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PhRMA

RE: Guidance for Industry CMC Postapproval Manufacturing Changes Reportable in Annual Reports, *Federal Register*, June 25, 2010 [docket No. FDA-2010-D-0283]

Dear Sir/Madam:

The following comments on the above guidance are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA is a voluntary, non-profit trade association representing the firms that discover, develop and produce prescription drugs and biologic products. The large majority of new prescription medicines approved for marketing in the United States are produced by PhRMA member firms.

PhRMA appreciates the effort by the Food and Drug Adminstration (FDA) in preparing this draft guidance on annual reportable manufacturing changes. Given the significant importance to PhRMA member companies, we ask that the following key themes and comments below, and in Appendix A, be given careful consideration by the FDA experts responsible for this guidance.

Key Themes

PhRMA companies agree that many of the changes proposed in this draft guidance have been treated previously by industry as annual reportable changes under current guidances. Other proposed changes are considered to be cGMP issues which are not reported in CMC supplements or annual reports. This guidance expands the list of annual reportable changes but will not substantially reduce the number of manufacturing supplements submitted to FDA. It will, however, increase the number of minor manufacturing changes reported in annual reports. These minor manufacturing changes have no impact on product quality and patient safety.

1. PhRMA recommends that all annual reportable changes be consolidated into a single, updated guidance document, such as the *Guidance for Industry, Changes to an Approved NDA or ANDA*. Currently multiple guidance documents provide recommendations for notifying the Agency of CMC annual reportable changes; such as the one noted above, various SUPAC guidances, and the current guidance being considered for annual reportable changes. Consolidation of all annual reportable changes will help ensure consistency, avoid confusion, and simplify the process for assessing change.

2. PhRMA supports several of the changes proposed in this draft guidance as they will facilitate industry's implementation and distribution of drug product made with minor changes. However, some of the proposed changes are inspectional issues and are not required to be reported in a post-marketing application. In these instances, this draft guidance will handicap companies who have interpreted those same changes as non-reportable and controlled by cGMP.

3. PhRMA recommends that FDA harmonize the list of annual reportable changes with

ICH Q11, the EU variations legislation, and the Canadian Guidance *Post-Notice of Compliance Changes: Quality Document*. This alignment will maximize the benefits to global pharmaceutical companies in assessing and reporting changes to marketed products. In addition, PhRMA recommends that the format of the list of changes be aligned with the CTD format. Both of these suggestions would significantly enhance the usefulness of a guidance covering CMC post-approval changes.

4. PhRMA recommends that future guidance documents include recommendations that reward or promote the application of Quality-by-Design principles and risk-based approaches in the assessment and reporting of CMC post-approval changes.

5. PhRMA recommends that any CMC post-approval guidance document include changes that can be applicable to both small and large molecules regulated under CDER and consistent with the change in regulation 21CFR601.12.

Your consideration of these comments is appreciated. Please contact me if you have any questions.

Sincerely,

Michael Garvin, Pharm.D.

Specific Comments – Appendix A

Section	*Change*	*Comments*
Components and Composition		
1.1	Elimination or reduction of an overage from the DP manufacturing batch formula that was previously used to compensate for manufacturing losses. Note that this does not apply to loss of potency during storage.	PhRMA supports.
1.2	Change in qualitative and quantitative coating formulation for IR solid dosage forms if the coating material and quantity have been approved in another product and the change in formulation does not alter release of the drug.	PhRMA supports this change and interprets the recommendation as including the addition of other components to the qualitative composition of the coating formulation.
1.3	New supplier of inactive ingredients that have a minimal effect on product performance in the DP, providing that acceptance criteria remain unchanged.	PhRMA supports this change provided it only applies to the suppliers of excipients that have a major effect on drug product quality and performance. Currently, CTD format, as per ICH M4Q, does not specify the reporting of excipient suppliers, except for suppliers of novel excipients. The inclusion of this change as proposed is inconsistent with risk-based regulation and PhRMA's experience to date.

