CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210089Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 132108

MEETING MINUTES

Mallinckrodt Nuclear Medicine LLC
Attention: Bridget Martin
Sr. Regulatory Affairs Specialist
2703 Wagner Place
Maryland Heights, MO 63043

Dear Ms. Martin:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Kit for the Preparation of Technetium Tc 99m Albumin Aggregated Injection.

We also refer to the meeting between representatives of your firm and the FDA on May 3, 2017. The purpose of the meeting was to discuss the reintroduction of a Kit for the Preparation of Tc 99m Aggregated Albumin into the US marketplace.

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 me at (301) 796-3908.

Sincerely,

{See appended electronic signature page}

Alberta Davis-Warren
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	May 3, 2017, 4:00 pm – 5:00 pm
Meeting Location:	White Oak 22, Conference room 1419
Application Number:	PIND 132108
Product Name:	Kit for the Preparation of Technetium Tc 99m Albumin Aggregated Injection
Indication:	Technetium Tc 99m Albumin Aggregated Injection is a lung imaging agent which may be used as an adjunct in the evaluation of pulmonary perfusion in adults and pediatric patients. Technetium Tc 99m Albumin Aggregated Injection may be used in adults as an imaging agent to aid in the evaluation of peritoneovenous (b) (4) shunt patency.
Sponsor/Applicant Name:	Mallinckrodt Nuclear Medicine LLC
Meeting Chair:	Libero Marzella, MD, PhD
Meeting Recorder:	Alberta Davis-Warren

FDA ATTENDEES

Libero Marzella, MD, PhD, Director, DMIP
Alex Gorovets, MD, Deputy Director, DMIP
Ira Krefting, MD, Medical Team Leader, DMIP
Qi Feng, MD, Medical Officer, DMIP
Jonathan Cohen, PhD, Pharmacologist, DMIP
Eric Duffy, PhD, Director, DNDPII, OPQ
Danae Christodoulou, PhD, Branch Chief, DNDPII, OPQ
Eldon Leutzinger, PhD, CMC Team Leader, DNDPII, OPQ
John Amartey, PhD, CMC Reviewer, DNDPII, OPQ
Stephen Langille, PhD, Acting Branch Chief, DMA, OPQ
Tien Mien Chen, PhD, Acting Biopharm. Lead, DB, ONDP, OPQ
Kelly Kitchens, PhD, Biopharm Reviewer, DB, ONDP, OPQ
Jagjit Grewal, MPH, ADRA, ODEIV

Jian Wian, PhD, Associate Director Regulatory Science, ODEIV
Hina Mehta, PharmD, DMEPA Team Leader, OSE
Idalia Rychlik, PharmD, DMEPA Reviewer, OSE
Janice Weiner, JD, MPH, Senior Regulatory Counsel, ORP
Anuj Shah, JD, Regulatory Counsel, ORP
Hari Cheryl Sachs, MD, Clinical Team Leader, DPMH
Timothy Jetton R.Ph., User Fee Staff, DUFMBF, OM
Alberta Davis-Warren, Regulatory Project Manager, DMIP

SPONSOR ATTENDEES
Ed Porter, Director Regulatory Affairs
Bridget Martin, Senior Regulatory Affairs Specialist
Katie Merkel, Senior Regulatory Affairs Product Specialist
Mark Puett VP Research and Development
(b) (4)

1.0 BACKGROUND

On March 10, 2017, Mallinckrodt Nuclear Medicine LLC submitted a meeting request to the Division of Medical Imaging Products. The purpose of the meeting is to discuss the reintroduction of a Kit for the Preparation of Tc 99m Aggregated albumin into the US marketplace. Prior to 2009, Mallinckrodt marketed the product under NDA 017842 Technescan MAA (Kit for the preparation of Technetium Tc99m albumin aggregated). On July 24, 2008, Mallinckrodt submitted a request to withdraw approval of NDA 017842 TechneScan MAA. Mallinckrodt requested withdrawal of approval of the application because they stopped marketing product under the NDA. FDA published a notice in the Federal Register on May 19, 2009, withdrawing approval of the application, effective June 18, 2009.

FDA sent Preliminary Comments to Mallinckrodt Nuclear Medicine LLC on May 1, 2017.

