements and other confidentiality agreements, requesting information from applicants, and requesting records and other information directly from facilities and other inspected entities.

Question 14: Within the context of a manufacturing site inspection, should production of GADOPICLENOL (Drug Substance) / GADOPICLENOL (Drug Product) be ongoing during the inspection? If yes, how Guerbet should communicate to the FDA the production plan in 2022?

FDA Response to Question 14:

For small molecules, it is not a requirement to have ongoing GADOPICLENOL (Drug Substance) / GADOPICLENOL (Drug Product) production during the inspection. However, should this be of value to the inspection team with regards to enhancing their evaluation, accommodating such Agency requests would be appreciated. Such requests may originate during application review and it is anticipated that they will be communicated as part of scheduling of any potential preapproval inspections.

Question 15: Based on FDA August 2020 Final Guidance Document, Manufacturing, Supply Chain, Drug and Biological Product Inspections During COVID-19 Public Health Emergency - Questions and Answers, could FDA indicate its preliminary intentions for the remote versus on-site US domestic and foreign inspections related to GLP/GCP/GMP sites described in the forthcoming NDA for GADOPICLENOL, drug product ?

In case of the remote inspections, will the US FDA propose a secured platform to allow proper exchanges of information and documents between the FDA inspectors and Guerbet, or shall Guerbet set-up such a platform for the inspectors?

In case of the remote inspections, will the FDA accept/propose a preliminary inspection meeting to manage communication software platform tests prior to the FDA remote inspection?

FDA Response to Question 15:

If FDA requests one of your facilities' participation in a remote evaluation, for security reasons, FDA will use its own IT platforms and equipment to host virtual interactions during remote interactive evaluations (e.g., videoconferences, livestreaming video of the facility and operations in the facility). If the facility confirms its willingness and ability to participate in a remote interactive evaluation, FDA will schedule a brief virtual meeting to discuss logistics, responsibilities, and expectations inclusive of tests of the technology and internet connections within the facility to verify adequacy to support a remote interactive evaluation.

For more information, please see the FDA guidances related to COVID 19. These guidances can be found at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders.

PRE-CLINICAL

Question 16: SEND datasets are required for certain nonclinical study types as defined by study initiation date (i.e., protocol signature date by study Director). The list of nonclinical studies and their initiation date appears in the Table below. No carcinogenicity study is available. Two repeat dose toxicity studies (in bold in the Table) started after December 17, 2016.

SEND Datasets will be provided only for these two studies in the Module 4 of the NDA dossier and not for other single- and repeat-dose toxicity studies and safety pharmacology studies initiated before December 17, 2016 and March 15, 2019, respectively.

Does the Agency agree with this regulatory submission approach?

FDA Response to Question 16:

Yes, we agree.

Question 17: The non-increase of the environmental exposure for the active moiety is the US criterion for the categorical exclusion in Environmental Assessment in the NDA, according to the guidance "Environmental Assessment of Human Drugs and Biologics – FDA July 1998", and 21 CFR 25.31(a).

The active moiety of GADOPICLENOL on MRI signal is the paramagnetic gadolinium (Gd) ion. This active moiety is also common to all already US-approved and marketed Gd-based contrast agents (ProHance, Gadavist, MultiHance, Dotarem, Clariscan, Omniscan).

The proposed indications for GADOPICLENOL will overlap with those already approved for the other agents mentioned above. However, for GADOPICLENOL, the posology (quantity of Gd injected) is much lower than for other approved gadolinium-based contrast agents.

Therefore, if the FDA approves GADOPICLENOL, this will not lead to an increase of environment exposure to the active moiety (Gd), as the low dose GADOPICLENOL will likely substitute the currently marketed gadolinium-based MRI contrast imaging products for the same indications.

Does the FDA agree that Guerbet can apply this categorical exclusion justification in Environmental Assessment in the NDA?

FDA Response to Question 17:

No, FDA does not agree with using the "no increased use" categorical exclusion from an environmental assessment (EA) in the NDA (21 CFR 25.31(a)). FDA considers this substance to be a new molecular entity (NME), based on the referenced FDA guidance (see definition of Active Moiety in Attachment G) and 21 CFR 314.108(a), and thus this substance will result in an increased use by definition. If the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb), however, the "1 ppb" categorical exclusion can be used (21 CFR 25.31(b)), assuming there are no extraordinary circumstances per 21 CFR 25.15(a) and (c). Otherwise, the substance will need to undergo an EA.