Section	*Change*	*Comments*
Manufacturing Sites		
2.1	Modifications of an approved mfg. facility that does not affect a product manufacturing area or sterility assurance and does not change product quality or specifications.	PhRMA supports this change provided it is clarified that it applies to sterile manufacturing areas only. For other dosage forms, this change is an inspectional issue that would increase the reporting burden.
2.2	Addition of barriers to prevent routine in-process human intervention in a filling or compounding area that is qualified and validated by established procedures.	PhRMA suggests that this change be removed from the guidance. If this change is retained, greater clarification is needed, including whether this covers aseptic filling areas.
2.3	Mfg. of an additional drug product (including investigational or developmental products) in an approved multiple-product area that is producing another product if:	PhRMA supports this change for large molecules (biologics) regulated under CDER. If this is intended to imply that manufacture of multiple products in a manufacturing area for small molecules be identified in each NDA application, then PhRMA recommends this item be removed from the guidance.
2.3.1	specific ID tests exist to differentiate between all products manufactured at the facility; and	See the general statement above (2.3). PhRMA recommends that if this level of detail is filed in an NDA then a change to multiple products should be annual reportable.
2.3.2	a change-over procedure between manufacturing processes is established; and	See general statement above (2.3).

Section	*Change*	*Comments*
Manufacturing Sites Cont'd		
2.3.3	the products do not represent an additional level of risk. Additional levels of risk might include, but are not limited to, the manufacture of highly toxic or potent products, highly immunogenic or allergenic products (e.g. penicillin), products that can accelerate degradation of another product (e.g. enzymes), products that represent a new or added risk for adventitious agents, or a product for adults added to a line manufacturing pediatric products.	Suggest removing the phrase, "for adults."
Manufacturing Process		
3.1	Process changes including any of the following:	PhRMA supports.
3.1.1	Addition of a sieving step(s) for aggregate removal if it occurs under nonaseptic conditions.	PhRMA supports.
3.1.2	Changes in mixing times for IR solid oral dosage forms and for solution products.	PhRMA supports.
3.1.3	Changes in drying times for IR solid oral dosage forms.	PhRMA supports.

Section	*Change*	*Comments*
Manufacturing Process Cont'd		
3.2	A scale change of pooled or separated batches to perform the next step in the manufacturing process if all batches meet the approved in-process control limits and the critical operating parameters for the next step remain unaffected.	PhRMA suggests that clarification is needed as to whether this scale change of pooled or separated batches pertains to drug product and/or drug substance, and if this change is intended to apply to any scale.
3.3	Replacement of equipment with that of the same design and operating principle that does not affect the process methodology on in-process control limits, with the exception of equipment used in aseptic processing (e.g. new filling lines, new lyophilizer).	PhRMA recommends that this change be removed since, as per current guidance, an equipment change of this type that does not affect any of the listed aspects would not be filed. Inclusion of this change, as written, in any final guidance would increase the reporting burden. Otherwise, please provide additional clarity and examples for this type of change.
3.4	Addition of a duplicate process chain or unit process in the drug substance and drug product manufacturing process with no change in in-process limits or product specifications.	PhRMA supports this change and recommends defining the terms "process chain", "unit process", and "duplicate process."
3.5	Addition of, deletion of, or change in a reprocessing protocol for refiltrations to control bioburden because of integrity test failures.	PhRMA requests additional clarification to indicate that this change refers to a bioburden reduction filtration rather than a sterile filtration. This change seems like a cGMP issue that would not need to be included in regulatory documentation.
3.6	Reduction of open handling steps if there is an improvement with no change to the process (e.g. implementation of aseptic connection devices to replace flame protection procedures).	PhRMA suggests this be deleted. If retained, clarify what is meant by the statement "if there is an improvement."

