CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215727Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 215727

MEETING MINUTES

AGEPHA Pharma Middle East Trading, LLC
c/o: AGEPHA Pharma USA, LLC
Attention: Rainer Riel Köllmann
US Agent
181 New Road, STE 304
Parsippany, NJ 07054

Dear Mr. Köllmann:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for colchicine tablets.

We also refer to the telecon between representatives of your firm and the FDA on August 5, 2022. The purpose of the meeting was to discuss deficiencies outlined in the Refuse to File Letter, dated June 11, 2022, and the General Advice Letter, dated June 30, 2022.

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

If you have any questions, please call Brian Cooney, Regulatory Project Manager, at (301) 796-0886.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: A
Meeting Category: Guidance

Meeting Date and Time: August 5, 2022 / 3:00 – 4:00 PM, EDT
Meeting Location: Teleconference

Application Number: 215727
Product Name: Colchicine tablets

Indication: To reduce the risk of myocardial infarction, stroke, coronary revascularization, (b) (4) , and cardiovascular (CV) death among patients with established atherosclerotic disease or with multiple risk factors for CV disease.

Applicant Name: AGEPHA Pharma Middle East Trading, LLC
Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Norman Stockbridge, MD, PhD
Meeting Recorder: Brian Cooney, MS, PSM

FDA ATTENDEES

**Office of Cardiology, Hematology, Endocrinology and Nephrology, Division of Cardiology and Nephrology*

Norman Stockbridge, MD, PhD	Director
Mary Ross Southworth, PharmD	Deputy Director for Safety
Michael Monteleone, MS, RAC	Associate Director for Labeling
Fred Senatore, MD, PhD, FACC	Lead Physician
Rosalyn Adigun, MD, PharmD	Physician

**Office of Clinical Pharmacology, Division of Cardiometabolic & Endocrine Pharmacology*

Snehal Samant, PhD	Clinical Pharmacology Team Leader (Acting)
Mohamad Kronfol, PhD	Clinical Pharmacology Reviewer

**Division of Pharmacology/Toxicology for Cardiology, Hematology, Endocrinology, and Nephrology*

Todd Bourcier, PhD	Director
Xuan Chi, MD, PhD	Non-clinical Team Leader
Rama Dwivedi, PhD	Non-Clinical Reviewer

Office of Pharmaceutical Quality, Office of New Drug Products

Theodore Carver, PhD, RAC	CMC Team Leader
Rao Kambhampati, PhD	CMC Reviewer

Office of Pharmaceutical Quality, Division of Biopharmaceutics

Kimberly Raines, PhD	Branch Chief (Acting)
Haritha Mandula, PhD	Biopharmaceutics Team Leader
Nadia Ahmed, PhD	Biopharmaceutics Reviewer

Office of Pharmaceutical Quality, Office of Pharmaceutical Manufacutirng Assessment

Daniel Obrzut, PhD	CMC Reviewer

Office of New Drug Policy, Division of Regulatory Policy

Elizabeth Goldstein	Science Policy Analyst

Office of Regulatory Operations, Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, & Nephrology

Anna Park, MS, RPh, RAC	Chief, Project Management Staff (Acting)
Alexis Childers, RAC	Sr. Regulatory Health Project Manager
Brian Cooney, MS, PSM	Regulatory Health Project Manager

SPONSOR ATTENDEES

Michael Riel, PhD	Managing Director
Susanne Riel	Chief Executive Officer
Elizabeth Lanz, BSc, MA	General Manager
Antonia Riel-Köllmann, BA, MA, MSc	Vice President, Business Development & Licensing
Meraj Shaikh , MPharm	Head of Regulatory Affairs
Erna Golubovic, PharmD	Quality Manager
Rizwan Shaikh, MPharm	Quality Expert – Regulatory Affairs
Tessy Binoy, MPharm	Quality Expert – Regulatory Affairs
Srilalitha Yerramilli, Pharm D	Clinical Expert – Regulatory Affairs
(b) (4)	Consultant

1.0 BACKGROUND

Colchicine is an anti-inflammatory, microtubule polymerization inhibitor approved as a capsule, tablet, or oral solution for the treatment of acute gout flares and familial Mediterranean fever. Cumulus Pharmaceuticals (Cumulus) developed a colchicine tablet (0.5 mg) and had several interactions with the Division under Pre-IND 119015. During the Type C Guidance meeting on December 2, 2019, Cumulus proposed a strategy for submitting a 505(b)(2) NDA for colchicine, a literature-based application, relying on COLCOT, LoDoCo-1, and LoDoCo-2 studies. The Division agreed that two

blinded trials with supportive evidence may be an acceptable approach to support approval for a 505(b)(2) NDA; however, the Division explained that patient-level data were desired. Cumulus would need to provide evidence that supports bridging their proposed marketing product to the product used in LoDoCo-2. Additional information was requested on products used in the cited studies (precise composition, active and inactive ingredients, release mechanism, in vitro dissolution, etc.).

