CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212905Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 131163

MEETING PRELIMINARY COMMENTS

Verrica Pharmaceuticals, Inc.
Attention: Patti Neall
Executive Director, Regulatory Affairs
10 N. High Street, Suite 200
West Chester, PA 19380

Dear Ms. Neall:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for cantharidin solution, 0.7%.

We also refer to your correspondence dated and received January 10, 2019 requesting a meeting to discuss content and format for New Drug Application (NDA).

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

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, call me at 301-796-4224.

Sincerely,

{See appended electronic signature page}

Barbara Gould, MBAHCM
Chief, Project Management Staff
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: March 27, 2019 @ 1:00 p.m.
Meeting Location: White Oak Building 21, Conference Room 1417

Application Number: IND 131163
Product Name: cantharidin solution, 0.7%.

Proposed Indication: For the treatment of molluscum contagiosum
Sponsor Name: Verrica Pharmaceuticals, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for March 27, 2019 from 1:00 p.m. to 2:00 p.m. between Verrica Pharmaceuticals, Inc. and the Division of Dermatology and Dental Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

The purpose of this meeting is to discuss the content and format of New Drug Application (NDA) for cantharidin solution, 7%.

Regulatory Correspondence History:

We have had the following teleconferences with you:

- 09/13/2017 End of Phase 2 Meeting
- 08/16/2016 PIND Meeting

We have sent the following correspondence:

- 03/08/2019 Information Request
- 03/05/2019 Pediatric Study Plan – Initial Agreement
- 07/27/2018 Advice/Information Request
- 07/03/2018 Change of Address
- 03/23/2018 Information Request
- 02/16/2018 Information Request
- 01/26/2018 Special Protocol – No Agreement
- 01/05/2018 Information Request
- 01/04/2018 Information Request
- 11/27/2017 Special Protocol – No Agreement
- 08/21/2017 Pediatric Study Plan – Written Response
- 06/22/2017 Study May Proceed Letter
- 04/12/2017 Information Request
- 04/06/2017 Information Request

2.0 DISCUSSION

2.1. Regulatory

GENERAL COMMENT:

If you intend to rely, in part, on information required for approval that comes from studies not conducted by you or for you or for which you have not obtained a right of reference (e.g., reliance on the FDA's finding of safety and/or effectiveness for a listed drug or published literature), then your marketing application will be a 505(b)(2) application.

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)).

Refer to the 505(b)(2) REGULATORY PATHWAY section below for information about submitting a 505(b)(2) NDA.

Question 13:

Can the Agency provide a determination regarding Verrica's Request for the Small Business Waiver of the PDUFA Application Fee prior to submission of NDA 212905?

FDA Response to Question 13:
For assistance with a small business waiver, you may contact the Center for Drug Evaluation and Research Small Business and Industry Assistance office (CDER SBIA).

See specific phone numbers and website information is provided below:

- (866)-405-5367
- (301)-796-6707
- CDER Small Business and Industry Assistance
- CDER Small Business & Industry Assistance: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/default.htm

2.2. Chemistry, Manufacturing and Controls (CMC)

Question 12:
Is the proposed approach for the USAN application acceptable to the Agency?

FDA Response to Question 12:
It is acceptable that the USAN application was submitted on 06-Dec-2018. At the time of NDA submission, provide the status of the USAN name. If it has not been accepted when the NDA is submitted, the USAN Council can be contacted to ensure that a decision is made prior to an action being taken on the NDA.

2.3. Nonclinical

There are no Nonclinical questions submitted for this meeting.

2.4. Clinical Pharmacology

There are no Clinical Pharmacology questions submitted for this meeting. We have the following comments:

- For your completed pharmacokinetic (PK) study VP-102-103, submit raw PK data and calculated PK parameters in SAS transport format (XPT format) in your NDA.

- Submit bioanalytical method validation report and bioanalysis report in your NDA, including information that would support long-term storage stability of the PK samples.

- Submit the amount of drug product used by subjects in the maximal use PK study and your Phase 3 studies.

