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Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers: Guidance for Industry (Docket FDA-2017-D-6821)

Dear Madam or Sir:

PDA appreciates the opportunity to comment on the Guidance for Industry on Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers.

PDA fully understands and supports FDA in its goal of ensuring the integrity of the data provided in support of products for approval. PDA encourages its members to work diligently to confirm and certify that all data used in support of product submissions are complete, truthful, and accurate. However, in our specific comments presented in the attached table, PDA encourages practical reconsideration of some of the requests that this information be provided as outlined. Certainly, additional information may be available to the Agency in different areas of the submission, or in the quality and developmental files of the sponsor. Sponsors should be able to quickly provide such information upon request. A major concern is that although this is a guidance, failure to provide the information in the exact manner specified will result in a refusal to file or a complete response.

In addition, while PDA appreciates FDA's attempt to clarify its expectations for both Form 356h and Module 3, PDA suggests in the attached comment table that FDA revise the guidance to limit the applicability of some of the language. For instance, we suggest that FDA revise the recommendation that the listing of "manufacturing establishments" include "research and development manufacturing and testing sites that generated data in support of the application" and sites that "developed analytical test methods."

We support FDA in developing a guidance that will help the Agency ensure the integrity of data provided in submissions without resulting in undue burden on and/or confusion for industry. We share this goal. In light of the significant changes that we and other commenters have identified as necessary, however, PDA suggests that FDA withdraw the guidance while revising it. Leaving the guidance in its "final" status while revising it will unnecessarily tax the resources of both the agency and the manufacturers, all of whom already are stretching to respond to coronavirus. As applicants review the under-revision guidance, they surely will have some of the same questions we pose in our comments. Reverting to the prior situation will avoid unnecessary confusion, agency follow-up, and application delays.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments have been prepared by PDA members with expertise in pharmaceutical, biopharmaceutical, and combination products manufacturing on behalf of PDA's Regulatory Affairs and Quality Advisory Board and Board of Directors.

If you have any questions, please do not hesitate to contact me via email at johnson@pda.org.

Sincerely,

Richard Johnson
President and CEO

cc: Glenn Wright, PDA; Ruth Miller, PDA

U.S. Food and Drug Administration
Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER – Questions and Answers
Guidance for Industry Revision 1
Oct. 2019

General Comments
While FDA states that this guidance is "intended to clarify Agency expectations," PDA believes that this guidance expands the scope of information to be submitted in applications beyond any current or historical expectations stated by the Agency or implemented in practice. While the current regulations require the submission of "the name and address of each manufacturer of the drug product; a description of the manufacturing and packaging procedures and in-process controls for the drug product," and similar for the drug substance, this guidance now "recommends" also the inclusion of facilities that generated historical data. Because this guidance expands well beyond the language of 21 CFR §§ 314.50 and 601.2 and FDA's past interpretations of those regulations, FDA is obligated to revise those regulations before implementing this guidance. Alternatively, if FDA previously has stated these broadened expectations *for regulatory filings*, PDA strongly suggests referencing such prior statements. Specifically, this guidance identifies two types of "manufacturing" establishments. The first, those "proposed to be involved in the disposition of commercial products" must be listed on Form 356h. PDA generally agrees that these establishments meet the current regulatory definition. The second type, "research and development manufacturing and testing sites that generated data in support of the application," FDA now specifies should be listed in Module 3. This is an unacceptable expansion of the existing understanding of "manufacturing establishments" in the application context. "Research and development manufacturing and testing sites that generated data in support of the application" have not been considered "manufacturing facilities" in the application context. The activities performed by these companies occur only during development and are not repeated as part of the manufacturing process. Therefore their identification in Module 3 has not been, and should not be, required. Another example of such expansion beyond the current regulatory language is the expectation expressed in Question 4 on page 7 that Module 3 identify the sites that developed analytical test methods. The inclusion of all of the facility and establishment information recommended in this Guidance would dramatically increase the post-approval burden for both sponsors and FDA. In alignment with FDA paperwork reduction initiatives and risk-based approaches, FDA could obtain some of the information it seeks via information requests. In that scenario, sponsors could provide information in Module 1 or during inspections, instead of adding it to FDA Form 356h or Module 3.
FDA must clarify the status of this non-binding guidance for applicants. If an applicant does not include all facilities that generated historical data, will the agency refuse to file (RTF) the application, or issue a Complete Response Letter (CRL)?
PDA suggests that FDA clarify how applicants should use Form 356h to meet the expectations expressed in the guidance. The guidance and the current version of Form 356h, including its instructions, are not consistent. For instance, Question 1, Bullet 3 on page 3 of this guidance outlines