In September 2020, the Division held a Pre-NDA meeting with Cumulus to discuss the results of published clinical trial data, mainly study results of LoDoCo-2, and the appropriateness of bridging data for proposed test products and products used in LoDoCo-2 trial. Cumulus requested feedback from the Agency regarding the sufficiency of the overall approach to support the submission of a 505(b)(2) NDA for the new 0.5- mg dose of colchicine and the new indication to (b) (4). On March 30, 2021, Cumulus notified the Division that PIND 119015 was transferred to AGEPHA Pharma Middle East Trading LLC (AGEPHA).

On April 13, 2022, AGEPHA submitted NDA 215727, literature-based 505(b)(2) application, with the following indication and posology:

- Indication: To reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, (b) (4), and cardiovascular death among patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease
- Posology: 0.5 mg once per day

To support this NDA, the Applicant submitted safety and efficacy information from published literature for the COLCOT, LoDoCo-1, and LoDoCo-2 studies. A bridging study (open label, randomized, bridging, crossover) was conducted by the Applicant to support the bioavailability (BA) and bioequivalence (BE) of colchicine tablets (0.5 mg) and Colgout (colchicine) tablets (0.5 mg) under both fasting and fed conditions in healthy volunteers. Colgout was approved in Australia (product ARTG ID 27909) and is not currently approved in the United States.

On June 11, 2022, the Division issued a Refuse to File letter to NDA 215727 stating:

> Adequate information to support the nonclinical sections of the proposed Prescribing Information has not been provided in your NDA submission. Therefore, your application is not complete, and we are unable to conduct a substantive review. You cannot rely upon foreign labeling for findings of safety and effectiveness to support your application.
>
> You need to provide information to support proposed labeling regarding risks of reproductive toxicity, developmental toxicity, carcinogenesis, mutagenesis, and impairment of fertility. This information might come from the literature or reliance

upon findings from an FDA-approved product. We can provide more detailed requirements in a subsequent advice letter.

A General Advice letter was sent to AGEPHA on June 30, 2022, requesting additional clinical pharmacology and product quality information if the application is resubmitted.

The purpose of this meeting was to discuss a path forward to address deficiencies outlined in the Refuse to File letter (June 11, 2022), and the General Advice Letter (June 30, 2022).

The Division sent Preliminary Comments to AGEPHA on July 29, 2022. In response to the Division's preliminary comments, AGEPHA provided written responses via email, dated August 3, 2022, received August 4, 2022, which are incorporated into section 2.1 below.

2.0 DISCUSSION

2.1. Questions for the Agency

Questions were renumbered by the Division

Regulatory

1. The sponsor is relying on the Agency's previous findings of safety for COLCRYS tablets 0.6 mg and MITIGARE capsules 0.6 mg. Does the Agency agree with this approach?

   FDA Preliminary Response:
   We agree that you can rely upon Colcrys and Mitigare as listed drugs (LD) for nonclinical information to support labeling for non-clinical safety, although it is not clear why you reference both of them when they contain the same information except that carcinogenicity data are absent from the Mitigare label.

   Describe specific sources of information upon which you rely and the scientific rationale in a non-clinical overview (eCTD 2.6) and nonclinical section (eCTD module 4).

   Your NDA should include copies of the key literature you intend to use to support in part the nonclinical sections of the drug label.

   AGEPHA Response:
   Based on FDA comments, AGEPHA is relying on the Agency's previous findings of safety of COLCRYS tablets 0.6 mg. Furthermore, AGEPHA will describe specific sources of information upon which Lodoco Tablets 0.5 mg rely and the

scientific rationale in a non-clinical overview (eCTD 2.6) and nonclinical section (eCTD module 4).

Discussion at the Meeting:
There was no discussion.

CMC

2. Does the Agency agree with AGEPHA assessment that excipients qualitative and quantitative differences between LODOCO tablets and products used in LoDoCo2 study have no significant impact on dissolution and clinical performance of colchicine as excipients present in products does not impact rate and extent of permeability/absorption of colchicine? (Applicant's Question 4)

FDA Preliminary Response:
We agree that the qualitative and quantitative differences in the products do not seem to have significant impact on dissolution.

AGEPHA Response:
AGEPHA has no further comment.

Discussion at the Meeting:
There was no discussion.