FDA Introductory Comments:
Your proposed kit for the preparation of Technetium Tc99m Albumin Aggregated Injection, composed of aggregated human albumin labeled with the ^{99m}Tc radioisotope, is a biological product. Furthermore, such a product meets the definition of a diagnostic radiopharmaceutical as described at 21 CFR 601.31 and is subject to licensing under a BLA pursuant to 21 CFR 601.30. However, section 7002(e)(2) of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) permits an application for a biological product to be submitted under section 505 of the FD&C Act not later than March 23, 2020, if the biological product is in a product class for which a biological product in such product class was approved under section 505 of the FD&C Act not later than March 23, 2010 (see FDA's draft guidance on *Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009* (March 2016) (Transition Draft Guidance)). FDA has interpreted the statutory term "product class" for purposes of determining whether an application for a biological product may be submitted under

section 505 of the FD&C Act during the transition period (see Q&A II.2 in FDA's guidance on *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* (April 2015)). Based on the information provided in your meeting package, you may be able to submit a marketing application under section 505 of the FD&C Act before March 23, 2020, pursuant to the "transition" provision described in section 7002(e)(2) of the BPCI Act. As explained in the Transition Draft Guidance, FDA currently interprets section 7002(e)(4) of the BPCI Act to mean that FDA will not approve any application under section 505 of the FD&C Act for a biological product subject to the transition provision that is pending or tentatively approved on March 23, 2020 (see section 7002(e)(4) of the BPCI Act and FDA's Transition Draft Guidance).

Also, you propose to "reactivate" the previously withdrawn NDA 017842 or submit a new 505(b)(2) NDA to reintroduce the product to market. Based on the information you have provided, FDA does not agree with your proposal to "reactivate" the previously withdrawn NDA 017842 through submission of a supplemental NDA. However, you may submit a new NDA for review (see 21 CFR 314.160 ("FDA may, on the basis of new data, approve an application or abbreviated application which it had previously refused, suspended, or withdrawn approval")) pursuant to the "transition" provision described above. As explained in the Transition Draft Guidance, you should evaluate whether your planned submission under section 505 of the FD&C Act would allow adequate time for approval of the NDA before March 23, 2020.

You indicate that your planned application will cross-reference the withdrawn NDA 017842 and rely upon FDA's finding of safety and effectiveness for DraxImage MAA (NDA 017881) and published literature. Therefore, your new NDA would need to be submitted through the 505(b)(2) regulatory pathway. Please refer to section 6.0 below for additional information on the 505(b)(2) regulatory pathway. Among other things, you must provide data or information to establish that reliance upon FDA's finding of safety and/or effectiveness for the listed drug and the published literature is scientifically justified. Note that if the published literature on which you propose to rely describes a listed drug, FDA considers this to be reliance on the Agency's finding of safety and/or effectiveness for that listed drug, and you must comply with the applicable statutory and regulatory requirements for a 505(b)(2) application for each listed drug relied upon.

Sponsor's response to FDA introductory comments regarding the regulatory pathway 505(b)(2) and reactivation of Withdrawn NDA:

Mallinckrodt Nuclear Medicine LLC/Curium Response to Regulatory Pathway 505(b)(2) introductory comments:

The Agency has provided information on comparative data and bridging. Curium's submission strategy is to cross-reference our original NDA 017842 and the listed DraxImage product in

order that FDA may rely on both the listed product and our original product for findings of safety and effectiveness. Because this product is an injectable we propose that a chemical quality comparison of:

Saclay EU MAA (marketed in EU)

Saclay pilot MAA (manufactured with US sourced HSA)

DraxImage MAA

Technescan MAA (NDA 017842)

(b) (4)

If the reliance on the original NDA and reference to DraxImage and the comparison of chemical testing support quality and consistency of the proposed product, we plan no PK or PD comparison to DraxImage MAA. Does the FDA find this supportive data package adequate?

Meeting Discussion: FDA replied that the sponsor is not expected to conduct PK studies if an adequate biowaiver request and justification is provided. The biowaiver request justification should include any differences between the proposed drug product and the listed drug (DraxImage MAA) relied upon. The sponsor asked if they can submit the biowaiver request under the IND. FDA noted that the biowaiver request should be submitted with the planned NDA. However, the sponsor may submit their biowaiver request with the PIND for informal FDA review and comments; formal concurrence will not be provided on the PIND submission. FDA also noted that all review disciplines will review the biowaiver request in the planned NDA.