2.5. Clinical/Biostatistics

Background:
The development program for VP-102 in the treatment of molluscum contagiosum in subjects age 2 years and older includes the following studies:

Phase 3:

- VP-102-101 (SPA in place): randomized, double blind, placebo controlled evaluating VP-102 24-hour application every 21 days up to 4 applications
- VP-102-102: identical to VP-102-101

Phase 2:

- VP-102-103: open label study in 33 subjects (17 subjects in maximum use cohort where more than 21 lesions were treated)

(b) (4)

Phase 3 trials
Primary efficacy endpoint:

- Proportion of subjects with complete clearance of treatable molluscum contagiosum lesion (baseline and new) at Day 84

Safety assessments: adverse events; local skin reactions, including post-24-hour investigator assessment after first treatment; and dermatologic examination.

Question 1:
Based on review of the topline safety and efficacy data from the pivotal studies, VP-102-101 and VP-102-102, along with the supportive safety data from the VP-102-103 exposure study, does the Agency agree that these data support the basis of submission of the NDA for the proposed indication?

FDA Response to Question 1:
Based on the information provided in the briefing package, the referenced studies would appear to be adequate to support a marketing application.

Question 2:
Does the FDA agree with the proposed plan for the pooling of safety and efficacy data for the NDA?

FDA Response to Question 2:
We agree with the proposed safety pooling strategy. In addition, for Pool C, we recommend you also include subjects from Study 16-10-195 Cohort 2, who received the same to-be-marketed drug formulation and dosing regimen as in the Phase 3 trials.

Including Pool A (VP-102-101 and VP-102-102) and Pool B (VP-102-103) in the ISE appears reasonable. We note that the objective of the ISE is to support the analysis results obtained from the individual trials and not to establish a new efficacy claim based on pooling data from the individual trials. Therefore, while analyses based on pooled data may be performed for the ISE, such analyses are considered exploratory. Establishing an efficacy claim will be based on efficacy data from the individual Phase 3 trials to provide replication of study findings.

The abbreviated SAP for the ISE states that assessments of clearance status that fall outside the visit window will not be considered for analysis, resulting in a missing assessment at that visit. It is not clear whether these subjects are excluded from the analysis or if they will be imputed as failures. We recommend analyzing the ITT population and handling missing data for Pool A in the ISE (Studies VP-102-101 & VP-102-102) using the same methodology as used for the analysis of the individual studies.

The abbreviated ISS SAP specifies that analyses by timepoint will be conducted according to study visit (i.e., Day 1, Day 21, Day 42, Day 63, and EOS visit), and subjects in Study VP-102-103 who achieve complete clearance early may have their EOS visit before Day 84. Subjects in Study VP-102-103 who achieve complete clearance prior to Day 84 should have their safety data from the EOS visit summarized with assessments in the pivotal studies from the closest study visit day instead of the Day 84 visit day. It may also be informative to summarize these safety data based on the number of treatments (i.e., 1, 2, 3, or 4).

Question 3:
Does the Agency agree that the Summary of Clinical Efficacy can serve as the Integrated Summary of Efficacy and the Summary of Clinical Safety can serve as the Integrated Summary of Safety and reside in Module 2.7 for this NDA?

FDA Response to Question 3:
The ISE and ISS are required in applications submitted to the FDA in accordance with the regulations for NDA submissions (21 CFR 314.50(d)(5)(v) and 21 CFR 314.50(d)(5)(vi)(a), respectively). There may be situations in which sections 2.7.3, Summary of Clinical Efficacy, and 2.7.4, Summary of Clinical Safety, would be sufficiently detailed to serve as the narrative portion of the ISE and ISS, respectively, while still concise enough to meet the suggested size limitations for Module 2. In such situations, the ISE and ISS can be split across Module 2 and Module 5, with the narrative portion located in section 2.7.3 or 2.7.4 and the appendices of tables, figures, and datasets located in section 5.3.5.3. If the ISE or ISS is split across modules in this way, it is critical to include a clear explanation of where the parts are located. This explanation should be placed both in Module 2 (section 2.7.3 or 2.7.4) and in Module 5 (section 5.3.5.3).