CLINICAL

Question 18: Considering that the product efficacy is assessed in the two indications/phase III studies with the same primary endpoint (i.e. lesion visualization) whatever the targeted organ, CNS and Body indications will be presented in one single ISE (with specific subsections) and data from the two pivotal adult phase III studies will be pooled for subgroups analyses.

Guerbet plans to present a single ISE for both CNS and Body indications (including data resulting from the pooling of two-Phase III studies, one in CNS indication and the other in Body indication).

Does the FDA consider this approach acceptable?

FDA Response to Question 18:

Yes, this approach is acceptable provided the studies are also analyzed separately in the corresponding Module 5 clinical study reports.

Question 19: As the ISE and ISS planned for this NDA dossier are not large documents, Guerbet plans to split these documents between Module 5.3.5.3 (tables and datasets) and Modules 2.7.3 and 2.7.4 (text portion), as proposed in the FDA Guidance for Industry (*Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*).

Sections 2.7.4 and 2.7.3 will refer the reader to section 5.3.5.3 for tables and datasets. Section 5.3.5.3 will refer the reader to section 2.7.4 for the text portion of the ISS and to section 2.7.3 for the text portion of the ISE.

Does the Agency concur that this would be an acceptable regulatory strategy for the submission of ISE and ISS in the forthcoming NDA submission?

***FDA Response to Question 19*:**

If the recommendations in "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document" (https://www.fda.gov/media/75783/download) related to size and content of the text portions of the summaries are followed, we concur with this approach.

Question 20: The ECG raw data of GDX-44-006 study (thorough QT study) have already been loaded by Guerbet on a previously available FDA ECG portal.
Does FDA require Guerbet to re-load these previously reported ECG data on the newly released FDA ECG warehouse?

FDA Response to Question 20:

No, there is no need for ECG waveforms to be resubmitted to the FDA portal.

Question 21:

Guerbet seeks the clarification regarding FDA expectations for GADOPICLENOL evaluation in the context of the FDA clinical PMR related to the potential neuro-cognitive effects, following multiple administrations of a GBCA.

The Applicant would appreciate FDA's feedback in-order to anticipate the timeframe in case the changes the scope of the Odyssey study will be required.

Can the FDA confirm that the current PMR (Odyssey study) applicable to other GBCAs will also be applicable to GADOPICLENOL, once its NDA is approved?

FDA Response to Question 21:

Currently the applicant would be obligated to perform the clinical PMR required of the other approved GBCAs:

> **A prospective two-arm clinical trial in neurologically normal adults (for example, patients undergoing breast cancer screening) compared to matched controls to evaluate the effects of repetitive administration of GBCA on neurologic and systemic function using a comprehensive battery of neurobehavioral testing and other clinical and laboratory tests over the course of at least five GBCA administrations. The trial should be sufficiently powered to exclude a pre-specified magnitude of decline. As a secondary objective, trial subjects should also have the option of providing blood and urine samples at the time of re-imaging, so that**

normative estimates of gadolinium concentration across an extended range of post-administration time points may be documented.

The applicant may negotiate with the other GBCA NDA holders to join the Odyssey study or propose an independent study which accomplishes the same goals. Note that the Odyssey study and the initial PMR request may be modified based on our review of the planned interim reports and other input from the NDA holders.

PHARMACOVIGILANCE

Question 22: GADOPICLENOL being a macrocyclic GBCA with high stability, Guerbet believes the current class safety mentions applicable to already approved macrocyclic GBCAs should be applicable to GADOPICLENOL (i.e. no contraindications in patients with severe renal impairment, etc).

Does the FDA agree with this assertion?

FDA Response to Question 22:

This appears to be reasonable based on the information provided in the briefing package, however safety labeling will be determined through complete review of the submitted NDA.

Question 23: GADOPICLENOL will not be approved yet anywhere in the world at the expected time of NDA submission and review by the FDA.
For safety data, Guerbet intends to submit:
- all safety data available at the time of NDA submission;
- and a safety update report 4 months after NDA submission with any new safety information that will be available at that time (e.g. coming from the ongoing PK study in Japan, and the deferred pediatric PK study for children under 2 years of age which will be initiated beginning 2022).

Does the FDA consider this as acceptable?

FDA Response to Question 23:

Yes, this safety data submission plan is acceptable.

