# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 211379Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 128569

**MEETING MINUTES**

Dexcel Pharma Technologies Limited
Attention: Jeanne M. Novak, PhD
Authorized Regulatory Representative and U.S. Agent
CBR International Corp.
2905 Wilderness Place Suite 202
Boulder, CO 80301

Dear Dr. Novak:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Dexamethasone. We also refer to the meeting between representatives of your firm and the FDA on November 8, 2017. The purpose of the meeting was to discuss the planned new drug application (NDA) with an indication that allows for the use of the product in combination with anti-Multiple Myeloma (MM) drugs for the treatment of MM, including the proposed indication, LDs, clinical information to support the NDA, and specific topics related to chemistry, manufacturing, and controls (CMC) and the pharmacokinetics (PK) studies.

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

If you have any questions, call Kimberly Scott, Regulatory Project Manager at (240) 402-4560.

Sincerely,

*{See appended electronic signature page}*

Romeo A. de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

**FOOD AND DRUG ADMINISTRATION**
CENTER FOR DRUG EVALUATION AND RESEARCH

# MEMORANDUM OF MEETING MINUTES

| | |
|---|---|
| **Meeting Type:** | Type B |
| **Meeting Category:** | Pre-NDA |
| **Meeting Date and Time:** | Wednesday, November 8, 2017<br>11:00AM to 12:00PM (EST) |
| **Meeting Location:** | 10903 New Hampshire Avenue<br>White Oak Building 22, Conference Room: 1315<br>Silver Spring, Maryland 20903 |
| **Application Number:** | PIND 128569 |
| **Product Name:** | Dexamethasone |
| **Indication:** | Treatment of patients with MM |
| **Sponsor Name:** | Dexcel Pharma Technologies Limited |
| **Meeting Chair:** | R. Angelo de Claro, MD |
| **Meeting Recorder:** | Kimberly Scott |

## FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)
Tamy Kim, PharmD, Associate Director of Regulatory Affair

Division of Hematology Products (DHP) in OHOP
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
R. Angelo de Claro, MD, Clinical Team Leader
Lori Ehrlich, MD, PhD, Clinical Reviewer
Theresa Carioti, MPH, Chief, Project Management Staff
Kimberly Scott, RN, BSN, OCN®, Regulatory Project Manager

OHOP/Division of Hematology, Oncology, Toxicology (DHOT)
Christopher Sheth, PhD, Supervisory Pharmacologist/Toxicologist
Matthew Thompson, PhD, Pharmacologist/Toxicologist

Office of Clinical Pharmacology/, Division of Clinical Pharmacology V
Guoxiang Shen, PhD, Clinical Pharmacology Reviewer
Gene Williams, PhD, Clinical Pharmacology Team Leader

Office of New Drug Products/Division of Biopharmaceutics V
Okpo Eradiri, PhD, Biopharmaceutics Team Leader
Om Anand, PhD, Biopharmaceutics Reviewer

Product Quality - ONDP
Rajiv Agarwal, PhD, Product Quality Reviewer

Office of Surveillance and Epidemiology (OSE)
Neil Vora, PharmD, RPh, MBA, Senior Regulatory Project Manager

**SPONSOR ATTENDEES**
Tomer Gold, BSc, MSc, Vice President, Research and Development
Sigalit Melcer, MSc, Manager, Clinical Trials Department
Keren Agmon, BPharm, MBA, Head of R&D Regulatory Affairs
Ilan Miller, Adv., Head of Intellectual Property and Medical Information
(b) (4)
(b) (4)
(b) (4)
(b) (4)

**Attending via Teleconference**
Valerie Azoulay, PharmD, Pharmaceutical R&D Manager
Liora Gerad, PhD Team Manager, Regulatory Affairs
Olga Dementyev, MSc Team Manager, Regulatory Affairs
Lihi Blesser, DVM Pharmaceutical R&D, Project Manager
Keren Schott, B.Ph, Bio Project Manager
(b) (4)
(b) (4)

## 1.0 BACKGROUND

The purpose of this Type B, Pre-NDA meeting is to discuss the information that will be included in the planned NDA, including the proposed indication, LDs, clinical information to support the NDA, and specific topics related to chemistry, manufacturing, and controls (CMC) and the pharmacokinetics (PK) studies.