Question 5:
Does the Agency agree with the proposed approach for the presentation of safety narratives in the VP-102 NDA?

FDA Response to Question 5:

In addition to proposed safety narratives, submit narratives of adverse events that led to subject discontinuation due to adverse events and adverse events that lead to dose reduction or addition of concomitant therapies.

Question 6:

Does the Agency have any comments on the proposed draft labeling text within the VP-102 Target Product Profile?

FDA Response to Question 6:

Your general approach to labeling appears reasonable. However, the adequacy of the labeling content and format will be determined during the review of the efficacy supplement. Your drug product labeling should comply with requirements of the published final rule: *Content and Format of Labeling for Human Prescription Drug and Biologic Products: Requirements for Pregnancy and Lactation Labeling*, referred to as the "Pregnancy and Lactation Labeling Rule [PLLR or final rule; 21 CFR 201.57 (c)(9)(i) through (iii)]. You may also refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biologic Products-Content and Format.*

Results for efficacy endpoints involving partial clearance of lesions are not considered to be clinically meaningful (meeting minutes dated 10/6/2017, SPA - No Agreement letter dated 11/27/2017, preliminary meeting comments dated 10/19/2018) and therefore are not expected to appear in labeling. P-values are also not expected to be included in labeling. A brief summary of the patient population is likely to appear in labeling rather than a full demographic table. From the Guidance for Industry, *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products - Content and Format*, "The primary objective of the CLINICAL STUDIES section is to summarize (1) the evidence supporting effectiveness in the subjects who were studied, (2) the critical design aspects of the studies, including the populations studied and endpoints measured, and (3) the important limitations of the available evidence. Ordinarily, safety data are described in the ADVERSE REACTIONS section."

Question 7:

Does the Agency agree with the plan to include detailed VP-102 Instructions for Use in the draft labeling with the NDA submission?

FDA Response to Question 7:

Your approach is reasonable. The determination if Instructions for Use will be included in labeling will be based on review of the completed, adequate Human Factors Study.

Question 9:

Does the Agency agree that the plan for the 120-day safety update is acceptable?

FDA Response to Question 9:

Along with the 120-day Safety Update Report, updated labeling, and updated Clinical Summary of Safety, include updated safety datasets from which the analyses are derived.

Question 10:

Does the Agency agree that continuous routine post-marketing pharmacovigilance surveillance of the safety profile for VP-102 will adequately assess potential patient risk in the patient population (molluscum contagiosum) and that a REMS program is not required?

FDA Response to Question 10:

Based on our review of the summary of safety information contained in your meeting package, REMS may not be required for the safe use of your product in the treatment of molluscum contagiosum. However, our final determination regarding the need for REMS will be based on the overall risk benefit assessment for your product at the time of the NDA review.

Question 11:

Does the Agency concur with Verrica's Agreed iPSP?

FDA Response to Question 11:

Yes, as per the March 5, 2019 Agreed Initial Pediatric Study Plan – Agreement letter.

2.6. eData/eSub

Question 4:

Does the agency agree with the proposed approach for submission of study data to support the VP-102 NDA?

FDA Response to Question 4:

Yes, we agree with the submit study data in Clinical Data Interchange Standards Consortium (CDISC) compliant datasets, along with all proper documentation to support the efficacy and safety analyses and analysis populations.

Question 8:

Does the Agency agree that the overall proposed NDA Table of Contents and organization of the 505(b)(1) NDA to be submitted electronically in eCTD format are acceptable?

FDA Response to Question 8:

From a technical standpoint (not content related) yes, the proposed format for the planned NDA is acceptable. We defer to eDATA team regarding the submission of full integration of the efficacy and safety data in the SCE and SCS in Modules 2.7.3 and 2.7.4 and Statistical Analysis Plan and all Tables, Figures, and Listings in Module 5.3.5.3. However, it is recommended that when splitting the ISS, the text portion is placed in Module 2 (section 2.7.4), and the appendices and datasets are placed in Module 5 (section 5.3.5.3). Section 2.7.4 refers the reader to section 5.3.5.3 for the appendices and datasets. Section 5.3.5.3 refers the reader to section 2.7.4 for the text portion of the ISS (refer to https://www.fda.gov/downloads/drugs/guidances/ucm136174.pdf.