Mallinkcrodt Nuclear Medicine LLC/Curium Response to Reactivation of Withdrawn NDA introductory comments:

Curium has reviewed the FDA position and requests further discussion in order to understand why NDA 017842 cannot be reactivated. NDA 017842 was originally submitted in 1973 to the Bureau of Biologics and approved as a biologic product in June 1974. In July 1975, FDA Commissioner published a regulation in the Federal Register ruling that all radioactive biological products would be regulated as drugs. Does this past biologic drug history create an opportunity to restore the previous biological approval?

Meeting Discussion: The sponsor requested further clarification on why the withdrawn NDA cannot be reactivated. FDA explained that there are differences with regards to the proposed product formulation and the manufacturing process, and there is limited characterization of the active ingredient, which is complex. Accordingly, FDA does not agree with the sponsor's proposal to "reactivate" the previously withdrawn NDA 017842

through submission of a supplemental NDA. As previously noted, the sponsor may submit a new application for review. With respect to the "past biologic drug history" described by the sponsor, FDA advised that this information does not affect the Agency's position on the sponsor's proposal to reactivate the previously withdrawn NDA.

2. DISCUSSION

Prior to the meeting, the sponsor provided slides containing their responses to FDA's preliminary comments which assisted in the meeting discussion. The comments from the slides are included in the meeting minutes.

We have reviewed the Meeting Package submitted on March 31, 2017, and provide the following responses to your questions. Your questions are in italic and our responses are in bold font.

CMC:

1. *Does the Agency agree that if the proposed finished product is tested as listed Tables 1 and 2 above and substantive process validation and stability test data are provided in the application, the FDA would view it reasonable to support an application for Tc-99m MAA kits?*

   FDA Response:
   The acceptance criteria for the TechneScan MAA vials and the reconstituted Tc-99m MAA Injection presented in the tables of the meeting package appear reasonable at this time. However, final decision on acceptance limits will be based on review of the data presented in your application.

   The proposed finished product specifications appear acceptable from the standpoint of product quality microbiology at this time. (b) (4) [redacted]

   Mallinckrodt Nuclear Medicine LLC/Curium Response:

   Curium has reviewed the proposed label storage against the planned testing that will be conducted as part of the technical transfer/process validation. (b) (4) [redacted]

   Curium will add the FDA proposed storage statement based on the studies described in the meeting package.

   Meeting Discussion: The sponsor would like to pursue (b) (4) [redacted] **FDA stated that** (b) (4) **may be acceptable if adequate information is provided** (b) (4) [redacted]

(b) (4)

2. *Does the Agency agree providing quality control and stability data for EU MAA Kit manufactured with EU sourced HSA in a direct side-by-side comparison with MAA kits* (b) (4) *provides sufficient evidence to support the chemistry, manufacturing and controls section of the planned application. Mallinckrodt proposes to include 6 months accelerated and 6 months real time data in the initial submission, and to update the submission with 12 month real time stability data as soon as the 12 month data is collected. Does the FDA consider this side-by-side quality and stability comparison plan acceptable?*

FDA Response:
Yes, the proposed approach seems reasonable at this time. Nonetheless, a final decision will be based on review of the data presented in your application.

In addition, please provide a side-by-side comparison table between the proposed and approved drug products with justification and supporting data demonstrating that any differences in:

1. **The active and inactive ingredients do not contribute to differences in the in vivo pharmacokinetic (PK) performance; and**
2. **The physicochemical characteristics including, but not limited to, the pH solubility profile, osmolality/tonicity, pH, viscosity, and other relevant physicochemical properties would not alter the safety and/or efficacy of the proposed drug product.**

Mallinckrodt Nuclear Medicine LLC/Curium Response:

Curium current direction is to transfer the (b) (4) *manufacturing process to Maryland Heights (MH), US. We plan to make 3 pilot batches in* (b) (4) *using US sourced HSA. We will complete a technical transfer and process validation at MH.*

Curium is planning on doing full scale pilot batches at (b) (4)*. Curium proposes to submit* (b) (4) *pilot stability data, of at least 6 months, technical transfer data, T=0 release data and validation summary from MH, and update the application with 6 months MH process validation lots/stability data. The commercial manufacturer being proposed is MH.*

Curium proposes that a chemical quality comparison of:

- *Saclay EU MAA (marketed in EU)*
- *Saclay pilot MAA (manufactured with US sourced HSA)*
- *DraxImage MAA*
- *Technescan MAA (NDA 017842)*

(b) (4)

Does the FDA agree with the concept that the submission would be accepted for filing with Saclay stability and initial MH data which would be updated during review?

