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Date: APR 07 2004

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

Re: Federal Register Docket Number No. 2003D-0571
Response to FDA Call for Comments
DRAFT Guidance for Industry: Drug Substance – Chemistry, Manufacturing, and
Controls Information

Dear Sir or Madam:

Reference is made to the Federal Register Notice [Federal Register Docket No. 2003D-0571] published January 7, 2004 announcing the request for comments on the draft “Guidance for Industry: Drug Substance – Chemistry, Manufacturing, and Controls Information”.

AstraZeneca has reviewed this draft guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Robert J. Timko, Associate Director, at (302) 886-2164.

Sincerely,

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PEMC

Enclosure

2003D-0571

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US Regulatory Affairs
AstraZeneca Pharmaceuticals LP
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AstraZeneca Comments
Draft Guidance for Industry: Drug Substance - Chemistry, Manufacturing, and Controls Information
Federal Register Docket No. 2003D-0571

Line Number	Draft Guidance Section	Current Guidance Cross Reference	Comment	Rationale	Importance 1= Major 2= Moderate 3=Minor
Overview			AstraZeneca welcomes the new guidance with the clarification of issues such as:		
			The introduction of CTD format		
			Elaboration of regulatory mechanisms for sunset testing, interim specifications and comparability protocols		
			Retention of data for inspection during GMP inspections rather than overburdening the NDA, e.g. No need to submit validation for process, reworks, reprocessing or Executed batch records. This should be extended to other aspects of GMP e.g. Environmental controls.		
			Review of the method of selection of Registered Starting Materials and identifying where possible the compound selected as the registered starting material in the NDA is the same as the compound identified using the ICH Q7A definition to commence the application of GMP manufacturing standards.		
			Confirmation that reprocessing does not have to be registered in the NDA		

			Confirmation of expectations on Reworks		
			However AZ notes the unprecedented rise in the level of detail required for the NDA. Specific examples are noted below. These issues should be reviewed with respect to these requirements delivering benefits to patient safety.		
301	III.A		Replace 'nickname' with 'in-house name' or 'trivial name'	Clarity	3
377 - 393	IV.A		This represents an excessive level of detail. It is recommended that this level of detail be removed since it is supplied on the Form FDA 356H facilities information attachment.	Duplication of information submitted.	2
398	IV.B		What is meant by 'complete' description of process..... suggest outline description of	Clarity of reviewer expectation will facilitate NDA review and approval.	2
406 / 414 - 431	IV.B		There appears to be an excessive requirement for information requested for inclusion on the process flow sheet. This should be rationalised with remaining data provided in tabular format. It is recommended that this information be included only in the process description. What is the Agency rationale for both a detailed process flow and description ?	Clarity of documentation will facilitate NDA review and approval.	2
422 / 841	IV.B.1		What is FDA's rationale for the inclusion of two new terms of; 'Post synthesis materials' and 'Unfinished Drug Substance'	Clarity of reviewer expectation will facilitate NDA review and approval.	2
427	IV.B.1		The filing of operating parameters should be restricted to those regarded as "Critical" to the production of a drug substance with the correct quality attributes.	Whilst ensuring appropriate regulatory control this will minimise unnecessary post approval submissions. The detail requested here is at times excessive and appears to be moving in the opposite direction wrt FDA's current thinking on science and risk based regulatory processes. Submission of excessive non-critical detail could result in difficulty in later making improvements or changes.	1
429	IV.B.1		The Final Intermediate should be agreed between the Agency and Sponsor at the EoPII meeting as part of the discussion on the selection of the Registered Starting Material.	Clarity of reviewer expectation will facilitate NDA review and approval.	2
436	IV.B.1		A definition of "side product" is missing from the glossary.	Clarity	3

440 - 447 / 473 / 521	IV.B.2		The filing of operating parameters should be restricted to those regarded as "Critical" to the production of a drug substance with the correct quality attributes.	Whilst ensuring appropriate regulatory control this will minimise unnecessary post approval submissions. The detail requested here is at times excessive and appears to be moving in the opposite direction wrt FDA's current thinking on science and risk based regulatory processes. Submission of excessive non-critical detail could result in difficulty in later making improvements or changes.	1
486 - 494	IV.B.2		Clarification of the term "facilities" is requested for this	Clarity	2
491-492	IV.B.2		The potential for cross-contamination is more suitably	Efficiency	2
502 - 506	IV.B.2		The definition of process controls is too broad as written.	Efficiency	1
521	IV.B.2 /		Definitions of "on-line, at line and off line" would be	Clarity	3
547	IV.B.2 Fig 1		The objective of Figure 1 is not clear. Why has S.3	Clarity	2
623	IV.B.3.c		Should say drug not drugs	Typo	3
628 - 643	IV.B.3.c		An unnecessary level of detail is requested in this section. Many of the issues could be covered by GMP inspections. The reuse of solvents should be controlled by its quality and not by the number of process cycles.	This does not reflect FDA science based risk approach to drug manufacture.	1
816	IV.D		When would an intermediate specification not be warranted?	Clarity	2
908	IV.F		Definition of "any significant differences" would be helpful to prevent misunderstandings.	Clarity	2
922	V		A clear definition of "manufacturability" is requested	Clarity	2
1059	V.B		It is unnecessary to burden the NDA file with information on the synthesis and characterization of all impurities and potential impurities in the API . Summary of the route of synthesis for an independently prepared impurity isn't relevant to patient safety and unnecessarily increases the data to be reviewed in the NDA. This information would be available for the PAI. However a summary of possible means of formation of impurities in the drug substance would be relevant, and isn't included in this list.	This does not reflect FDA science based risk approach to drug manufacture.	2
1129	VI.Table 1		Appearance – it is not possible to say a substance is crystalline by visual assessment and should be changed to white powder.	Technical accuracy	2
1129	VI.Table 1		Tests should be presented in the order of ICH Q6A.	Consistency with ICH Q6A	3
1240	VI.D		In the interests of brevity, batch data should be presented as data tables rather than Certificates of Analysis	Efficiency	2