The Sponsor plans to submit a new drug application (NDA) for Dexamethasone 20 mg via the 505(b)(2) pathway for the treatment of multiple myeloma (MM).

FDA sent Preliminary Comments to Dexcel Pharma Technologies Limited on October 30, 2017.

## 2. QUESTIONS

***Question 1:***

***a. Does the Agency agree that it is sufficient to cite Thalomid® and Velcade® as LDs in the NDA to support the proposed indication?***

***b. Does the Agency agree that reliance on FDA's finding of safety and effectiveness for Thalomid® (NDA 020785), and for Velcade® (NDA 021602), and on published literature is sufficient to support the proposed indication?***

**FDA Response to Question 1:**

a. The Agency typically does not advise a Sponsor on the selection of a particular listed drug that may be relied upon to support approval of a proposed product. However, your proposal to rely on Thalomid and Velcade appears acceptable for the following indication: Dexamethasone 20 mg tablet (b) (4) .

Of note, we acknowledge that you intend to also rely upon Decadron, NDA 011664, which also appears to be acceptable.

b. No, the reliance on Thalomid and Velcade would not support a broad indication of dexamethasone in combination with anti-myeloma drugs.

**Discussion 1a:** The sponsor accepted FDA's response, no discussion occurred.

**Discussion 1b:** At this time, the Agency cannot provide specific advice on data that would be required to support a broad indication for MM. The Agency discussed clinical and regulatory considerations that would have to be addressed in order to grant a broad MM indication. The Agency would be open to have future discussions regarding modifications to the indication.

***Question 2: Does the Agency agree that reliance on FDA's findings of safety and effectiveness for the proposed LDs (Thalomid® and Velcade®) and data from published literature are sufficient to support the proposed alternative indication and dosing regimen?***

**FDA Response to Question 2:**

Your approach appears acceptable to support the proposed alternative indication. Please also refer to the response to question 1a.

**Discussion:** The sponsor accepted FDA's response, no discussion occurred.

***Question 3: Does the Agency agree that a scientific bridge to Decadron has been established and no additional studies beyond the BA/BE study will be required?***

**FDA Response to Question 3:**
We do not have enough information on bridging the proposed Dexamethasone 20 mg tablets to Decadron. As per the Orange Book, ANDA 084612 (West-Ward's Dexamethasone, 4 mg tablet) was approved prior to Jan 1, 1982 and has a Therapeutic Equivalence (TE) code of "BP". Therefore, ANDA 084612 and Decadron (NDA 011664) may have had bioequivalence problems. The demonstration of bioequivalence of the proposed drug product to the generic listed drug product (ANDA 084612) does not therefore assure adequate bridging of your proposed drug product to Decadron tablets.

To establish a scientific bridge between your proposed Dexamethasone 20 mg tablets and Decadron, select a listed drug product (TE code: AB), which was previously demonstrated to be bioequivalent to Decadron.

**Discussion:** We agree with the Sponsor's proposal to bridge using the 4 mg dexamethasone for ANDA 084612 provided the history confirms that ANDA 084612 was bioequivalent to the listed drug, Decadron.

**Post-Meeting Addendum (November 13, 2017):** The Agency confirms that ANDA 084612 was bioequivalent to Decadron.

***Question 4: Does the Agency concur that the data on the linearity of dexamethasone PK from published literature are sufficient, and that further testing for linear PK is not required?***

**FDA Response to Question 4:**
In principle, yes, but we cannot answer definitively until the bridging issue (Question 3) is resolved.