Biopharmaceutics

3. Does the Agency agree that in vitro (characterization) data of reference products Colgout, Colchicine TioFarma 0.5 mg and Colchicine Teva 0.5 mg (product used in LoDoCo2 trial) in addition to comparative bioequivalence data to support the bridging is sufficient for review of LODOCO tablets? (Applicant's Question 5)

FDA Preliminary Response:
Yes, we agree that the provided in vitro characterization data in addition to the comparative BE study data is sufficient for review.

AGEPHA Response:
AGEPHA has no further comment.

Discussion at the Meeting:
There was no discussion.

Nonclinical

4. Does the Agency agree with the proposed individual and total impurities specifications of LODOCO tablets 0.5 mg? (Applicant's Question 2)

FDA Preliminary Response:
Your approach to setting the proposed acceptance criteria for impurities appears reasonable. If the acceptance criterion for a specified degradation product does not exist in the USP and this degradation product can be qualified by comparison to a U.S. listed drug (LD), the acceptance criterion should be similar to the level observed in the LD. Alternatively, justify limits for individual impurities based on toxicological or other supporting sources of information.

AGEPHA Response:
Our proposed limit for non-specified and specified degradation products are based on ICH guidance, colchicine API monograph as per European Pharmacopeia, stability data of Lodoco tablets 0.5 mg and/or DMF holder (already reviewed by the FDA). The applicant would like to clarify the agency with the following justification for the proposed specifications limit:

The maximum daily dose of LODOCO is 0.5 mg.

Impurities	European Pharmacopeia limit (API)	ICH	DMF holder	Proposed limit (%)	Justification if proposed AC (%) > Regulatory QT Threshold (%)
				(b) (4)	The limit is set based on stability data of Lodoco Tablet 0.5 mg, Colchicine API EP monograph as well as Colchicine API manufacturer (b) (4)
					(b) (4) Based on Ph. Eur. Monograph for colchicine, the (b) (4)
					(b) (4) limit is set based on Colchicine API manufacturer #

					(b) (4)
				(b) (4)	
					The proposed acceptance limit is below the ICH limit.
					(b) (4)
					The proposed acceptance limit is below the ICH limit.
					The proposed acceptance limit is in line with the ICH limit.
Any individual unknown impurity	NMT (b) (4)	(b) (4)	-	NMT (b) (4)	The proposed acceptance limit is in line with the ICH limit.
Total unknown impurities	-	(b) (4)	-	NMT (b) (4)	The proposed acceptance limit is in line with the ICH limit.

AGEPHA will analyze Colcrys Tablets 0.6 mg and Mitigare Capsules 0.6 mg for the impurities. However, API source, excipients, excipients source, manufacturing method, equipment and package material, and packaging configuration of Colcrys Tablets 0.6 mg and Mitigare Capsules 0.6 mg are significantly different from the Lodoco Tablets 0.5 mg. Due to these differences, stability behavior of Lodoco Tablets 0.5 will be different from Colcrys Tablets 0.6 mg and Mitigare Capsules 0.6 mg. It is expected that impurities profile of Lodoco Tablets 0.5 mg will be different from Colcrys Tablets 0.6 mg and Mitigare Capsules 0.6 mg. If the impurity profiles of Lodoco Tablets 0.5 mg are significantly different from Colcrys Tablets 0.6 mg and Mitigare Capsules 0.6 mg, AGEPHA will propose impurity specifications based on the stability data of Lodoco Tablets 0.5 mg, DMF holder, ICH and EP pharmacopeia.

Discussion at the meeting:

AGEPHA stated they will conduct an impurity analysis for Colcrys (tablets, 0.6 mg) and Mitigare (Capsules, 0.6 mg); however, due to a change in the excipient source, there is an anticipated difference in impurity profiles for proposed colchicine product (LODOCO tablets, 0.5 mg) when comparing to Colcrys and Mitigare. If there is a significant difference, AGEPHA

intends to forgo the proposed assessment for stability and provide new impurity specifications based on the stability data of LODOCO tablets, DMF holder, ICH, and EP pharmacopeia. AGEPHA asked FDA if this approach was acceptable. FDA responded that the acceptance criteria and justification for impurities in the drug product specification will be assessed during review of the NDA resubmission, including justifications provided for the drug substance in the DMF, the levels measured for the listed drug product, compendial specifications, and other information. FDA also indicated that justifying the acceptance criteria for impurities using only stability data for the proposed drug product, without other supporting justification, is not an acceptable approach.