Your application is required to be complete at the time of filing. For approval, you will need to provide sufficient information to establish that your drug product is safe and effective for the proposed indication.

We have the following additional comments regarding the NDA content and format:

1. Provide a table with the following columns for each of the completed Phase 3 clinical trials:
    a. Site number
    b. Principle investigator
    c. Location: City State, Country
    d. Number of subjects screened
    e. Number of subjects randomized
    f. Number of subjects treated who prematurely discontinued
    g. Number of protocol violations (Major, minor, including definition)

2. Discuss study-to-study differences in efficacy results and any efficacy issues that may need further exploration. Provide your statement as to why the data presented represents a demonstration of substantial evidence of effectiveness for the proposed indication.

3. Include shift tables for all vital signs for both outside the normal range and outside the range that is considered clinically significant. Provide the normal range of values for all parameters, the threshold for concern for a clinically significant change and your justification for why this threshold is appropriate.

4. Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. See Guidance for Clinical Investigators, Industry, and FDA *Staff Financial Disclosure by Clinical Investigators*.

5. The following comment applies to all safety analyses (individual studies and applicable pooled analyses):

    a. For the placebo-controlled period through Day 84, provide raw incidence rates (at ≥1%) by treatment group.
    b. Include definition (start and end dates) for treatment-emergent adverse event flag used in datasets (e.g., 30 days after last study visit).

6. Include the coding dictionary used for mapping investigator verbatim terms to preferred terms or identify where this will be located in the proposed submission. The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped.

7. Include the full-text version of any referenced articles with hyperlinks to each article, as appropriate.

3.0 Administrative Comments

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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 or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) 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 the latest version of the molecular target list, please refer to https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm544641.htm

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 OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@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.

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 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* (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.

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.				

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.

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 (February 2018) and the associated 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:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

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

/s/

BARBARA J GOULD
03/25/2019 03:45:31 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 131163

MEETING PRELIMINARY COMMENTS

Verrica Pharmaceuticals, Inc.
Attention: Matthew Davidson, PhD
Founder and CEO
200 Garrett Street, Suite #S
Charlottesville, VA 22902

Dear Dr. Davidson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for cantharidin topical solution, 0.7%.

We also refer to your correspondence submitted and received June 29, 2017, requesting a meeting to discuss the development program for cantharidin topical solution, 0.7%.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

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, call me at (301) 796-7475.

Sincerely,

{See appended electronic signature page}

Barbara Gould
Chief, Project Management Staff
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: End-of-Phase 2

Meeting Date and Time: September 13, 2017 at 8:30 - 9:30 a.m. (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22
Silver Spring, Maryland 20903

Application Number: IND 131163
Product Name: cantharidin topical solution, 0.7%
Proposed Indication: for the treatment of molluscum contagiosum
Sponsor Name: Verrica Pharmaceuticals

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 13, 2017 at 8:30 - 9:30 a.m. (EST) between Verrica Pharmaceuticals and the Division of Dermatology and Dental Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Regulatory Correspondence History

We have had the following teleconferences with you:
08/16/2016 PIND Meeting

We have sent the following correspondence
04/06/2017 Information Letter
04/12/2017 Information Letter
06/22/2017 Study May Proceed Letter

1.1 Purpose

To develop cantharidin topical solution, 0.7% for the treatment of molluscum contagiosum

2.0 DISCUSSION

2.1 Chemistry, Manufacturing, and Controls

Question 1:

In regard to comment 8 in the Study May Proceed Letter, dated 22 June 2017, we have started contracting for extractable and leachable studies that will be conducted under GLP with the to-be-marketed applicator. We have determined, given the nature of this drug and device, the topical route of administration, and the small volume of study drug being administered, that the potential biocompatibility risk is minimal. Nonetheless, Verrica has contracted with (b) (4) to conduct a multi-part evaluation of Verrica's proposed applicator in accordance with ISO 10993 guidelines including: a) an extractable/leachable study with the VP-102 components (ampule, tube, (b) (4), tip and cap); and b) a toxicological risk assessment including cytotoxicity (L929 neutral red uptake test), irritation (intracutenous injection test) and sensitization (Klingman maximization test).