Meeting Discussion: FDA stated that the MH release data and summary validation are crucial and FDA prefers 12 month stability data at the time of submission on the pilot scale batches. FDA acknowledges submitting with 6 months of stability data on pilot batches from Saclay and release data from process validation lots manufactured at Maryland Heights is acceptable for filing. FDA also noted that the sponsor would need to provide adequate scientific justification to support the relevance of the Saclay European data to support approval of the proposed product in the planned marketing application.

Addendum: Subsequent to Agency's minutes, sponsor submitted an email communication dated June 20, 2017 on the Agency's version of the minutes and requested FDA amend minutes to include an additional statement that the 6 months of stability data and release data from process validation lots manufactured at Maryland Heights is acceptable for filing. Agency agreed, sentence has been added.

Nonclinical:

3. *Considering that various MAA kits have been in routine clinical use on a worldwide basis since the 1970's, and have a well established record of safety and efficacy, does the FDA consider this to be a reasonable approach to support the nonclinical section of the NDA?*

FDA Response:
Yes. We agree that your proposal to cross-reference the animal studies originally conducted to support the approval of TechneScan MAA (NDA 017842) and rely upon FDA's finding of safety and effectiveness for DraxImage MAA (NDA 017881), is a reasonable approach to support the nonclinical section of your planned 505(b)(2) NDA. However, we cannot say definitively that no additional nonclinical studies are needed until the NDA has been submitted and reviewed with respect to product quality and consistency.

Mallinckrodt Nuclear Medicine LLC/Curium Response to question 3 and 4:

Curium will cross-reference our original NDA, as well as reference the listed product DraxImage MAA, in order that FDA may rely on both the listed product and our original product for a finding of safety and effectiveness. Further, we will summarize the data provided and provide clean copies of the referenced data from Mallinckrodt's previous NDA (Technescan MAA) to facilitate your review.

Meeting Discussion: FDA stated that the sponsor's proposal is acceptable with respect to its proposed 505(b)(2) application.

Clinical:

4. *Does FDA agree in concept that the strategy listed above would be acceptable to support the clinical efficacy and safety of this proposed application to support reintroduction of Technescan MAA?*

FDA Response:
We agree with respect to your proposed 505(b)(2) application. Please also refer to FDA's Introductory Comment.

Meeting Discussion: See the response to question 3.

5. *Does the FDA agree that in concept the review of marketed product safety information and benefit risk assessment is adequate to support NDA safety requirements?*

FDA Response:
Yes, we agree.

Meeting Discussion: No discussion occurred.

Prescribing Information:

6. *Does the FDA agree with Mallinckrodt's strategy to propose the current approved MAA indication?*

   FDA Response:
   Yes, we agree with this approach based on your proposal to submit a 505(b)(2) application that relies, in part, on FDA's finding of safety and/or effectiveness for DraxImage MAA (NDA 017881).

   Meeting Discussion: No discussion occurred.

7. *Does the FDA agree with this approach for Adult and Pediatric dosing?*

   FDA Response:
   Yes, we agree with the approach based on your proposal to submit a 505(b)(2) application that relies, in part, on FDA's finding of safety and/or effectiveness for DraxImage MAA (NDA 017881).

Additional Labeling Comments:
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). Please refer to section 4.0 PRESCRIBING INFORMATION below.

In addition, we request that you submit a clean version and an annotated version of your proposed PI in Microsoft Word format. The annotated PI should identify your proposed changes to the last FDA-approved PI labeling for NDA 017842 Technescan MAA and indicate the source(s) of information relied upon to support the changes.

Meeting Discussion: No discussion occurred.

