AstraZeneca

September 9, 2010

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

Re: Docket Number FDA-2010-D-0283
Response to FDA Call for Comments
Draft Guidance for Industry on Chemistry, Manufacturing and Controls Postapproval Manufacturing Changes Reportable in Annual Reports

Dear Sir or Madam:

Reference is made to the June 25, 2010 Federal Register notice announcing the request for comments on Draft Guidance for Industry on Chemistry, Manufacturing and Controls Postapproval Manufacturing Changes Reportable in Annual Reports.

AstraZeneca has reviewed this draft guidance and our comments are attached.

Please direct any questions or requests for additional information to Lora Radzieta, CMC Regulatory Compliance Senior Account Manager, at (302) 886-8501.

Sincerely,

/DT

Lora Radzieta

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Enclosure

Regulatory Affairs
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FDA Draft Guidance for Industry "CMC Post Approval Manufacturing Changes Reportable in Annual Reports"

General Comments

- Comment 1

  This guidance has been highly anticipated by industry and the spirit of the guidance is generally welcomed. AstraZeneca commends the Agency for exhibiting its continuation of its risk-based approach to CMC review, which enables the Agency to focus and allocate its review resource in the most effective manner while minimizing risk to patients.

- Comment 2

  FDA has recognized that the number of CMC supplements has continued to increase over the last several years and that the review system is over-burdened. In response, FDA has applied a retrospective analysis of the supplements submitted over the years and determined that many changes being reported in supplements are very low risk changes, not requiring supplement submission, and identified those changes in this June 2010 draft Guidance. According to the June 25, 2010 Federal register announcement, "FDA has evaluated the types of changes that have been submitted in CMC post approval manufacturing supplements and determined that many of the changes being reported present very low risk to the quality of the product and do not need to be submitted in supplements" and "Part of the intent for this draft guidance is to reduce the burden of reporting some manufacturing changes". While the Guidance should accomplish the reduction of the burden of FDA review and issuance of action letters for the list of changes included in the Guidance, it won't reduce the burden of reporting of these manufacturing changes on industry, and could in fact have the opposite effect. While some of the changes listed are agreeable and welcomed as annual reportable changes, as these will help facilitate industry implementation and distribution of product made with these minor changes, some of the other changes listed are viewed as GMP changes that should not require any regulatory action. The approach of retrospective analysis of the types of changes that have been submitted to FDA in the past and the issuance of this guidance as the vehicle to communicate that a supplement is not needed for those cases, may in essence handicap companies who would have viewed those same changes as non-reportable changes that are controlled by GMP.

- Comment 3

  We would prefer to see that the Agency instead consider incorporating the changes listed in this draft guidance into an updated version of the "Changes to an Approved NDA Guidance", as an alternative to publishing this stand-alone Annual Report guidance. The existence of multiple guidances on categorization of post-approval changes adds complexity and potential for confusion to the post-approval CMC regulatory environment for the US.

- Comment 4

  The format and content of Appendix A is not very comprehensive or consistent with other regulatory regions. A more comprehensive approach and format to Appendix A would be to use the CTD numbering system for listing the types of changes. In an effort to harmonize with other post approval guidances, we suggest the Agency consider adopting a format similar to EU and Canada post-approval guidances which list Description of Change, Conditions to be Fulfilled, and Supporting Data.

- Comment 5

  It is not clear how the proposed guidance encourages the application of Quality-by-Design principles, which should support the principle that the reporting of changes within the established design space is not required (ICH Q8). This guidance only seems to address annual reportable changes in the 'conventional' NDA paradigm.

- Comment 6

  In light of the above comments and concerns, we would like to suggest that the Agency consider not finalizing this Guidance at this stage and that the Agency re-considers their approach to defining low risk changes, utilizing a more holistic and globalized approach, rather than a stand-alone publication of overly specific examples from historical supplements.

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Specific Comments on FDA Draft Guidance for Industry "CMC Post Approval Manufacturing Changes Reportable in Annual Reports"		
Section	**Page or Line Number**	**Comment or proposed replacement text**
I	Line 24-27	Regarding the text: "previously submitted under manufacturing supplements that we have determined to be generally low risk to product quality". Some of the changes listed are GMP and would not have previously been reported at all by AZ. The suggestion that these changes do not belong in supplements but should be annual reportable has the potential to over-burden industry. Suggest some of these changes could be communicated 1:1 with the company as not requiring regulatory action.
III	Line 77	Suggest changing language to 'low risk' instead of 'very low risk'.
III	89-94	Consider adding the annual reportable changes listed in the 'Changes to an Approved NDA' Guidance to this Guidance so that there is one comprehensive guidance on all annual reportable changes, i.e., not having to look across two guidances.
IV	Lines 131-132	With the exception of natural product, recombinant DNA-derived protein/polypeptide, complex or conjugate of a drug substance with a monoclonal antibodies [Reference 21CFR 314.70(d)(3)(5)], cross references to validation protocols and standard operating procedures should not be necessary and should be kept on-site for inspection. This is an increase in regulatory burden for changes that FDA judges to be of little risk to quality.
IV	Line 132	List of all drug products involved in the change should not be required as each change will be submitted to each individual NDA affected.
IV	Line 135	21 CFR 314.81(b)(2)(i) is an inappropriate CFR reference. The CFR reference cited is for 'A brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labelling of the drug product. This does not fit with the definition of 'Annual reportable' changes which are low risk changes that have minor potential to have an adverse effect on the quality of the product. The appropriate CFR references should be 21 CFR314.81(2)(iv)(b).
IV	Line 135-137	Not relevant to the Section IV. 'Contents'. Should go in 'Discussion' section.
Appendix A Section1	147-149	Can we use 'bracketing' i.e. if the proposed coating change is between quantities in other approved products it is still annual reportable? If so change to read: "Change in qualitative and quantitative coating formulation for immediate-release solid dosage forms if the coating material and quantity have been approved in another product or if the new quantity falls with the brackets of other approved products...."