Clinical Pharmacology

5. Does the Agency agree that provided information on formulation used in LoDoCo, COLCOT (^{Pr}MYINFLA^{TM}) and LoDoCo2 is appropriate for review of the LODOCO NDA 215727? (Applicant's Question 3)

FDA Preliminary Response:
You acknowledge the need to your to-be-marketed product and the product used in the trials you are submitting as a basis of substantial evidence of effectiveness. We ask that you address the following:

1. Clarify your plan to bridge your to-be-marketed formulation to the US listed drugs upon which you propose to rely (i.e., Colcrys and Mitigare).
2. Clarify your plan to bridge your to-be-marketed formulation to Myinfla used in COLCOT. The indirect comparison of the PK data for your formulation to the Myinfla product monograph is not easily interpretable.

AGEPHA Response:
No bridging for the AGEPHA product and the product used in Colcot will be provided.

Reason:

Previous agreement and instructions by agency, specifically by Dr. Norman Stockbridge, to rely on Lodoco data only in preparation of the meeting we would ask agency to review all minutes and reconsider. Please see the summary of relevant minutes below.

*As advised by the agency in type C, Pre-IND meeting minutes dated Dec 19, 2019 "…**it would be preferable to compare the proposed drug product with those used in LoDoCo2**" and in type B, Pre-NDA meeting dated Sept 08, 2020 "Because there are three colchicine products used in the LoDoCo-2 trial, FDA ask that you identify the product to be used as reference in the comparative BA study*

and adequately justify your selection", AGEPHA has performed comparative in-vitro multimedia dissolution and bioequivalence study to bridge the to-be-marketed drug product (LODOCO) and reference product (Colgout®). The dissolution and pharmacokinetic profiles of LODOCO is similar to Colgout®. Please refer to the Pre-IND Type C meeting minutes page 7 of 15, meeting discussion) [redacted] (b) (4) *and Pre-NDA Type B meeting minutes page 5 of 42, FDA response to question 3* [redacted] (b) (4)

Discussion at the Meeting:
AGEPHA specified they will rely on Colcrys for nonclinical safety information as Colcrys has a higher dosing strength (0.6 mg) in comparison to AGEPHA's proposed dosing strength (0.5 mg) for LODOCO. For efficacy data, AGEPHA will rely on published literature from LoDoCo-1 and LoDoCo-2 clinical trials. Dr. Stockbridge acknowledged the bridging strategy discussed during the previous Type C meeting (PIND 119015, minutes dated December 19, 2019) and clarified this approach will remain sufficient for FDA to conduct their review. FDA added that evaluating the in vitro dissolution profile to support bridging from Colcrys to LODOCO will be considered a review issue.

3.0 OTHER IMPORTANT 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.[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 Information[3] and Pregnancy and Lactation Labeling Final Rule[4] 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

[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
[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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

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

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).[5] 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 Regulations.gov.[6]

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

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

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.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the 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.[7]

4.0 ATTACHMENTS AND HANDOUTS

To facilitate this discussion, AGEPHA's response document, dated August 3, 2022, received August 4, 2022, was displayed during the meeting. AGEPHA's responses have been incorporated into section 2.1.

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

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/

NORMAN L STOCKBRIDGE
08/31/2022 11:24:07 AM

NDA 215727

REFUSAL TO FILE

AGEPHA Pharma Middle East Trading, LLC
C/o: AGEPHA Pharma USA, LLC
Attention: Rainer Riel Köllmann
US Agent
1 N. Ocean Ave.
Cayucos, CA 93430

Dear Mr. Köllman:

Please refer to your new drug application (NDA) dated and received April 13, 2022, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for colchicine tablets.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

Adequate information to support the nonclinical sections of the proposed Prescribing Information has not been provided in your NDA submission. Therefore, your application is not complete, and we are unable to conduct a substantive review. You cannot rely upon foreign labeling for findings of safety and effectiveness to support your application.

You need to provide information to support proposed labeling regarding risks of reproductive toxicity, developmental toxicity, carcinogenesis, mutagenesis, and impairment of fertility. This information might come from the literature or reliance upon findings from an FDA-approved product. We can provide more detailed requirements in a subsequent advice letter.

While not issues related to our refusal to file of this application, you should address the following issues if the application is resubmitted.

Nonclinical

- Provide scientific justifications or specific sections of the submitted NDA to support the impurity thresholds proposed for your drug product.

Clinical Pharmacology

- Only one of the study formulations used in LoDoCo2 was compared to the to-be-marketed formulation in dedicated relative bioavailability studies. Please provide the percentages of usage of the three formulations used in LoDoCo2.

- Reliance on COLCOT is more problematic as it appears that there is no information on formulations used in that study.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review. If there is additional advice pertaining to the resubmission, we will provide comments in a separate advice letter.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee. If you choose to file over protest, FDA will generally not review any amendments to the application and will generally not issue information requests during the review cycle. Resubmission goals will not apply to any resubmission of this application.