**Discussion:** Refer to discussion for Question 3.

***Question 5: Does the Agency agree that the proposed sources as well as the proposed targeted time windows are sufficient to support the safety portion of the NDA?***

**FDA Response to Question 5:**
Your approach for the ISS (integrated summary of safety) generally appears acceptable. Your literature and database sources should be limited to single-agent dexamethasone for the treatment of myeloma (b) (4) (b) (4). Safety information of dexamethasone in combination with other anti-myeloma agents can be submitted as supportive safety information, but does not need to be integrated with the other safety analyses in the ISS. You should also include safety information for single-agent dexamethasone from the dexamethasone prescribing information.

**Discussion:** The sponsor accepted FDA's response, no additional discussion occurred.

***Question 6: Does the Agency agree that the proposed sources of information are appropriate and sufficient to support the efficacy portion of the NDA?***

**FDA Response to Question 6:**
Efficacy information in the Thalomid and Velcade labels and clinical trials conducted with these products in the published literature is sufficient to support the indication proposed in Question 2. Because you will not be relying on other anti-myeloma drugs RLDs, information from the published literature for dexamethasone in combination with other anti-myeloma agents need not be included in the ISE.

Information from in vitro studies for dexamethasone in the treatment of myeloma should not be included in the ISE. This information can be submitted in the non-clinical section.

**Discussion:** The sponsor accepted FDA's response, no additional discussion occurred.

***Question 7: The labeling of the proposed product will be based on Decadron, Thalomid®, Velcade®,literature, and DPT's own study (PK). The Sponsor has provided tables (see Section 10.5.1) outlined by label section which indicate the sources on which the Sponsor intends to rely and a list of proposed statements to be included. One table will be specific to the general indication (see Question 1), and the other table will be specific to the alternative indication (see Question 2).***

***a) Does the Agency agree with the proposed sources of information for use in the proposed Prescribing Information?***

***b) Does the Agency agree with the proposed statements to be included in the proposed Prescribing Information?***

**FDA Response to Question 7:**

a. The proposed sources of information appear appropriate.

b. No. We have the following suggestions:

In Section 3, we refer you to the *"Guidance for Industry: Tablet Scoring"* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269921.pdf to determine whether you may include the term "functionally scored" in the tablet description throughout labeling.

In Section 4, per this *"Guidance for Industry,"* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf; only known hazards and not theoretical possibilities should be listed. Conduct a literature review to determine whether any actual hypersensitivity reactions have occurred and describe the type and nature of reactions here. Word Contraindications in

precise language (e.g., "DRUG-X is contraindicated in patients with a history of a hypersensitivity reaction to [active ingredient]. Reactions have included anaphylaxis *[see Adverse Reactions (6.1)]*."

In Section 5, the subsection headings should briefly describe the risk; i.e., instead of "vision", use "Visual Disturbances". Draft the warning and precaution to include a succinct description of the adverse reaction (AR) and outcome; numerical estimate or AR rate; known risk factors for the AR; and steps to take to prevent, mitigate, monitor for or manage the AR. Avoid ambiguous and uninformative statements such as "Use with caution" or "monitor more frequently." Instead, where possible, provide specific treatment or management strategies.

In subsections 8.1 and 8.2, your prescribing information (PI) must comply with the Pregnancy and Lactation Labeling Rule (PLLR) content and format requirements [see *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014), codified at 21 CFR 201.56 and 201.57(c)(9)]. The submission should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, which should be located in Module 1. Refer to the *draft "guidance for industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format"* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

In subsection 8.4, Per 21 CFR 201.57(c)(9)(iv)(F) for products that do not have a pediatric indication, this verbatim statement should be included; "Safety and effectiveness have not been established in pediatric patients."