ADDITIONAL FDA COMMENTS:

Clinical Pharmacology

1. The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with FDA Guidance for Industry, “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products –Content and Format” (available at:

https://www.fda.gov/media/74346/download). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

2. Address the following questions in the Summary of Clinical Pharmacology:
   a. What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
   b. What are the dose-exposure or exposure-response relationships for efficacy, safety and biomarkers?
   c. What is the effect of gadopiclenol on the QT/QTc interval?
   d. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?
   e. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as body weight, sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?

3. Apply the following advice in preparing the clinical pharmacology sections of the original submission:
   a. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
   b. Provide a final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.
   c. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
      - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
   d. Submit the following for the population pharmacokinetic analysis reports:
      - Standard model diagnostic plots
      - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
      - Model parameter names and units in tables.
      - Summary of the report describing the clinical application of modeling results.

      Refer to the following pharmacometric data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.
   e. Submit the following information and data to support the population pharmacokinetic analysis:
      - SAS transport files (*.xpt) for all datasets used for model development and validation

- A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
- Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)

f. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf for population PK, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for exposure-response relationships, and http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm for pharmacometric data and models submission guidelines.

Human Factors

We note you are proposing to supply the drug product in pre-filled syringes. We recommend you conduct a comprehensive use-related risk analysis if you have not already completed one. 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) for 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.

If models of the same or similar combination products exist, your use-related risk analysis should incorporate applicable information on known use-related problems with those products. Useful information can be obtained from your own experience as well as from public sources such as literature, adverse event reports, and product safety communications. See draft guidance for industry Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development.

Additionally, if models of the same or similar combination products exist, it may be useful to conduct comparative analyses such as a labeling comparison, a comparative task analysis, and a physical comparison between your proposed product and the comparator for the purposes of identifying what differences exist between the user interfaces and where the same or similar risks may apply to your proposed product.

Based on the aforementioned information and data, you should 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 an HF validation study does not need to be submitted for your product, submit your risk analysis, comparative analyses, and justification for not submitting the HF validation study to the Agency for review under the IND. The Agency will notify you if we concur with your determination.

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.

OTHER IMPORTANT MEETING INFORMATION:

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[1]

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*.[1] 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.[2]

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 Information6 and Pregnancy and Lactation Labeling Final Rule7 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 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

[1] 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.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

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.

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 356h16 and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[17]. 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.

NEW MOLECULAR ENTITY (NME)

FDA has made a preliminary determination that the application for this product would be reviewed as a new molecular entity (NME) and therefore subject to the Program, under PDUFA VI. Please note that this is a preliminary determination, based on information available to FDA at this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or marketed. Please also note that the NME determination for an application is distinct from and independent of the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA.

NEW CHEMICAL ENTITY (NCE)

Please be advised that the Agency does not make exclusivity determinations pursuant to sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.108, 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. Please also note that the New Molecular Entity (NME) determination for an application is distinct from and independent of the New Chemical Entity (NCE) determination and any related exclusivity determinations.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI)

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 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.*[20]

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 FDA.gov.[3]

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 FDA.gov.[4]

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).

[3] http://www.fda.gov/ectd
[4] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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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.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 123,673

MEETING MINUTES

Guerbet Group
Attention: Alice Lorenzo
Compliance Officer, North America
Head of Regulatory and Quality
821 Alexander Road, Suite 204
Princeton, NJ 08540

Dear Ms. Lorenzo:

Please refer to your Investigational New Drug Application (IND) and submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for G03277 Injection (Gadopiclenol).

We also refer to the meeting between representatives of your firm and the FDA on August 23, 2018. The purpose of the meeting was to discuss the clinical development plans for the phase 3 trials along with a pediatric protocol for the CNS MRI indication in children 2 years of age and older.

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, please don't hesitate to call (301-796-1994) or e-mail me at sharon.thomas@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Sharon Thomas
Senior Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
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:	End of Phase 2 (EOP 2)
Meeting Date and Time:	August 23, 2018, 12:00 PM- 1:00 PM (ET)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1313 Silver Spring, Maryland 20903
Application Number:	IND 123,673
Product Name:	G03277 Injection (Gadopiclenol)
Indication:	Central Nervous System (CNS) MR imaging in adult and pediatric patients (2 year of age and older) and (b) (4).
Sponsor/Applicant Name:	Guerbet Group