PROPOSED PROPRIETARY NAME

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at OSECONSULTS@cder.fda.gov.

If you have any questions, please call Brian Cooney, Regulatory Project Manager, at (301) 796-0886.

Sincerely yours,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
06/11/2022 06:18:34 PM

PIND 119015

MEETING MINUTES

Cumulus Pharmaceutical LLC
Attention: Meraj Shaikh
Regulatory Project Manager
1712, Pioneer Avenue, Suite 1377
Cheyenne, WY 82001

Dear Mr. Shaikh:

Please refer to your Pre-Investigational New Drug Application (PIND) file for colchicine.

We also refer to the meeting between representatives of your firm and the FDA on September 8, 2020. The purpose of the meeting was to discuss results of LoDoCo-2 trial to support effectiveness for the submission of a new drug application (NDA) (b) (4) (b) (4)

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

If you have any questions, please call Maryam Changi, Regulatory Project Manager at (240) 402-2725.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Sponsor's slides and additional literature

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: September 8, 2020; 10:00 am to 11:00 am ET
Meeting Location: Teleconference

Application Number: 119015
Product Name: colchicine 0.5 mg Tablets

Indication: (b) (4)
Sponsor Name: Cumulus Pharmaceutical LLC
Regulatory Pathway: 505(b)(2) of the Food, Drug, and Cosmetics Act

Meeting Chair: Norman Stockbridge, MD, PhD
Meeting Recorder: Maryam Changi, PharmD

FDA ATTENDEES

Division of Cardiology and Nephrology:
Norman Stockbridge, MD, PhD Director
Mary Ross Southworth, PharmD, Deputy Director for Safety
Michael Monteleone, MS, RAC, Associate Director for Labeling
Fortunato (Fred) Senatore, MD, PhD, Clinical Team Leader

Office of Clinical Pharmacology, Division of Clinical Pharmacology I:
Kunal Jhunjhunwala, PhD, Clinical Pharmacology Reviewer
Anusha Ande, PhD, Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality:
Mohan Sapru, PhD, CMC Team Leader
Parnali Chatterjee, PhD, Biopharmaceutics Reviewer
Poonam DelVadia, PhD, Biopharmaceutics Team Leader

Office of Biometrics, Division of Biometrics I:
Jialu Zhang, PhD Statistical Team Leader
Ququan Liu, PhD Statistician

Division of Pharmacology & Toxicology-Cardiology, Hematology, Endocrinology, &Nephrology:
Xuan Chi, PhD, Non-Clinical Team Leader
Rama Dwivedi, PhD, Non-Clinical Reviewer

Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, & Nephrology:
Maryam Changi, PharmD, Sr. Regulatory Health Project Manager

Office of Surveillance and Epidemiology, Division of Risk Management:
Donella Fitzgerald, PharmD, Senior Risk Management Analyst

SPONSOR ATTENDEES
Cumulus Pharmaceuticals LLC
Dr. Michael Riel, Managing Director
Ms. Susanne Riel, CEO
Wolfgang Kratky, PhD, VP Research and Development
Ms. Elizabeth Lanz, COO
Ms. Antonia Riel-Köllmann, Vice President-Business Development & Licensing,
Mr. Meraj Shaikh, Regulatory Project Manager
Ms. Mubeena Khan,Assistant Manager-Regulatory Affairs
Ms. Erna Golubovic, Quality Manager

Consultant (Scientific Advisor)
Dr. Paul M Ridker, MD, MPH, Professor of Medicine; Harvard Medical School and Brigham and Women's Hospital

1.0 BACKGROUND

Colchicine is an anti-inflammatory drug approved by FDA for the treatment of gout and familial Mediterranean fever. Cumulus is interested in marketing colchicine (b) (4) (b) (4)

Cumulus met with the Division in 2014 to discuss use of the LoDoCo trial, a trial conducted in Australia, and additional studies that may be required, to support a new drug application (NDA). The LoDoCo trial employed a prospective, randomized, observer-blinded endpoint design; the objective of the study was to determine whether colchicine 0.5 mg/day could reduce the risk of cardiovascular events in patients with clinically stable CAD. According to the published results, colchicine 0.5 mg/day administered in addition to other standard secondary prevention therapies reduced the risk of major acute cardiovascular (CV) events by 67%. The Division opined that the findings from the LoDoCo study alone would not suffice for Cumulus's proposed NDA and recommended a phase 3 confirmatory trial.

In June 2014, Cumulus submitted a request for a Special Protocol Assessment of a phase 3 clinical trial; the Division responded with a No Agreement Letter in July 2014. In its letter, the Division indicated that while the general protocol seemed reasonable, the protocol lacked important details. Cumulus subsequently determined that it would not be feasible to conduct a large trial.