Proprietary Name:

8. *Does the Agency agree that* [redacted] (b) (4) *is an acceptable proprietary name for use for the reintroduced product?*

   FDA Response:
   The acceptability of the proposed proprietary name will be a review issue. We recommend you submit a request for a proprietary name review. You may also

submit your request for proprietary name review under the IND. If you require information on submitting a request for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)

Mallinckrodt Nuclear Medicine LLC/ Curium Response:

The name proposed (b) (4) *Curium does not consider this product to require a full proprietary name review* (b) (4) *In this case, would all components of a names review be required? For this situation, are there components that should be focused on more than others?*

Meeting Discussion: FDA stated a full review is required for all proprietary names; please refer to the Guidance for details. FDA acknowledges the history of the proprietary name and the sponsor can include the history of the name in their submission. FDA also mentioned the proprietary name can be reviewed under the IND.

User Fee:

9. *Does the Agency agree that an application fee would not be incurred for a CMC supplement submitted to a reactivated NDA and that a ½ user fee would be applicable if a new 505(b)(2) application is submitted taking into account that there will not be any new or incremental clinical study data or reports?*

FDA Response:
We do not agree that a CMC supplement may be submitted to reactivate the application (see the FDA Introductory Comments). However, you may submit a 505(b)(2) application that includes no new clinical data and pay half an application fee. Please note that the final determination regarding user fees will be made when the application is submitted in its entirety to the Agency.

Meeting Discussion: No discussion occurred.

Mallinckrodt Nuclear Medicine LLC/Curium BLA question provided on May 3, 2017:

Curium will move towards a 505(b)(2) submission 12-15 months prior to March 23, 2020. In consideration of associated regulations, we find submission content requirements similar for drugs and biologics respectively. Should the project timeline shift and a biologic application be necessary, would the FDA comment on the application of the current strategy related to safety, efficacy and quality?

Meeting Discussion: FDA recommended the sponsor review FDA's Transition Draft Guidance (referenced in the FDA Introductory Comments) for additional information, and evaluate whether their planned submission of a 505(b)(2) application would allow adequate time for approval before March 23, 2020. FDA noted that if a sponsor is unsure whether its proposed product may receive approval under the FD&C Act by March 23, 2020, the sponsor should consider submitting a biologics license application (BLA) under the Public Health Service Act (PHS Act) instead. FDA explained that there isn't an approval pathway under the PHS Act that precisely corresponds to section 505(b)(2) of the FD&C Act, and noted that the draft guidance provides recommendations to sponsors. The sponsor inquired if the product would be considered a biosimilar and asked for FDA's input on whether they should pursue that pathway. FDA suggested that the sponsor refer to the Transition Draft Guidance for considerations related to modifying a development program to support submission of a 351(a) BLA. With regard to the 351(k) pathway for a proposed biosimilar --which requires, among other things, a demonstration that the proposed product is "highly similar" to a reference product --. FDA explained that biosimilars fall under the BsUFA program, which provides for a separate process to request meetings and solicit advice from FDA. The sponsor should consider FDA's comments on their planned development program and challenges in characterization of the product in determining their path forward.

3.0 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.

4.0 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.

5.0 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.				

6.0 505(b)(2) REGULATORY PATHWAY

At this time[1], the 505(b)(2) approval pathway may be used for a proposed Technetium Tc99m Albumin Aggregated Injection product that is demonstrated to be sufficiently similar to a listed drug to permit reliance, where scientifically justified, on FDA's finding of safety and/or effectiveness for the listed drug to support approval of an NDA. A demonstration of similarity to the listed drug may include, for example, comparative physico-chemical tests and bioassay, nonclinical data (which may include bridging toxicology studies), pharmacokinetic (PK)/pharmacodynamic (PD) data, and clinical data (which may include an assessment of immunogenicity).

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, in part, on FDA's finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed

[1] See draft guidance for industry on *Implementation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM490264.pdf.

drug product that represent modifications to the listed drug. You should establish a "bridge" 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, in part, 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 (e.g., by trade name(s)) in the published literature.

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug or published literature describing a listed drug (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. 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.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug or on published literature. In your proposed 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.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing 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.	

7.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion

8.0 ACTION ITEMS

FDA would provide additional comments regarding product holding times

9.0 ATTACHMENTS AND HANDOUTS

Sponsor slide presentations

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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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.

/s/

ALBERTA E DAVIS WARREN
07/11/2017