Does the Agency agree that the proposed studies are the only necessary lab based studies needed to demonstrate biocompatibility?

FDA Response:

You are proposing that they will be conducting cytotoxicity, sensitization, and irritation testing for this device. We agree that these would be the only testing necessary according to ISO 10993-1 to establish biocompatibility of the device.

2.2 Nonclinical

Question 2:

Based on the completion of the agreed upon studies, Verrica believes that the requirements of the standard battery for in vitro genotoxicity testing have been satisfied. In Comment 10 in the Study May Proceed letter, the Agency requested that an "in vitro genotoxicity test battery must be completed."

Is the Agency requesting an additional study beyond the Ames test and the in vitro mammalian cell chromosomal aberration study that have been completed?

FDA Response:

Yes. Because the conducted in vitro chromosome aberration test in human lymphocytes did not provide useful information (inconclusive under the study conditions), an additional in vitro

genotoxicity assay (i.e., a mouse lymphoma Tk gene mutation assay or an in vitro micronucleus test) should be conducted to complete the in vitro genotoxicity test battery, per the ICH S2(R1) guidance document.

Question 3:

Pending clarification on question 2 above, does the Agency agree that the non-clinical package and the accompanying waiver requests submitted with the IND application are adequate to support registration and that no additional nonclinical studies are required?

FDA Response:

Your nonclinical package appears reasonable to support a NDA submission. No additional nonclinical studies are needed, provided that the in vitro genotoxicity test battery is completed and the genotoxicity data are determined to be adequate after the review of submitted full study reports.

2.3 Clinical/Biostatistics

Introductory Comments

You are currently conducting two Phase 2 trials. (b) (4) Study VP-102-103 has currently enrolled 7 subjects for 24-hour treatment application. As these are small, ongoing, open-label studies which involve different treatment durations and have several dropouts due to adverse events, it would be difficult to draw conclusions about the results of these studies.

You plan to conduct two Phase 3 trials, each with 250 subjects randomized in a 3:2 ratio to VP-102 and vehicle with stratification factors for the presence/absence of active atopic dermatitis and baseline lesion count (1-20, 21-40, and >41 lesions). You power your trials using assumed response rates of 45% for VP-102 and 20% for vehicle which you state are based on the placebo arms in the Aldara® Phase 3 trials, your open-label Phase 2 trials, and the literature. We still have concerns about whether you selected the appropriate dose (concentration, frequency of use, treatment duration) to be investigated in the Phase 3 trials. We acknowledge that you increased your sample size from 100 to 250 in response to the Agency's previous comments; however, we reiterate our comments on the need to conduct an appropriate dose-ranging study of large enough size to investigate concentration, frequency, and treatment duration to select the appropriate dose and to get a reliable estimate of the treatment effect for powering your Phase 3 trials.

The following are general comments:

- Termination of sites for reasons such as noncompliance or unsatisfactory enrollment may bias study results, as such information is still relevant for interpretation of study findings.

- You state that you plan to stratify randomization by presence/absence of active atopic dermatitis and baseline lesion count (1-20, 21-40, and >41 lesions). However, it is not clear what the basis is for this selection of strata. Stratification is meaningful when the factors have an impact on efficacy. You do not provide any information about how either stratification factor may affect efficacy, and it is unclear how you chose the cut points for

the baseline lesion count strata, as this is a continuous variable. Investigating site-to-site reliability is recommended for appropriate interpretation of study findings, and we reiterate our comments from the Study May Proceed letter dated 6/22/2017 that randomization should be stratified by site.