In 2017, Cumulus submitted a meeting request to discuss using (b) (4) (b) (4) to qualify for Accelerated Approval. Following an informal teleconference with the Division, Cumulus decided not to pursue the (b) (4) approach".

The Sponsor met with the Division on December 2, 2019 to discuss the use of Real-World Data (RWD) to generate additional efficacy data to support the safety and efficacy of colchicine for the proposed indication. Specifically, Cumulus proposed to conduct 2 observational studies to support a 505(b)(2) marketing application for a new dose and indication.

Following submission of the meeting background package, Cumulus alerted the Division to the results of the COLCOT trial, a randomized, double-blind trial of colchicine 0.5 mg/day in patients recruited within 30 days after a myocardial infarction. Cumulus requested this meeting to discuss the results of published clinical trial data mainly study results of LoDoCo-2 and the appropriateness of comparative bridging data for proposed test products and products used in LoDoCo-2 trial. Cumulus is also looking for feedback from the Agency the sufficiency of the overall approach is to support the submission of an NDA for the new dose of colchicine (0.5 mg) and the new indication of (b) (4) .

The FDA sent the Preliminary comments to Cumulus Pharmaceuticals LLC on September 2, 2020.The Sponsor used the appended slides to lead the discussion.

2.0 DISCUSSION

The Sponsor started the meeting with Dr. Paul Ridker's presentation on the latest updates from ESC about LoDoCo-1, COLCOT, LoDoCo-2, and Australian COPS trials and the anti-inflammatory property of colchicine and its effect on cardiovascular events. Dr. Ridker provided evidence from recent trials of two independent pathways leading to major adverse cardiac events: hypocholesterolemia and an inflammatory state. The COLCOT trial and the LoDoCo trial, each studying two different populations, point to the benefit of colchicine-mediated anti-inflammation.

> ***Question 1:*** *Do the consistent LoDoCo-2 clinical trial results, in conjunction with the COLCOT, LoDoCo-1 studies, and other published clinical evidence, represent a sufficient approach to support the proposed new indication of* (b) (4) *?*
>
> ***FDA Response to Question 1:***
> LoDoCo-2 evaluated colchicine in patients with stable CAD for 6 months where 84% of the ITT population (n=5522) had a prior ACS and 76% of the ITT population had prior PCI. COLCOT evaluated patients post-MI (within 30 days). The primary

efficacy endpoints in each trial are similar. If the results of LoDoCo2 are positive, then both trials support a [redacted] (b) (4) claim.

Discussion:
No further discussion.

Question 2: *Could the FDA please provide their expert advice for the appropriate labelling indication for proposed test product based on results of these supporting efficacy studies (COLCOT, LoDoCo-2, and LoDoCo-1)?*

FDA Response to Question 2:
The proposed indication should refer to components of the composite endpoint that contributed the results of the trials.

Cumulus Response:
The applicant proposes the following indication and would appreciate the agencies feedback:

[redacted] (b) (4)

Discussion:
The Division stated that separate claims for [redacted] (b) (4) use were reasonable, but those claims would reflect components of the composite endpoints that contributed to the observed effects.

Question 3: *Do the comparative bridging data (viz. composition, active and inactive ingredients, in-vitro dissolution etc.) for products used in LoDoCo-2 trial and proposed product is sufficient for bridging?*

FDA Response to Question 3:
Your proposal to bridge the proposed (to-be-marketed) product and the drug products used in LoDoCo-2 trial based on comparative in vitro dissolution is not sufficient. This is because the to-be-marketed drug product is qualitatively different in composition than the drug products evaluated in the LoDoCo-2 phase 3 clinical study. Therefore, a relative bioavailability study is warranted to bridge the to-be-marketed drug product and drug products administered in the LoDoCo-2 clinical study. Because there are three colchicine products used in the LoDoCo-2 trial, we ask that you identify the product to be used as reference in the comparative BA study and adequately justify your selection.

You intend to use dissolution methods stated in the USP Monograph for quality control of your product. For quality control dissolution testing, if high solubility of colchicine is demonstrated, standard dissolution testing condition as outlined in the FDA Guidance (August 2018) on "Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances" may be considered provided the proposed product meets eligibility criteria in the guidance.

Discussion:
The Office of Clinical Pharmacology reminded the Sponsor that because there are three colchicine products used in the LoDoCo-2 clinical trial, it is important to identify which drug product will be used as reference in the comparative bioavailability study along with the justification for that choice.

Question 4: *To what extent the minimum stability data is acceptable by FDA under exceptional cases?*

FDA Response to Question 4:
Generally, it is our expectation that the NDAs include at least twelve (12) months of long-term stability data and six (6) months of accelerated stability data at the time of submission as per ICH QIA(R2). The Division believes that these standards apply here.