In subsection 8.5: No. Your labeling must be in compliance with 21CFR 201.57, which states that, specific statements on geriatric use of the drug for an indication approved for adults generally, as distinguished from a specific geriatric indication, must be contained in the "Geriatric use" subsection and must reflect all information available to the sponsor that is relevant to the appropriate use of the drug in elderly patients. This information includes detailed results from controlled studies that are available to the sponsor and pertinent information from well-documented studies obtained from a literature search. Controlled studies include those that are part of the marketing application and other relevant studies available to the sponsor that have not been previously submitted in the investigational new drug application, new drug application, biologics license application, or a supplement or amendment to one of these applications (e.g., postmarketing studies or adverse drug reaction reports). The "Geriatric use" subsection must contain the following statement(s) or reasonable alternative, as applicable, taking into account available information.

We have the following recommendations:

- If clinical studies (either in or not in NDA/BLA) included enough elderly subjects to make it likely that differences in safety or effectiveness between elderly and younger subjects would have been detected, but no such differences (in safety or effectiveness) were observed, and other reported clinical experience

has not identified such differences, the "Geriatric use" subsection must contain the following statement: “Of the total number of subjects in clinical studies of (name of drug ), __ percent were 65 and over, while __ percent were 75 and over. (Alternatively, the labeling may state the total number of subjects included in the studies who were 65 and over and 75 and over.) No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.”

- If evidence from clinical studies and other reported clinical experience available to the sponsor indicates that use of the drug in elderly patients is associated with differences in safety or effectiveness, or requires specific monitoring or dosage adjustment, the "Geriatric use" subsection must contain a brief description of observed differences or specific monitoring or dosage requirements and, as appropriate, must refer to more detailed discussions in the "Contraindications," "Warnings and Precautions," "Dosage and Administration," or other sections.

In Section 17, Patient Counseling Section of Labeling Guidance (http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm368602.pdf). This guidance recommends “the use of subheadings to organize and differentiate topics within the PATIENT COUNSELING INFORMATION section is recommended because they allow the reader to quickly identify the major concepts. Subheading titles should clearly identify the focus of each discussion (e.g., Acute Hepatic Failure rather than simply Hepatic), and a consistent formatting of the subheading titles (e.g., underlining or italicizing) is recommended.” Numbering is NOT recommended for these subheadings. A cross-reference should be inserted to direct the health care provider to the more detailed discussion elsewhere in labeling.

Include information a healthcare provider should convey to a patient (or caregiver) during a counseling discussion. Refer to the Patient Counseling Section of Labeling Guidance (http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm368602.pdf). This guidance recommends “the use of subheadings to organize and differentiate topics within the PATIENT COUNSELING INFORMATION section is recommended because they allow the reader to quickly identify the major concepts. Subheading titles should clearly identify the focus of each discussion (e.g., Acute Hepatic Failure rather than simply Hepatic), and a consistent formatting of the subheading titles (e.g., underlining or italicizing) is recommended.” Numbering is NOT recommended for these subheadings. A cross-reference should be inserted to direct the health care provider to the more detailed discussion elsewhere in labeling.

This section is specific to your product; you need not refer to other product labeling here.

**Discussion 7a:** The sponsor accepted FDA’s response, no additional discussion occurred.

**Discussion 7b:** The Agency acknowledges that numerical estimates for adverse reaction rates are not available from Decadron Warning and Precautions. The Sponsor's plan to mirror the wording of Decadron W&P is acceptable provided that vague descriptors are avoided.

(b) (4)

## 3.0 OTHER IMPORTANT INFORMATION

**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 marketing applications for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines 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. 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 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 additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, "*Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans"* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

## PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – "*Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*" (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

## 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).

**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.

## 4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

## 5.0 ACTION ITEMS

No action items identified.

## 6.0 ATTACHMENTS AND HANDOUTS

The slide presentation (and handout) "Pre-NDA (Type B) Meeting, Dexamethasone 20 mg Tablets" presented by the Sponsor during the November 8, 2015 meeting are attached.

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

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/s/

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ROMEO A DE CLARO
11/13/2017