1257	VI.D		Remove word 'crystalline'	Technical accuracy (Can't assess visually)	2
1263	VI.D.1		The request for all batch data is considered unnecessary. Some tests performed during development are not designed to form part of the specification and may not be considered supportive data nor suitable for review. There is a concern that analysis recorded for information purposes during development can sometimes be inconclusive. This may lead to non value added analyses being requested in the specification. Thus only relevant batch data should be reported in the NDA. Tests omitted should be included in the Justification of Specification section (S4.5)	This does not reflect FDA science based risk approach to drug manufacture.	1
1324	VI.E		The concept of sunset test protocol is strongly supported. If sunset criteria are filed in the NDA, it should be possible to discontinue a particular test with out further Agency review. This could be achieved by providing the Agency with the information using "New Correspondence". This approach could be elaborated in Footnote 22.	Minimise the delay to the implementation of scientific advances.	1
1386	VI.E		Change "not viable or warranted" to "not used". It should be acceptable to use non-specific assay if mass balance can be supported by other methods.	Appropriate use of scientific judgement	1
1666 <i>et al</i>	Attachment 1		Registered Starting Materials should be selected on the scientific basis of the sponsor demonstrating adequate process, analytical and change control for the proposed registered starting material(s). The 'new' terminologies of significant or non-significant pharmaceutical market and the associated selection principles may be too restrictive / non scientific.	The new definitions are considered restrictive without improving patient safety or facilitating industry / Agency agreement on the selection of Registered Starting Materials.	1
1683	Attachment 1		An approved drug substance should be regarded as an acceptable registered starting material, for example salbutamol base used in the manufacture of salbutamol sulphate. This request is particularly unreasonable if the material meets a compendial specification, such as USP/NF, or has an adequate specification and impurity profile	The new guideline is considered restrictive without improving patient safety.	1
1740 / 1907	Attachment 1		Could a clearer alternative term to "Propinquity" be used. It does not readily convey the FDA's expectations particularly for those for whom English is not their first language. This term should be added to the Glossary.	Clarity	2

1744	Attachment 1		Please clarify "several" reaction steps.	Clarity	2
1753	Attachment 1		It is not accepted that a reaction has more impact on quality than a purification stage implied by this statement.	Appropriate use of scientific judgement	1
1764	Attachment 1		It is not accepted that well controlled distillations or extractions cannot lead to high purity product.	Revise in line with industry experience.	2
1790 / 1932	Attachment 1		It is considered entirely unreasonable to restrict the registered starting material to 0.10% in the drug substance. What if degradants of drug substance are the same structure as registered starting material? Limits should be set on the basis of toxicological qualification, process capability and stability data.	This does not reflect FDA science based risk approach to drug manufacture.	1
1792 -1797	Attachment 1		The requirement to define a registered starting material prior to a stage which TSE agents could be introduced would unnecessarily lengthen the synthetic route filed in the NDA. It is recommend that compliance to CFR requirements or International TSE guidance e.g. European Union "Notes for Guidance on The Risk of Transmitting Animal Spongiform Encephalopathies via Human and Veterinary Medicinal Products (EMEA/410/01/Rev 2)" be stated in the NDA (Section S2.3 or P4.5).	This does not reflect FDA science based risk approach to drug manufacture.	1
1805	Attachment 1		Multiple chiral centres should not necessarily result in a longer synthetic route being declared in the NDA. A good example are steroids where many of the chiral centres are fixed by the plant prior to extraction and subsequent processing. In this situation there is no risk to the patient of isomers being present in the drug substance. As stated elsewhere in these comments, analysis of chiral molecules has advanced significantly over recent years and now provides robust quality control methodologies.	This does not reflect FDA science based risk approach to drug manufacture.	1

1815	Attachment 1		The definition of advanced analytical techniques needs to be reviewed as chiral HPLC for example has been around ~ 20 years. NMR applications are growing rapidly in the field of pharmaceutical analysis and can be powerful in distinguishing positional isomers. The use of advanced techniques can only enhance quality control and care should be taken not to discourage pharmaceutical companies from using these on starting materials. Also if these techniques are being transferred to manufacturing then they should be considered established and not advanced techniques.	This does not reflect FDA science based risk approach to drug manufacture.	1
1834	Attachment 1		It is considered an unnecessary burden to present stages prior to the proposed registered starting material. This is especially true where the Registered Starting material has been agreed between the sponsor and the FDA at the End of Phase II meeting	Unnecessary expansion of documentation.	1
1859	Attachment 1		If the technically demanding and economically punitive requirement to control all unknown impurities to 0.10% is imposed, it would be reasonable to expect that the number of stages disclosed in an NDA would be significantly reduced. Alternatively the limit should be relaxed to 0.1 or 0.2%.	This does not reflect FDA science based risk approach to drug manufacture.	1
1886	Attachment 1		It is not understood how the requirements in this bullet point improve patient safety. It could actually lead to a lower quality supplier being used for the registered starting material supply.	This does not reflect FDA science based risk approach to drug manufacture.	1
2202	Attachment 2		Add a definition of Propinquity	Clarity	3
2245	Attachment 2		Does the definition of unfinished drug substance apply to physical form changes (morphs/solvents etc) or to mechanical changes (milling, micronisation etc), or to both?	Clarity	3