FDA ATTENDEES

Alex Gorovets, M.D., Deputy Director, Division of Medical Imaging Products (DMIP)
August (Alex) Hoffling, M.D., Medical Officer, DMIP
Anthony Fotenos, M.D., Ph.D., Clinical Team Leader, DMIP
Mona Khurana, M.D., Team Leader, Pediatrics, Division of Pediatric & Maternal Health (DPMH)
Erica Radden, M.D., Medical Officer, DPMH (Phone)
Olayinka Dina, Ph.D., Pharmacologist, DMIP
Sue Jane Wang, Ph.D., Associate Director for Adaptive Design and Pharmacogenomics
Joyti Zalkikar, Ph.D., Lead Mathematical Statistics
Anthony Mucci, Ph.D., Reviewer, Mathematical Statistics
Christy John Ph.D., Clinical Pharmacology Lead, DCPV
Sharon Thomas, BS, CCRP, Regulatory Project Manager

SPONSOR ATTENDEES

Valérie Brakni, Clinical Project Manager, Guerbet Group
Philippe Bourrinet, Global Head Regulatory Affairs, Non-Clinical Development, Guerbet Group
Pierre Desche, Senior VP Medical and Regulatory Affairs, Guerbet Group
Jing Hao, Global Head of Medical Affairs & Clinical Development, Guerbet Group
Anne Chibois, Project Leader, Guerbet Group
Alice Lorenzo, North America Head, Regulatory Affairs, Guerbet LLC
Alpa Jain, Regulatory Associate II, Guerbet LLC

1.0 BACKGROUND

On May 18, 2018, Guerbet submitted a type B, End-of-Phase 2 meeting request to discuss plans to submit a supplemental new drug application (sNDA) for a pivotal phase 3 trial in CNS imaging and a pivotal phase 3 trial (b) (4). Guerbet also plans to submit to an initial pediatric protocol for the CNS MRI indication in children 2 years of age and older using a dose of 0.05 mmol/kg BW. On August 14, 2018, FDA provided preliminary comments to the Guerbet's questions provided in the briefing package dated June 29, 2018. On August 22, 2018, the Guerbet decided to proceed with the meeting to obtain clarification on the FDA's response to questions 3 and 4 along with two additional references (Attachment 1). The following section constitutes the discussion that occurred at the face-to-face meeting on August 23, 2018.

Guerbet's questions are in regular font, the FDA Responses in **bold**. The Discussion points are indicated in ***bold italics*** below.

2.0 DISCUSSION

2.1.

Nonclinical

Question 1:
Does FDA agree that the nonclinical studies already conducted will support Phase III clinical trials in the U.S. and that the proposed remaining nonclinical program will be adequate to file the NDA?

Company's position
Guerbet has already conducted a significant nonclinical study program (pharmacodynamics, safety pharmacology, pharmacokinetics and toxicology) to support Phase III clinical trials. Guerbet will have completed all non-clinical pre-requisites before starting phase III clinical trials in U.S. The list of non-clinical studies already conducted is provided in this briefing document. Guerbet intends to perform additional nonclinical studies to support NDA application.

Guerbet considers that there are sufficient guarantees to ensure the safety of gadopiclenol administration in male and female patients in phase III clinical trials. Guerbet also believes the proposed program fulfils regulatory requirements for the single dose intravenous administration of gadopiclenol.

FDA Response to Question 1:

We agree. The completed nonclinical studies are acceptable and the ongoing/planned studies are reasonable to support Phase III clinical trials. Please note that the adequacy

of your ongoing and planned studies is a review issue. Together, the nonclinical studies appear adequate for NDA submission.

Discussion point:

None

Clinical

Question 2:

Guerbet proposes to perform two Phase III trials in adults to support two proposed indications. One pivotal Phase III trial will be conducted to support an indication for CNS imaging and one pivotal Phase III trial will be conducted to support an indication (b) (4). Assuming both trials are adequately designed and have positive results for their respective primary criterion, does the Agency agree that two indications could be achieved based on a single positive pivotal trial per indication?

Company's position:

This approach was encouraged by the FDA during the pre-IND meeting. Then we received a complement written response from FDA on November 2015 to confirm this approach (reference ID: 3855413).

FDA Response to Question 2:

See FDA response to Question 3 below for more detail regarding recommended primary efficacy endpoints in a "positive pivotal trial". We agree that two indications could be achieved based on a single positive pivotal trial per indication and emphasize that both trials should be positive as a prerequisite for any indication.