Cumulus Response:
Would the agency be willing to consider a staggered-review of our application, to allow the agency to begin review whilst stability studies are still ongoing?

In this case, our application would be ready to submit end of 2020. Waiting for the complete stability data, would delay submission by 10 months.

Discussion:
The Office of Pharmaceutical Quality (OPQ) reiterated the need for including twelve months long-term stability data and six months of accelerated stability data at the time of NDA submission. OPQ reminded the Sponsor that in the case that the Division grants an expedited review designation e.g., Fast Track or Breakthrough Therapy; see discussion under Question 7, then nine months of long-term, and six months of accelerated stability data, with the commitment to receive the additional data during the first three months of NDA submission, may be acceptable.

Question 5: *Will comparative multimedia dissolution data between proposed product and products used in LoDoCo-2 trial sufficient to obtain the bio-waiver?*

FDA Response to Question 5:
We noted that the to-be-marketed drug product (manufactured by AGEPHA Pharma, s.r.a) is qualitatively different in composition than the drug products used in the LoDoCo-2 phase 3 clinical study. Therefore, we do not agree that comparative multimedia dissolution data for the drug product administered in the LoDoCo-2 clinical study and the proposed to-be-marketed drug product can be used to obtain a biowaiver for your drug product. We recommend that a relative bioavailability study be conducted with the to-be-marketed drug product and drug products administered in the LoDoCo-2 clinical study. Please refer to the FDA's Draft Guidance (Feb 2019) on "Bioavailability Studies Submitted in NDAs or INDs - General Considerations" for conduct of a relative bioavailability study for the to-be-marketed drug product.

Discussion:
No further discussion.

Question 6: *What quality data (CMC) does applicant supposed to submit for Breakthrough Therapy designation application?*

FDA Response to Question 6:
Breakthrough therapy designation does not change CMC requirements for an NDA. For guidance regarding the CMC requirements, content and format of an NDA, refer to 21 CFR, Part 314.50**.** For additional details, refer to: https://www.fda.gov/drugs/types-applications/new-drug-application-nda.

Discussion:
No further discussion.

Cumulus Question 7:
How can the applicant speed-up the regulatory approval to provide the proposed treatment to patients as quickly as possible?

FDA Response to Question7 and Discussion:
The Division spoke about regulatory programs available for an expedited review. The Division recommended the applicant refer to the *Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics* (https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf) and follow the procedures and guidance discussed there.

The Division asked the Sponsor to seek access to the LoDoCo-2 and COLCOT study data to facilitate the requisite substantive review.

Agency's Additional Comments:

1. A 505(b)(2) NDA will require datasets rather than the journal publications for a substantive review. The following information should be submitted at the time of NDA submission:

   a. Randomization

      1) Prior to enrollment in your phase 3 trials, please submit to the IND an encrypted SAS dataset of the randomization list including the randomization number, treatment arm, and stratification factors (if any). Please include an unencrypted define file describing the randomization list variables. Submit the encryption key with your NDA submission, and reference the date and serial number of submission of the encrypted dataset to the IND.

Appears this way on original

      2) A dataset _____that links the subject's randomization number and unique subject ID to the allocated medication kit/box number, medication name, and associated define file.

   b. Protocol and Statistical Analysis Plan (SAP)

      1) All versions of the protocol for the LoDoCo-2 and COLCOT trials and the date when changes were implemented. Include a Summary of Changes for each version.

      2) All versions of the SAP for the LoDoCo-2 and COLCOT trials. Include a summary of changes for each version and the number of subjects enrolled in the trial at the time the change was made.

   c. Clinical Trial Materials

      Case report forms (CRFs) and narratives for all subjects who died, dropped out, discontinued study drug for any reason, experienced a serious adverse event (SAE), or reached an efficacy endpoint. Please note that CRFs must include all clinical documents collected regardless of whether you label them as "CRFs" (Medwatch forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.).

      1) Sample clinical trial kits, from both treatment arms, identical to those used during the LoDoCo-2 and COLCOT trials. Ship them to Maryam Changi desk address in the same packaging as will be used for shipping to investigative sites. Please email Ms. Changi when she should expect this shipment.

      2) All data management plans for the LoDoCo-2 and COLCOT trials. Cite all amendments for each data management plan, including all manual and programmatical checks.

3) All site monitoring plans for the LoDoCo-2 and COLCOT trials. If changes to your site monitoring plans were not documented contemporaneously by formal signed amendments, explain the amendment process.

4) A description of the responsibilities of each academic research organization (ARO) or clinical research organization (CRO) used in the LoDoCo-2 and COLCOT trials.