- We note that you provided further details on the per protocol (PP) population in the amended protocol; however, the PP population should be fully pre-specified in the protocol in order to maintain the integrity of the trial and reduce the chance of bias.

- You state that, "In general, analyses will be carried out with the data available with no imputation for missing data. One notable exception is for analysis of the primary endpoint." The intent-to-treat population should be the primary analysis population for all endpoints. Therefore, you should pre-specify a plan for handling missing data for your secondary endpoints as well; otherwise, you are performing a complete case analysis which violates the intent-to-treat principle.

- Whether the proposed (b) (4)
(b) (4)

- In the case that households enroll more than 1 subject in your Phase 3 trials, include a variable that identifies subjects from the same household for submission to the Agency.

Question 4:

Does the Agency agree that the Phase 3 protocols are registration enabling as currently designed? More specifically;

a) Are the primary and secondary endpoints acceptable for registration?
b) Are the inclusion and exclusion criteria acceptable for registration?
c) Does the Agency agree with the planned statistical analyses of the primary and secondary endpoints as specified in the SAP?
d) Does the Agency agree that the randomization scheme and study sizes are adequate for registration?

FDA Response:
See Section 2.3 Clinical/ Biostatistics Introductory Comments.

a) Your proposed primary endpoint is the "proportion of subjects exhibiting complete clearance of all treatable molluscum lesions (baseline and new) on or before Day-84 (EOS)." For the indication of treatment of molluscum contagiosum, the recommended primary endpoint is the complete clearance of lesions, on Day-84. Provide clear definition of "untreatable" lesions supported by adequate rationale. We recommend that all lesions in genital area, old and new, be considered treatable.

Secondary endpoints based on partial clearance of molluscum lesions are not considered clinically meaningful and will not be included in labeling.

You propose (b) (4)
(b) (4)

(b) (4)

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(b) (4)

b) You did not specify a minimum baseline number of molluscum lesions that will qualify subjects for inclusion. In your protocol you state that VP-102 label will focus on treatment of subjects with "any" number of molluscum lesions (page 29 of protocol, appendix C). Therefore, subjects with a single lesion will be eligible for enrollment. Specify in your protocol the minimum number of lesions that will qualify subject for inclusion into the trial.

c) See Section 2.3 Clinical/Biostatistics Introductory Comments.

d) See Section 2.3 Clinical/ Biostatistics Introductory Comments.

Question 5:

The planned safety database for VP-102 includes subjects from two planned identical Phase 3 studies (total of 300 subjects to be treated with VP-102), the data obtained from Study VP-102-103 (at least 22 subjects to be treated with VP-102), (b) (4)

Does the Agency agree that the safety database that will be obtained from the planned studies and clinical literature is sufficient for submission of the NDA and registration?

FDA Response:

Because repeated use of your product can be anticipated in patients who do not get complete clearance of all lesions after the four treatments, you will need to address long-term safety in sufficient number of relevant subjects to inform safety. In your briefing materials (page 26 of protocol, appendix C), you refer to study by Garelik et al. in which subjects achieved complete clearance of molluscum lesions after up to 9 visits. For the number of subjects and duration of exposure the investigational product, you are referred to ICH E1A: Guideline for Industry – "The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment Non-Life-Threatening Conditions" and Guidance for Industry: Premarketing Risk Assessment".

You plan to use literature reports to provide support the safety of your product. It is difficult to provide comments on whether the literature you plan to submit includes results from well-designed and conducted clinical trials to enable drawing conclusions about the safety of your product for the indication you are seeking. You will need to address whether the literature you

plan to submit is adequate to provide safety information regarding your product's specific formulation, and whether the submitted literature for other cantharidin products with different formulations, concentrations, treatment regimens is relevant to your product. Safety information should be obtained from relevant population and from clinical trials that represent expected length of treatment, dose, frequency and how cantharidin will be administered for the treatment of molluscum contagiosum. For more information, refer to guidance for industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

Question 6:

(b) (4)

Does the Agency agree with this exclusion based upon the supported rationale?