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detailed and specific requirements for inclusion of facility information related to combination products. The instructions for Form 356h, however, do not include any specific direction for combination products establishment information for Field 28.
If it is FDA's intention or goal to harmonize expectations for all submissions, regardless of type, with the June 2019 "ANDA Submissions – Content and Format; Guidance for Industry" (ANDA Guidance), it would be helpful if FDA stated as much. Some of the expectations described in the current document appear to be aligned with the ANDA guidance. Specifically, on page 16 of the ANDA Guidance, FDA outlines the information for each drug substance manufacturer that should be documented in Section 3.2.S.2.1 of the ANDA. On page 21 of the ANDA Guidance, FDA outlines the information about the drug product manufacturer(s) that should be documented in Section 3.2.P.3.1 of the ANDA. The current guidance appears to request the same types of manufacturer information (e.g., FEI numbers, contact information, etc.) in all submissions.

Specific Comments to the Text

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Pg. 1	This guidance applies to all manufacturing locations, including facilities that perform functions under contract.	Please specify what FDA intends by "all manufacturing locations." Applicability of this Guidance to all contract manufacturers (drug substance manufacturing or drug product fill/ finish or packaging) is understandable; however, if the use of the term "manufacturing" by FDA is intended to be broader (i.e., inclusive of all contract testing facilities, such as subcontracted testing sites) then the post-approval burden for maintenance of this information by sponsors will increase significantly, with limited return. Consider using a risk-based approach and limiting the term "manufacturing" to activities involved in routine commercial manufacturing.
Pg. 2, Form FDA 356h Questions/ Answers, Q. 1, second bullet	This includes sterilization and micronization sites.	Please clarify the statement relating to sterilization and micronization sites to be more specific, e.g., "This includes intermediate and final drug substance sterilization and micronization sites." Otherwise, it could be interpreted as requiring listing of sterilization sites for components or other intermediates.
Pg. 3, Form FDA 356h Questions/ Answers, Q. 1, third bullet	For combination products, facilities manufacturing a constituent part of a co-package or single entity combination product, or drug-device combination product that are proposed to be	PDA asks FDA to revise the language stating that facilities involved in design control activities for a device constituent part should be identified in Form 356h. Such facilities should not be included in this Form because they are not involved with commercial product disposition and are not part of the control strategy for the final combination product.

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	involved in the disposition of commercial product. This includes . . . facilities that conduct design control activities, including verification and validation, of a device constituent part.	The language in red is inconsistent with FDA's expectations for Form 356h for other products. In general, Form 356h is to include information about facilities "proposed to be involved in the disposition of commercial products." For combination products, however, FDA is requesting information that does not relate to commercial product disposition. PDA does not object to the statement that "facilities manufacturing a constituent part of a co-package or single entity combination product, or drug-device combination product that are *proposed to be involved in the disposition of commercial product*" should be listed in Form 356h. This language on its own is consistent with the rest of the guidance. The language that follows, however, expands the expectation beyond facilities involved in commercial disposition to also include facilities that conduct design control activities, including verification and validation, of a device constituent part. While footnote 2 on page two argues that assays and resulting data that are used to make disposition decisions are part of the commercial process control strategy, device design control activities are in no way comparable. Design control is not a part of the control strategy for the final combination product. As 21 CFR 210.2(b) and 820.1(a)(1) describe, an entity that engages in only some operations subject to the regulations in parts 210, 211, 600 through 680, 820, and 1271, need only comply with the regulations applicable to those operations. Further, inclusion of other facilities, such as those performing device design control activities, including design verification or validation, is not aligned with the regulatory requirements for Class II and Class III medical devices. Under 21 CFR 814.20(b)(4)(v), only those facilities used for "manufacture, processing, packing, storage, and, where appropriate, installation of the device" must be listed. For example, a laboratory performing electrical safety design verification testing for medical devices is not required to be listed as part of a 510(k) or premarket approval application. (continued)