5) All charters for committees involved in conducting the LoDoCo-2 and COLCOT trials (Data Safety Monitoring Board [DSMB], Steering Committee, etc.)

6) All meeting minutes of all groups with any responsibility for the management of the trial, e.g., Executive Committee, Clinical Endpoint Committee, Steering Committee and DSMB. Include agendas and all data/slides presented to the Committee. Indicate whether the meeting was opened or closed. Ensure that these packages include a table of contents and are bookmarked by date.

7) All newsletters and all other communications to investigational sites and national coordinators from the groups responsible for the conduct of the LoDoCo-2 and COLCOT trials. Please bookmark the communication by date.

d. General Data and Analyses

1) All code and datasets used to create your analyses found in the main sections of your Summary of Clinical Efficacy, Summary of Clinical Safety, and Phase 3 trial clinical study report.

2) Footnote the tables and figures featured in the main clinical efficacy and safety sections of the NDA with the name of the script used to create the table or figure.

3) List of datasets that you assert are of high quality for review. Explain how you assessed the quality of your datasets and what you did to ensure your datasets are suitable for an NDA review. Submit code that was used to create or clean up your analysis datasets.

4) Kaplan-Meier time to event analysis datasets and codes (both safety and efficacy) censoring subjects without an event at the date of last known information about the event of interest (not vital status check at the end of the study). Indicate how censoring was determined (e.g., by a patient visit or by telephone call). This dataset should allow one to analyze by intent-to-treat (ITT) as well as on-treatment. The events should include all adjudicated

events, any important composite endpoints, important adverse events, and laboratory parameter changes of interest.

5) Subject ID variable for all open label extension study datasets that links the subject to the ID used in the pivotal trial datasets.

6) Dataset that contains all subjects that were unblinded. Include the unique subject ID, the treatment received, who requested unblinding, date of unblinding, and the reason for unblinding.

7) Dataset that contains a list of all subjects for whom you submitted a CRF, narrative, or adjudication packages. The dataset should contain four variables with an indicator for whether each item was submitted.

8) A table set up similarly to the dataset requested above, but with a hyperlink to the respective document. The table could be further organized by reason for narrative submission (subjects with cardiovascular events of interest, subjects with hepatic laboratory anomalies of interest, etc.).

9) One table which includes the following information for the LoDoCo-2 and COLCOT trials:
   - Dates of first patient and last patient visits
   - Date of data lock
   - Dates for each interim analysis
   - Dates of all versions of the SAP (with a hyperlink to each SAP)
   - Dates of the initial protocol and all revisions. (with a hyperlink to the protocol and each revision).

e. Important Endpoints

1) An adjudication dataset for the LoDoCo-2 and COLCOT trials that contains one line per event. The columns in the dataset should include the study number, unique subject id, randomized treatment, actual treatment, flag that indicates subject is included in the ITT analysis, flag that indicates the subject is included in the safety analysis, the event type being adjudicated (i.e., stroke, major bleed, death, hospitalization for heart failure, etc.), date of event, what triggered the event for adjudication (i.e., investigator, laboratory result, etc.), the investigator's assessment of the event, each adjudicators' result (in chronological order across the dataset), date of each adjudication, final adjudication result and date.

2) A comprehensive description of the algorithm used to identify potential endpoint events in your final clinical study report. If your algorithm changed, you should also provide detailed information on its evolution, including when and why changes were made.

Other

1) Statement of Good Clinical Practice confirming that all clinical studies were conducted under the supervision of an Institutional Review Board and with adequate informed consent procedures. If you were granted an IRB Waiver during this trial because a specific site or country operated under a Central Ethics Committee (CEC) and/or Local Ethics Committees (EC), please reference the waiver and include the date.

2) Rationale for assuring the applicability of foreign data to U.S. population/practice of medicine in the submission for those phase 3 trials conducted primarily outside of the United States (OUS)

   There are two major pieces to this applicability of foreign data issue as follows:

   - Are the patients the same (US versus rest of the world)?
   - Are the medical systems treating the disease the same way with respect to interventions and background therapy on a region-specific basis?

3) An annotated version of the pre-NDA meeting minutes that include a hyperlink, when applicable, to the analysis and/or documents requested. This document is usually placed in Module 1.

3.0 OTHER IMPORTANT MEETING LANGUAGE:

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 Information[3] and Pregnancy and Lactation Labeling Final Rule[4] 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

[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
[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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 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.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

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

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

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

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

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

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[5] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[6]. 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.

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).[7] 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 Regulations.gov.[8]

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

[5] https://www.fda.gov/media/84223/download
[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[7] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[8] http://www.regulations.gov

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.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the 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*.[9]

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

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