FDA Response:

No we do not agree. (b) (4)

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Question 7:

(b) (4)

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(b) (4)

Does the Agency agree that, provided reasonable measures are taken to ensure investigators and patients/caregivers are blinded, the Phase 3 studies will be deemed blinded, well-controlled, and adequate for registration?

FDA Response:

No, we do not agree. It is not clear what "reasonable measures" you plan to employ to minimize functional unblinding of investigators given high frequency of LSR expected from cantharidin treatment. We recommend evaluation of efficacy and safety be conducted by blinded assessor. In addition, we recommend you query subject/caregiver for their perception as to which treatment group they were assigned.

Regarding your proposed Phase 3 trial, we have the following comments:

- You propose that adverse events (AEs) reports will not include expected local skin reactions such as: minor pain that does not require a pain reliever, small blisters localized to the treatment sites, mild or moderate pruritus, erythema, flaking/scaling/dryness, scabbing/crusting and post-inflammatory pigment changes. A reaction to drug administration will be considered an AE if it:
    - Results in development of individual blisters that are greater than 20mm in diameter. (An aggregated blister composed of a number of smaller blisters is not considered an AE).

- Produces blistering distal to the treatment site.
- Requires any medical intervention including administration of mild over-the-counter (OTC) pain relievers.
- Causes secondary infection.
- Results in severe pruritus.
- Results in scarring
- Results in discontinuation from the study.
- Any other unexpected reaction or incident that is untoward whether it is related or unrelated to the Study drug.

We do not agree with your proposed reporting of AEs. Report all AEs irrespective of severity and whether they are expected or not. All AEs should be assessed for relation to the study drug administration. Omitting reporting of "expected" skin reactions will result in inadequate evaluation of your product's safety.

(b) (4)

2.4 Clinical Pharmacology

There are no questions for Clinical Pharmacology. However, we have the following comments regarding to your Study VP-102-103.

- The lower limit of quantitation of your current bioanalytical method is 1 ng/mL which is equivalent to 5 nM. We recommend that you improve the sensitivity of the bioanalytical method to be able to detect plasma cantharidin concentrations of ≤ 1 nM. Currently we do not know your plan for conducting a thorough QTc study. A waiver for conducting a thorough QTc study could be possible only if you are able to demonstrate that the systemic exposure under maximal use conditions is sub-nanomolar and there is no positive signal in an in-vitro hERG assay.

- We note that you plan to enroll at least 3 subjects 2-5 years of age in the pharmacokinetic (PK) exposure group. The proposed number of subjects (at least 3) in the 2-5 year age range is very few. We recommend that you enroll sufficient numbers of subjects within the lowest age range (2-5 years) so that robust PK information is produced.

- You proposed to collect sparse PK blood samples prior to cantharidin treatment, and at 2, 6, and 24 hours following application of the first dose in the exposure group. The purpose of the maximal use PK trial is to assess a complete PK profile following application of your drug under maximal use conditions. We recommend that you collect more intensive PK samples to fully characterize the PK profile of your product [parent and metabolite(s)].

- We note that the maximal use PK study enrolls subjects with ≥ 21 molluscum lesions for PK assessment. This may not represent maximal use conditions. We recommend that you

enroll subjects with lesions that represent the upper end of disease severity as anticipated in your Phase 3 trials to inform systemic safety of your product.

- You should record the amount of formulation used in each subject.

3.0 ADMINISTRATIVE COMMENTS

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because none of the criteria apply at this time to your application, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DATA STANDARDS FOR STUDIES

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

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format.

This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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

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

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

COMPOUNDED DRUG PRODUCT REQUIREMENTS

As described at 21 CFR 210.2(c), a drug product, including a compounded product, intended for use in a clinical study must be prepared in accordance with the current good manufacturing practice requirements appropriate for the product. For questions or clarification, contact Compounding@fda.hhs.gov.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

SECURE EMAIL COMMUNICATIONS

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

505(b)(2) REGULATORY PATHWAY

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

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

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

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s)

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

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

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

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

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

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**

1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

PATIENT-FOCUSED ENDPOINTS

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BARBARA J GOULD
09/08/2017