Section	*Change*	*Comments*
Manufacturing Process Cont'd		
3.7	Changes to filtration process parameters (such as flow rate, pressure, time or volume, but not filter material or pore size) that are within the currently validated parameters and therefore would not warrant new validation studies for the new parameters.	PhRMA suggests this be deleted.
3.8	For sterile drug products, changes from a qualified sterilization chamber (ethylene oxide (EtO), autoclave) to another of the same design and operating principle for container/closure preparation when the new chamber and load configurations are validated to operate within the previously validated parameters. This does not include situations that change validation parameters.	PhRMA supports this change and suggests that the scope be broadened to include a change to a new site utilizing the same sterilization process for container/closure systems.
Specifications		
4.1	Addition of a specification for existing excipients.	PhRMA recommends clarifying that this change pertains only to non-compendial excipients. Also, consider revising this statement to include deletion of a specification and the widening of acceptance criteria.
4.2	Change to a drug substance or drug product to comply with the official compendia can be reported in an annual report if it is:	PhRMA supports this change provided it includes all changes for an excipient, drug product, or drug substance to align with the official compendia.

Section	*Change*	*Comments*
Specifications Cont'd		
4.2.1	A change to tighten an existing acceptance criterion; or	PhRMA recommends removing items 4.2.1. and 4.2.2 so that any change made to align with official compendia can be reported in the annual report, whether it results in a tightening, relaxation or deletion of a test or specification.
4.2.2	Other changes, except for changes to assays, impurities, product-related substances, or biological activities in approved NDAs and ANDAs.	See comment above (4.2.1).
4.3	Change in the approved analytical procedure if the revised method maintains basic test methodology and provides equivalent or increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it claims to have or is represented to possess and the acceptance criteria remain unchanged (e.g., change in the flow rate or sample preparation for a high performance liquid chromatography (HPLC) method).	PhRMA supports.
4.4	Replacement of a nonspecific identity test with a discriminating identity test that includes a change in acceptance criteria (e.g., replacing SDS-PAGE11 with peptide map).	PhRMA supports.
4.5	Addition of an in-process test.	PhRMA supports.

Section	*Change*	*Comments*
Specifications Cont'd		
4.6	Replacement of blend uniformity and in-process homogeneity tests with other appropriate testing that assures adequacy of mix.	PhRMA recommends that items 4.6, 4.7, and 4.8 be combined to state "replacement or deletion of blend uniformity and in-process homogeneity tests that are demonstrated to be redundant and does not impact final product specifications."
4.7	Revision of tablet hardness if there is no significant change in the dissolution profile.	PhRMA recommends clarifying whether this refers to a revision of a tablet hardness specification and define "significant change in dissolution profile." PhRMA recommends adding "e.g., by f^2 similarity factor" after "dissolution profile" to provide additional clarity.
4.8	Elimination of an in-process disintegration test where a dissolution test is required for release.	PhRMA supports.
4.9	Deletion of the homogeneity test as a routine test from the application provided the applicant has process controls in place to demonstrate the product's homogeneity.	PhRMA suggests clarifying whether this change refers to an in-process homogeneity test.
4.10	Addition of a test for packaging material to provide increased assurance of quality.	PhRMA supports this change and suggests that this change be moved to the Container/Closure System section.
4.11	Tightening of an existing acceptance criterion.	PhRMA supports.

Section	***Change***	***Comments***
Container/Closure System		
5.1	A change in the container/closure system for the storage of a nonsterile drug substance when the proposed container/closure system has no increased risk of leachable substances in the extractable profile (for liquids) and equivalent protection properties.	PhRMA supports.
5.2	Use of a contract manufacturing organization (CMO) for the washing of a drug product stopper, provided the applicant certifies that the CMO's washing process has been validated and the CMO's site has been audited by the applicant (or by another party sponsored by the applicant) and found CGMP compliant.	PhRMA supports this change and suggests it be expanded to include siliconization of drug product stoppers, and any part of a container closure system, provided the CMO site is cGMP compliant.
5.3	For solid oral dosage forms:	
5.3.1	Elimination of bottle dunnage.	PhRMA suggests removing this change, or at minimum, defining the meaning of the term "bottle dunnage" as typically this level of detail is not included in an application.
5.3.2	Change in type of desiccant to another equivalent desiccant that was previously used in another approved product.	PhRMA suggests this change be reworded to read, "Change in type of dessicant to another equivalent desiccant." The use of a desiccant in another approved product is not necessarily a relevant factor in judging quality impact because each approved product will have a different moisture sensitivities and stability profile. The dessicant chosen should be suitable for its intended use as it pertains to the drug product.
Section	***Change***	***Comments***