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Section	**Page or Line Number**	**Comment or proposed replacement text**
Appendix A Section 1	149	Change 'release' to 'release or bioavailability'.
Appendix A Section 1.3	Line 151-153	Suppliers of inactive ingredients are not typically named in NDAs. A change in suppliers of non-novel inactive ingredients should not need to be reported to the Agency if the quality standard is the same and if the suppliers are not named in the NDA.
Appendix A Section 2	Line 155	Add to the list "Deletion of a registered manufacturing/testing site"
Appendix A Section 2	Line 155	Add to the list "A move to a different manufacturing site for testing if the provisions of the PAC-ATLS/Changes to an Approved NDA Guidance are met." These submissions are low risk changes that merely consist of confirmation that (1) the approved test procedures are used, (2) all post approval commitments made by the applicant relating to the test procedures have been fulfilled (e.g., providing methods validation samples), and (3) the new testing facility has the capability to perform the intended testing and (4) the new site has a satisfactory CGMP inspection for the type of operation being moved. Analytical testing site changes are low-risk if the above conditions are met, and furthermore, since there is no content for FDA to review in these submission cases, an annual report seems more appropriate regulatory avenue.
Appendix A Section 2.1	Lines 157-159	Modification of a facility that does not affect product manufacturing area or sterility assurance is a structural change in facility and and not specific to an NDA therefore should be covered under GMPs and require no regulatory action.
Appendix A Section 2.2	Lines 161-162	Addition of barriers is a structural change in facility and not specific to an NDA and therefore should be covered under GMPs and require no regulatory action.
Appendix A Section 2.3	Lines 164-176	Naming of manufacture of additional products and the measures to prevent cross-contamination are GMP aspects and not specific to an NDA and therefore should require no regulatory action.
Appendix A Section 3.1.2	Lines 184-185	Agree, so long as mixing time is not a critical process parameter and any key product quality attributes/in-process controls are met.
Appendix A Section 3.1.3	Line 186	Agree, so long as drying time is not a critical process parameter and any key product quality attributes/in-process controls are met.
Appendix A Section 3.3	Lines192-193	Propose to remove this 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

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		guidance would increase the reporting burden. Otherwise, please provide additional clarity and examples for this type of change.
Appendix A Section 3.4	Lines 197-199	Addition of duplicate process chains is not a CMC manufacturing process change and presents no risk to product quality and therefore should require no regulatory action.
Appendix A Section 3.7	208-210	This should be deleted as it is considered a cGMP issue.
Appendix A Section 4.1	Line 220	Additional specification for existing excipients should not be needed unless the additional specification is a critical quality attribute (CQA). Otherwise, the additional specification should be handled internally under GMP.
Appendix A Section 4.2	Lines 222-226	All changes to comply with an official compendia should be regarded as low risk changes that are annual reportable. Add the text from 2004 guidance:"Relaxing an acceptance criterion or deleting a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements" thereby downgrading from CBE-30 to AR.
Appendix A Section 4.5	Line 240	This should normally be outside the scope of the NDA unless is involves control of a CQA.
Appendix A Section 4.10	Line 253	This should normally be outside the scope of the NDA unless is involves control of a CQA. If kept in Guidance it should be moved to Container/Closure System section of Guidance.
Appendix A Section 4.11	Line 255	In order to avoid confusion with non-registered in-process test criterion, suggest clarifying that this only applicable to cases of registered release/stability specification, or if the acceptance criterion is a registered critical quality attribute.
Appendix A Section 5.2	Lines 264-267	Move to Manufacturers section.
Appendix A Section 5.3.1	Line 271	The term 'dunnage' is not clear. Define in other words and/or give examples.
Appendix A Section 5.3.2	Lines 272-273	Change to read 'Change in type of desiccant to another equivalent desiccant'. Use in another approved product is not necessarily a relevant factor in judging quality impact. Each approved product will have different stability profiles/moisture sensitivities. The desiccant chosen should be suitable for its intended use as it pertains to the product.
Appendix A Section 5.5	Line 278-279	Regarding the text "provided that there are no changes to the labelling or the color" implies that a filing category higher than annual reporting is needed in these cases. This would be an increase in

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		regulatory burden and in conflict with the 2004 Guidance which states that "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" is annual reportable.
Appendix A Section 6	Line 282	Add to list of Miscellaneous Changes: "For a change previously approved in a supplement for a defined set of product strengths or product pack sizes, the same applicant can add other strengths or pack sizes of the same drug product in the annual report, if the change is fully consistent in scope and fulfils the same requirements as in the previously approved supplement."
Appendix A Section 6.4	Lines 293-296	This is a regulatory procedural issue. If the concept is that changes that have been previously approved by the Agency can be introduced for other products providing that they are fully consistent in scope and requirements, the regulatory mechanism shouldn't matter i.e., whether the change was submitted originally as a 'bundled' supplement or stand-alone supplement does not impact on the potential to affect quality.