Discussion point:

None

Question 3:

Guerbet intends to perform the two Phase III trials versus gadobutrol injection (b) (4). Each trial will include two parts, one designed to achieve a non-inferiority demonstration for gadopiclenol at 0.05 mmol/kg BW for CNS pathologies (CNS trial) and for (b) (4) Based on this program, Guerbet intends to seek the following:

- Achieve approval for one indication as far as the non- inferiority of gadopiclenol v. gadobutrol is demonstrated in the corresponding trial part for this indication
- Achieve approval for the two indications as far as the non-inferiority of gadopiclenol v. gadobutrol is demonstrated in the corresponding trial part for these two indications
- Obtain superiority claim of gadopiclenol v. gadobutrol in the two indications assuming

positive results in the corresponding trial part of both trials

– Obtain superiority claim of gadopiclenol v. gadobutrol for one indication in case the superiority is demonstrated in only one of the two corresponding trial parts of these two Phase III trials

Does the Agency agree Guerbet can achieve these objectives based on proposed design?

Company's position:
Guerbet believes that the proposed trial design containing 2 parts within each trial is appropriate to test 2 doses of gadopiclenol for each of the two proposed indications. The two parts within the trial are considered independent one from the other (i.e. each trial part will be statistically powered); consequently, when one part of the trial is positive, the corresponding claim should be justified.

FDA Response to Question 3:

We first address part 1 of both of your proposed phase III protocols, where a lesion visualization claim in the CNS and (b) (4) are pursued.

- **To support these claims, we recommend that primary efficacy analysis demonstrate superiority of combined pre- and post-P03277 images versus pre-P03277 images alone. Success of such analysis in one relevant CNS trial and one relevant (b) (4) trial would support approval of both respective claims.**

- **Your proposal to omit the above recommended analysis and focus solely on evaluation of post-P03277 images versus post-active comparator images would involve the following additional considerations. Given the uncertainty inherent in defining non-inferiority thresholds for qualitative endpoints that are assessed independently of a truth standard, such as those that you propose in your CNS lesion visualization trial, we recommend that you consider a demonstration of superiority rather than non-inferiority of P03277 versus active comparator as it would more clearly support a CNS visualization claim. Demonstration of non-inferiority of P03277 versus active comparator would be more reasonable in the evaluation of (b) (4). Thus, for approval of both CNS lesion visualization and (b) (4) claims with a single active comparator trial per claim, we recommend that the CNS trial demonstrate superiority of P03277 while the (b) (4) trial demonstrate either superiority or non-inferiority of P03277.**

(b) (4)

Discussion point:
Guerbet discussed the design and dosing for two trials, one for the CNS and the other for the (b) (4) ***Guerbet stated that they plan to utilize an active comparator (gadobutrol) in each trial with no comparison between unenhanced images and post-gadopiclenol images.***

Guerbet inquired about FDA's recommendation for a primary efficacy analysis demonstrating superiority of combined (pre + post) gadopiclenol images vs. pre- contrast images. FDA emphasized that gadopiclenol could be approved based upon the comparison of combined pre and post vs pre images. FDA noted that active comparator analysis would require more robust results and would be at greater risk for trial failure and potential lack of approval.

Guerbet's discussed plans to compare gadopiclenol vs. gadobutrol to position gadopiclenol efficacy among other GBCAs available in the market. FDA stated that evaluation of an active comparator would be reasonable for secondary analysis as long as primary analysis compared the combined pre- and post- vs pre- contrast images of P03277.

FDA stated that the visualization endpoints for the CNS trial are qualitative and not based on a truth standard, making the selection of a non-inferiority margin difficult. Therefore, FDA recommended demonstrating superiority rather than non-inferiority in a CNS visualization trial using an active comparator. FDA emphasized that comparative analysis was not a requirement. FDA mentioned the Gutierrez et al paper provided as a reference as support for the secondary nature of active comparator analysis.

(b) (4)

Discussion moved to the proposed indications. Guerbet confirmed that they plan to pursue indications in adults for CNS and (b) (4) ***in pediatrics. FDA asked why they were no longer seeking a whole body indication. Guerbet explained that they were hesitant about focusing on a single body organ*** (b) (4)***. FDA explained that a variety of body organs such as liver and kidney could be grouped into a***

single analysis using lesion visualization endpoints. Under such an approach, individual organs would not need to be individually powered for statistical purposes. Thus, combined analysis of lesion visualization parameters for a variety of organs could support a general body imaging indication. (b) (4)

Question 4:
Guerbet intends to utilize an active comparator in each trial with no comparison between unenhanced images and gadopiclenol enhanced images. Guerbet believes that when an imaging contrast agent is developed as an alternative or improvement over registered diagnostic agents, comparative trials with the approved agents should be preferred. It is only when no active comparator is registered that the unenhanced imaging procedure may serve as an appropriate comparator. Does the Agency agree with efficacy achieved by active comparator only?