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		In response to question 5 on page 4, FDA repeats this expansion and expectation of the inclusion of facilities that conduct design control activities in accordance with 21 CFR 820.30 for the device constituent part. That text also should be revised.
Pg. 3, Form FDA 356h Questions/ Answers, Q. 1, fourth bullet	All facilities used for storing or warehousing drug substance, in-process material, and commercial drug product under quarantine prior to a disposition decision, including any facilities that solely store the stability samples.	Temporary storage of materials under quarantine prior to disposition decision is a business process and should be a GMP inspection item, rather than an item included in registration. Requiring applicants to include this information in FDA Form 356h may limit an entity's flexibility to segregate quarantine and non-quarantine material, which is standard GMP practice. During inspection, the applicant could demonstrate the storage conditions of the product at the storage facility or warehouse, including provision of applicable internal procedures and/or quality agreements.
Pg. 3, Form FDA 356h Questions/ Answers, Q. 2	Facilities that do not impact or inform the commercial control strategy do not need to be listed on Form FDA 356h.	Please define the facilities that, in FDA's view, inform the control strategy. At a minimum, clarification or inclusion of examples is needed so that applicants can implement this expectation.
Pg. 4, Form FDA 356h Questions/ Answers, Q. 6	Having an FEI number and DUNS number will facilitate the application process and establishment registration.	Please clearly state whether FDA expects inclusion of both FEI and DUNS numbers for all facilities listed on the FDA Form 356h. For facilities involved in manufacturing, labeling, and packaging, which undergo the most frequent inspections, DUNS and FEI numbers are expected. However, for facilities not involved in direct manufacture or testing (for example, storage sites), only a DUNS number may be available. In the preamble to the FDA final rule on Requirements for Foreign and Domestic Establishment Registration and Listing for Human Drugs, Including Drugs That Are Regulated Under a Biologics License Application, and Animal Drugs, FDA specified that that a storage facility is not required to be FDA registered establishments, provided that drugs are not manufactured, repacked, relabeled, or salvaged at that location. 81 Fed. Reg. 60170, 60184 (Aug. 31, 2016). Therefore, these locations may not have an FEI number.
Pg. 4, Form FDA 356h Questions/ Answers, Q. 6	FDA recommends that at the time of registration, the owner or operator obtain an FEI number. Although the	PDA asks FDA to clarify the impact to the review of including in the application a facility that does not have a FEI. With the expansion of the types of companies that FDA is requesting be identified in the submission, submissions may now include entities that are

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	absence of the FEI number may hinder the timeline for assessment of the establishment information contained within your application, you should not delay submitting your application due to the absence of an FEI number. Rather, you should request an FEI number as soon as possible.	not legally required to register (e.g., storage sites). Furthermore, third party establishments, especially those used historically, cannot retrospectively be required to obtain an FEI in order to submit supplements to applications.
Pg. 6, Module 3 Questions/ Answers, Q. 1	Module 3 should contain all facilities listed on Form FDA 356h, as well as research and development manufacturing and testing sites that generated data in support of the application.	Beyond our General Comments above, PDA suggests that FDA limit its expectations for this identification in two ways, considering the long development time of some drugs and the ongoing changes occurring in the marketplace. First, data that is used in support of the application may have been created years before an application is submitted. As a result, the research and development manufacturing or testing site that generated such data may have changed its name, merged or been bought or sold, changed its business, or no longer be operating at the time of submission. In these cases, the applicant may only have the original name and information, which can be submitted. The applicant should not be required to trace all the business changes which have occurred, nor required to submit current contact information. Second, PDA suggests that FDA clarify and limit the scope of this request by specifying the development sites that must be included. Finally, we suggest that FDA clarify the proper location for this information relating to research and development sites. These sites should not be included in 3.2.S.2.1 (Manufacturer) or 3.2.P.3.1 (Manufacturer), as they are not utilized in the manufacturing or control of the commercial product. If sites are used for manufacturing or testing at point-in-time (e.g., for "research and development," non-human use or pilot scale manufacture, or characterization testing), then it seems acceptable that some of these sites, at sponsor's discretion for direct applicability, would be specified in, for example,

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		manufacturing history sections or analytical comparability either in text or as footnotes to data tables.
Pg. 6, Module 3 Questions/ Answers, Q. 1	This includes facilities that manufactured or tested any lots of the product.	Please clarify that FDA will not consider the filing deficient if a contract manufacturing organization refuses to reveal complete information about testing labs that are managed solely by the contract manufacturing organization, especially if these details have been placed in a DMF for proprietary reasons or if the contract manufacturing organization had discontinued use of that lab or facility. Further, while we urge FDA to limit this requirement as discussed in the previous comment and the General Comments, PDA also asks FDA to clarify the scope and intent of the reference to "any" lot. "Any" is extremely broad, so additional clarity would aid companies in complying.
Pg. 6, Module 3 Questions/ Answers, Q. 1	For combination products only: • Provide a detailed list of all manufacturing facilities; what activities occur at the site (e.g., assembly filling, sterilization, testing, other); and what constituent parts are at the site (e.g., drug only, device only, both drug and device). For each facility that has at least two different constituent part manufacturing operations (e.g., drug and device) identify which CGMP operating system is established at the site per 21 CFR 4.4(a).	As written, this list appears to exceed the requirements of 21 CFR Part 4, as interpreted in FDA's "Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products" (2017) (Combination Product Guidance). This section should be revised to clarify that the list must include only facilities that manufacture a finished constituent part or a finished product (combination of constituent parts, e.g., a single entity or co-packaged finished product), and that the list need not include component suppliers and other non-GMP suppliers. The Combination Product Guidance clearly distinguishes between components and constituent parts. On page 13, that guidance specifies that "a facility that manufactures only device components, including device components used in a combination product, is not made subject to the device QS regulation by part 4." It goes on to state that a facility that manufactures a finished drug-device combination product formed from components is subject to 21 CFR Part 4. As such, component manufacturers should not be included in the Module 3 listing. (continued)

