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Connecting People, Science and Regulation ®

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Division of Docket Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Reference: FDA Guidance for Industry Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products
Docket: [FDA-2015-D-1659]

Dear Sir/Madam,

PDA appreciates the FDA taking steps to define "established conditions" and clarify the post approval reporting expectations. At the same time, PDA encourages FDA to continue to work towards harmonized expectations for post approval changes globally with other Health authorities such as the existing and planned ICH framework, especially ICH Q12 for post approval changes, and current WHO guidelines including June 2015 revised WHO general guidance on variations to multisource pharmaceutical products. Such an approach could substantially reduce the regulatory burden for regulator and industry alike and encourage technological advances and continual improvement and avoid confusion among all stakeholders implementing these concepts.

PDA also encourages FDA to include additional information on identifying established conditions for integrated drug delivery combination product information submitted in BLAs and NDAs.

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 were prepared by a committee of experts with experience in pharmaceutical manufacturing including members representing our Board of Directors and our Regulatory Affairs and Quality Advisory Board.

If there are any questions, please do not hesitate to contact me.

Sincerely,

Richard Johnson
President, PDA

CC: Richard Levy, PDA; Denyse Baker, PDA

Food and Drug Administration Draft Guidance

Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products

Guidance for Industry

July 31st, 2015

General Comments

General Comments	Rationale
PDA welcomes FDA's steps to define "established conditions" and the clarification of post approval reporting expectations. PDA agrees with the stated rationale that clarification of what constitutes "established conditions" should reduce the number of regulatory submissions and clarify when a pre-approval submission is required. In addition to this guidance, PDA hopes that FDA will continue to actively work towards achieving harmonized, global requirements for post approval changes such as ICH, particularly Q12 for post approval changes and current final or draft WHO guidelines including June 2015 revised WHO general guidance on variations to multisource pharmaceutical products.	Differences in post approval change requirements in terms of reporting levels, documentation requirements and timing, encourages maintaining the status quo. This reduces the incentive to introduce desired technical innovations and improved process and product control systems. While many Health Authorities, including FDA, individually encourage innovation, collectively the above mentioned effect is still apparent. Harmonizing requirements should shorten timelines for approvals, enhance international collaboration, and overall require fewer resources spent by both industry and the Health Authorities for the same change. Because similar concepts are included in this draft and the ICH Q12 concept paper, PDA respectfully suggests the longer term goal to be a single guidance to avoid confusion among all stakeholders implementing these concepts.
This document does not address information provided in BLA or NDA submissions for integrated drug delivery combination products, nor does it exclude them. For example, there is no mention of whether or not design verification or design validation data submitted under a BLA or NDA for the device constituent part or combination product would meet the definition of established conditions.	PDA recommends FDA identify elements of established conditions for combination products information submitted in a BLA or NDA or alternately include a list of the combination product information included in a BLA or NDA that would not be considered an "established condition" and therefore managed within a firm's QSR framework and reviewed upon inspection such as Design History File or Management Controls. More specifically, we recommend that narratives describing combination product information to inform assessment of compliance with 21 CFR 820.30, 21 CFR 820.50 and 21 CFR 820.100 be limited to regional information captured in 3.2.R in the original application, and that this not be considered an established condition.
This guidance as written does not provide clarity on the definition of "established conditions" in special	PDA recommends that FDA clarify the guidance to allow flexibility in the pathway to finalize established conditions corresponding with alternative

General Comments	Rationale
circumstances like orphan products or accelerated review pathways. In some of these cases, standard batch information may not be available at time of submission and FDA has made allowances to accept additional batch information following approval. PDA recommends similar allowances for determination of the "established conditions" following approval.	submission approval pathways such as accelerated or breakthrough. For example, established conditions may be finalized through a post approval submission in the case that final specifications or batch records are not determined at time of initial NDA or BLA approval .
Several of the footnotes contain substantial information. For example, footnotes 12 and 13. PDA believes that these should be moved to the body of the document.	Footnotes are generally perceived as having less significance whereas here they seem to be fairly substantial. Therefore, for clarity they might be better placed in the body of the document.

Specific Comments to the Text

Line No.	Current Text	Proposed Change	Rationale
Lines 45 - 60	The regulations at 21 CFR 314.50(d)(1) and 314.54(a)(1) require… Similarly, under 21 CFR 601.2…	Add citation to regulations applying to combination products. For example: 21 CFR 820.30, 21 CFR 820.50 and 21 CFR 820.100. See related comments below for lines 186-190 and Table entries for 3.2.R.	PDA recommends that this opportunity be used to clarify submission expectations for combination products and that established conditions be similarly defined for this information, as provided in original NDAs or BLAs.
Lines 154	"DS/DP (including in-process materials) manufacturing and testing facilities."	DS/DP (including in-process materials) manufacturing and testing facilities **locations or addresses and primary contact.**	PDA recommends this clarification to align this bulleted list with description in table and to ensure there is no confusion regarding what facilities information is included as control strategy elements.