Container/Closure System Cont'd		
5.4	For parenteral drug products, a change in glass supplier without a change in glass type or coating and without a change in container/closure dimensions.	PhRMA supports this change and suggests that a change in glass coating be allowed provided an evaluation has been made to ensure no change to the final drug product.
5.5	Changes to a crimp cap (ferrule and cap/overseal), provided that there are no changes to the labeling or the color and that container and closure integrity have been demonstrated using a validated test method.	PhRMA suggests the scope of this change be expanded to incorporate changes such as a change in the flip seal cap color as long as the cap color is consistent with any established color coding system for that class of drug products and changes to the wording on the ferrules, caps/overseals. This would align the change with USP's restrictions on wording and logos that can appear on injectable product caps and overseals.
Miscellaneous Changes		
6.1	Extension of expiry based on real-time stability data from pilot scale batches following an approved stability protocol.	PhRMA supports this change and suggests including in the description of the change to allow for extension of expiry based on real-time stability data from pilot scale "or "larger" batches following an approved stability protocol.
6.2	Reduction of expiration dating for a drug product for reasons other than stability failures.	PhRMA supports this change and suggests that some examples be included with the recommendation.
6.3	If a dissolution test is performed, elimination of a nonstability indicating tests for identity or hardness from an approved stability protocol.	PhRMA supports this change, but suggests the scope be expanded to include other non-stability indicating tests, such as OVIs, etc.

Section	*Change*	*Comments*
Miscellaneous Changes Cont'd		
6.4	For changes in an application that are fully consistent in scope and requirements with changes previously approved in a bundled supplement, the same applicant can add similar drug products. (See MAPP 5015.6, "Review of the Same Supplemental Change to More than One NDA or ANDA in More Than One Review Division.")	PhRMA supports this change but seeks an explanation as to the reasoning for including this provision pertaining only to previously approved 'bundled' supplements. If FDA's perspective is that precedence can be used to apply the same change to other products then the administrative route of that original supplement should not be a factor. It is suggested to re-word this annual reportable change to read "For changes in an application that are fully consistent in scope and requirements with changes previously approved in a supplement, the same applicant can add the same change to similar drug product dosage forms via the product's annual report."
Additional Changes and Comments that Should be Included in the Guidance		
1	Any revised or future guidance on annual reportable changes should include additional recommendations that reward or promote the application of Quality-by-Design principles and risk-based approaches in the assessment and reporting of CMC post-approval changes. The inclusion of this consideration would represent a significant improvement in the utility of guidance on annual reportable CMC post-approval changes.	
2	The additional change of a move to a different site for testing should be annual reportable if the provisions of the PAC-ATLS are met. This change is considered low risk and the current supplemental requirements consist of confirmation statements only, i.e., no actual data is provided as required by current SUPAC Guidances.	
3	Addition or removal of debossing, or removal or addition of printing ink (ink used on previously approved products) for controlled release tablets when drug release is unaffected as determined by the f^2 similarity factor or other appropriate test.	
4	Reduction of annual stability testing time points after the accumulation of a significant body of data from the commercial product is available. For example, removal of intermediate time points such as 3, 9, and 18 months.	

Additional Changes and Comments that Should be Included in the Guidance Cont'd	
5	Removal of a test shown not to be stability-indicating from an approved stability protocol. For example, OVI testing on a drug product.
6	An addition of a new test, acceptance criteria and associated analytical procedures to a specification that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess.
7	Addition of a site change for the manufacturing, packaging, labeling or testing *within the same company* (i.e., managed by the same quality systems, having a satisfactory cGMP compliance status for the operation being transferred, and the facility is owned and operated by the NDA holder of the product) for immediate release solid oral dosage products, where there are no changes to the manufacturing process and the same procedures approved in the NDA are used.