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		Likewise, FDA should clarify that facilities that are involved in the manufacture, assembly or sterilization of components, but that do not perform constituent part manufacturing operations, are excluded from this listing.
Pgs. 6 & 7, Module 3 Questions/ Answers, Q. 2 & Q. 3	Question 2: All manufacturing and control sites should be in either the drug substance (3.2.S.2.1) or drug product (3.2.P.3.1) sections of Module 3. Question 3: To facilitate FDA's assessment and inspection planning process, the Agency recommends that you clearly identify all facilities associated with your application in a table format at the beginning of the relevant section in Module 3.	In FDA's answer to Question 3, it is unclear whether the "relevant section" would be sections 3.2.S.2.1/3.2.P.3.1 or some other section. Please clarify.
Pg. 7, Module 3 Questions/ Answers, Q. 3	Additionally, FDA recommends that you provide the name and title of an onsite contact person, including their phone number, fax number, and email address.	Because FDA may ask for and obtain this contact information from the sponsor through informal means at any time, including before a planned on-site inspection, PDA suggests that FDA delete this sentence. Adding details such as onsite contact, phone number, etc. increases the burden of lifecycle management and reportability for Module 3. If FDA chooses to retain the sentence, PDA strongly suggests that FDA clarify that these contact details will not be considered Established Conditions and need not be updated after the Pre-Approval Inspection. If the name, phone number, and email address of each contact person at each listed facility were considered to be an Established Condition, the applicant's reporting burden and FDA's monitoring burden would rise exponentially.
Pg. 7, Module 3 Questions/ Answers, Q. 3	Each facility should be ready for an inspection at the time of submission.	PDA asks FDA to clarify that this statement applies only to those facilities identified in Form 356h as relevant to commercial disposition. It should not apply to historical sites that provided data that is incorporated in the submission but that have no role in the

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		commercial phase of manufacturing, or to R&D development sites that are listed in Module 3 but not Form 356h.
Pg. 8, Module 3 Questions/ Answers, Q. 4	Yes. The information for such firms should be provided in Module 3 of the application.	Please clarify the value that adding the analytic method developer facility information would have to the review of the application or the commercial control strategy. The acceptability of the analytical method is fully the responsibility of the sponsor, not the method developer.
Pg. 8, General Questions/ Answers, Q. 1	The facility information contained within a DMF properly incorporated by reference should be included on both Form FDA 356h and in Module 3 of the application, as appropriate. The recommended placement of the DMF facility information in the application follows the same logic as any other facility that is not part of a DMF.	PDA suggests that FDA revise this expectation to reflect the confidentiality practices of DMF holders. As FDA knows, the applicant generally is not the DMF holder. Historically, DMF holders have provided all required information to FDA directly, but have withheld certain commercial confidential information from their customers, the applicants that use their substances in manufacturing of drug products. If FDA now, through this guidance, is expressing its view that DMF holders must make all commercial confidential information available to their customers, PDA asks FDA to recognize that such a change will take a significant amount of time to implement and that applicants are unlikely to be able to provide all of the specific information that FDA seeks until DMF holders make that change.
Pg. 8-9, General Questions/ Answers, Q.1 and Q.2	If a DMF is referenced in my marketing application, should I list the facilities associated with the DMF in my NDA/ANDA application? Do I need to list research and development or testing site DMF facilities that generate release data or stability testing data to support my NDA or ANDA?	In the answers to these two questions, FDA provides recommendations relating to a referenced DMF. What recommendations would apply when other marketing authorizations (e.g., other NDAs) are cross-referenced in an application?
Pg. 9, General Questions/ Answers, Q. 2	Yes. If a facility referenced in a DMF is to be utilized for research and development or testing, this is	Please revise to indicate that facilities that were used as part of development should not be included in the application unless they will continue to be used to support commercial manufacturing or testing.

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	considered part of the commercial control strategy and should be included in your application.	