Line No.	Current Text	Proposed Change	Rationale
Line 166	"Maintenance strategy for chemometric and/or multivariate models (e.g., for models that may have a high impact on product quality.)"	Maintenance strategy for chemometric and/or multivariate models (e.g., for models **used in QbD type filings or models** that may have a high impact on product quality.)	Change for clarity.
175	FDA will consider these aspects when assigning allowable variations.	…when ~~assigning~~ **reviewing proposed** allowable variations	Change for clarity
186-190	…these elements are not generally considered established conditions:	Add bullet point to clarify combination product submission expectations, such as: • **Part 820 narratives in original applications for combination products**	Expanding the scope to include combination products will greatly benefit the industry and facilitate "right first time" submission content. In addition, it serves to facilitate consistency in the exercise of review expectations across review divisions.
Line 186, Footnote 13	"The batch record should reflect the current manufacturing process and the associated in-process parameters and controls …"	"The batch record should reflect the current manufacturing process and the associated ~~in~~ process parameters and **in-process** controls…"	PDA requests clarity and separation between process inputs (controlled parameters) and process outputs (IPC tests) respectively.
footnote 13 (in line 186)	…if there is a change to the control strategy that impacts the batch record, a current batch record should be provided in the appropriate regulatory	…should be provided in the appropriate regulatory submission **usually the annual report.**	A control strategy change may not have been implemented in manufacturing before submission of a supplement (eg, release specification change), therefore, a

Line No.	Current Text	Proposed Change	Rationale
	submission.		representative batch record may not be available for inclusion in the initial supplement. PDA recommends this additional language to clarify that the "appropriate regulatory submission" is generally the next annual report.
Lines 204-205	"This table is intended as a guide to assist the applicant and FDA in identifying established conditions. The relevant information would still be considered an established condition even if it is located in a CTD section not specified below."	"This table is intended as a guide to assist the applicant and FDA in identifying established conditions. ~~The relevant information would still be considered an established condition even if it is located in a CTD section not specified below."~~	The list of established conditions is not all inclusive. It appears FDA is trying to ensure the location of the information would not be a determining factor in whether something is an established condition. PDA supports this premise but proposes a reverse approach to the table whereby each CTD section where the entire section would constitute "established conditions" is identified and for other CTD sections, give examples of the types of information considered as established conditions.
212-219	The applicant should provide a summary of the proposed established conditions in the application. For ease of review and to facilitate identification and discussion of established conditions in the application, we recommend that the applicant's summary be provided in …Module 2, section 2.3 of the CTD,	The applicant should provide a summary of the proposed established conditions in the application. **or describe how the established conditions will be managed.** ~~For ease of review and to facilitate identification and discussion of established conditions~~	Including the summary in section 2.3 is inconsistent with the current harmonized approach to Module 2 of the CTD. Including information that must be maintained current in this module could create extra maintenance and updating of the hyperlinks. PDA recommends FDA allow the flexibility for an application to

Line No.	Current Text	Proposed Change	Rationale
	Introduction to the Quality Overall Summary	~~in the application, we recommend that the applicant's summary be provided in Module 2, section 2.3 of the CTD, Introduction to the Quality Overall Summary~~	reference the established conditions information throughout the CTD in order to reduce potential administrative errors that could arise from producing duplicate information in Module 2. For example in a post approval supplement, many marketing authorization holders currently supply a replacement for those CTD section(s) impacted by a change PDA suggests that perhaps. FDA could use the electronic submission document structure to access all the established condition information without having it repeated in a separate section.
Lines 223-227	"Demonstration of risk mitigation within the application can allow for greater operational flexibility for certain parameters typically considered established conditions. As such, those parameters may be determined to not be established conditions by FDA, and therefore can be changed solely within the manufacturer's PQS, and without the need for submission of a supplement or notification in an annual report."	"Demonstration of risk mitigation, **prior knowledge, technical or scientific justification** within the application can allow for… *PDA suggests articulating what sections should provide risk mitigation, or provide examples of this proposed content in section 208.*	PDA recommends adding other informational sources for supporting greater operational flexibility and for determining information in a submission that could be considered not an "established condition" and therefore managed within a firm's quality system. In addition, it is not clear which sections of the application should articulate "risk mitigation to allow for great operational flexibility for certain parameters typically considered established conditions."
Lines	"As such, those parameters may be	PDA recommends FDA consider the	Applicant will need a reference from the

Line No.	Current Text	Proposed Change	Rationale
225-228	determined to not be established conditions by FDA, and therefore can be changed solely within the manufacturer's PQS, and without the need for submission of a supplement or notification in an annual report. FDA will consider the established conditions to be finalized at application approval or licensure.	possibility of positive communication with the manufacturer, for example: FDA communicates with applicant about changes to proposed established conditions as a result of the submission review and the applicant would submit an amendment to the submission with the final established conditions.	approved submission in order to update the PQS with those conditions defined to be 'established conditions" It is not clear how the FDA will communicate the finalized established conditions. Based on this statement as well as instruction on providing a summary of the established conditions (lines 212-219), there seems to be an expectation to tabulate the established conditions. Suggestion to provide more specific guidance on how FDA will notify the sponsor of the final established conditions, once approval is received. This further clarification will also assist an investigator in knowing the established conditions for each product at the facility and what parameters are within the scope of the site quality system only.
Section IV A table entries 3.2.S.5 and 3.2.P.6	Reference Standards or Materials Qualification protocols for new and existing reference standards or materials	Qualification protocols for new and existing **primary** reference standards or materials	Secondary standards should be controlled within the PQS and available for review upon inspection. PDA recommends that the Agency clarify that qualification of the primary reference standards would be an established conditions and secondary

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			reference standards are managed within a firm's quality system.
Section IV A table entries under 3.2.R	Regional Information	Add line for: Part 820 narratives in original applications for combination products	Information to assess Part 820 compliance should be limited to regional dossier content section, limited to narrative description with confirmation of detailed documentation during the pre-approval inspection, and not considered an established condition. The sponsor documentation to support Part 820 compliance contains living content that should be managed through the firm quality system, and verified as part of change control evaluation during subsequent inspections. Including this documentation within scope of "changes to be reported" expectations would increase submissions workload for both sponsors and the agency for a scope of control with limited product risk after entering post-market lifecycle management.