Company's position
Based on the guidance for Industry June 2004, developing Medical Imaging Drug and Biological product (part 3) (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ ucm071604.pdf), if the test agent is being developed as an advance over an approved drug, it is recommended that a direct comparison to the approved comparator(s) be performed.

FDA Response to Question 4:
See above FDA response to Question 3.

Discussion point:
See *above Discussion point.*

Question 5:
Guerbet intends to submit an initial pediatric protocol for the CNS MRI indication in children of 2 years of age and older using a dose of 0.05 mmol/kg BW to the NDA. This trial will be submitted as a 'PROPOSED PEDATRIC STUDY REQUEST' for pediatric exclusivity. Guerbet will submit a pediatric protocol for CNS and others indications in children less than 2 years of age as a post marketing commitment. Guerbet will submit an amendment to the currently approved iPSP for the CNS MR imaging indication (b) (4) Does the Agency agree with the proposed pediatric clinical development plan for gadopiclenol?

Company's position
(b) (4)

FDA Response to Question 5:
Your proposal to submit an amendment to your iPSP to specify your plan to study a lower dose of 0.05 mmol/kg based on data from your adult program is reasonable.

However, we previously advised you that we disagree with deferring the study of patients less than 2 years of age and further advised that "0 to 23-month-olds should be integrated into the staggered protocol you currently propose for 2 to 17-year-olds, with the study of 0 to 23-month-olds initiated once early safety data is available in the cohort of 2 to 5-year-olds." Accordingly, this recommended approach was included in the Agreed iPSP. Therefore, please clarify why you are now proposing to defer studying patients less than 2 years of age. (b) (4) **Also, provide justification for your revised proposed dose of 0.05 mmol/kg BW. Note that you should plan to submit your amended iPSP at least 210 days prior to NDA submission.**

With regards to your proposal to request a Written Request (WR), we recommend you submit a Proposed Pediatric Study Request (PPSR) for our review. Your PPSR should detail the pediatric studies you intend to conduct not only for the indications currently specified in your Agreed iPSP but also for any indications where the active moiety (gadopiclenol) could provide a health benefit in the pediatric population, regardless of whether or not the indication(s) have been previously approved or are being sought in adults. Please note that a WR may include studies in addition to those required under PREA and in patients down to birth, including neonates. Also, note that you should consider the timing of submission of your PPSR relative to your NDA submission since if pediatric study information contained in your PPSR has already been submitted to your NDA submission, FDA may not issue a WR, even if the pediatric information is not yet included in the labeling.

<u>Discussion point:</u>
FDA explained the CNS trial would meet the obligations under PREA for pediatrics (including less than 2). FDA asked about the request to defer 0-2 and explained that Guerbet could amend the current agreed upon iPSP and remove non-CNS patients, (b) (4) ***and a deferral for 0-2.***

FDA inquired why Guerbert wanted to modify the agreed upon iPSP. Guerbet explained the history with EMA and FDA regarding the pediatric program for P03277. Guerbet noted that EMA refused the modification and agreed to have full trial review of 2-17, and that EMA was in disagreement to include non-CNS patients, as well as the recruitment of patients ages 0-2 years old is challenging.

FDA requested a rational for the EMA refusal and requested scientific justification such as wanting to see data in older children and adults first, provide a justification regarding the difficulty in enrolling patients age 0-2 (resulting in delay of approval) or looking at other approved products where FDA deferred less than 2 years even if FDA's position today may be different, these are possible justifications for deferral.

For the PPSR, FDA encouraged Guerbet to include the indication for all ages and broader terms for the written request for pediatric exclusivity.

ADDITIONAL FDA CLINICAL COMMENTS:

1. **We note that your completed and planned clinical trials, including your phase 3 protocol synopses, do not feature specific safety evaluation for potential chronic retention of P03277 or associated gadolinium. Upon NDA approval, this safety evaluation would be expected through integration of P03277 in the ongoing postmarketing requirement for FDA-approved GBCAs.**

   Discussion point:
   Guerbet agreed to meet the GBCA Post Marketing Requirements involving gadolinium retention.

3.0 OTHER IMPORTANT MEETING 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.

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 pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

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* and *Pregnancy and Lactation Labeling Final Rule* 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.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which 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* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

- None

5.0 ACTION ITEMS

- Guerbet to submit revised protocols when ready.

6.0 ATTACHMENTS AND HANDOUTS

- Guerbet's reference documents and power point presentation (Attachment 1)

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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/

SHARON P THOMAS
09/22/2018