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

**Re: Draft Guidance for Industry on Drug Substance; Chemistry, Manufacturing,  
and Controls Information** [Docket No. 2003D-0571, 69 *Federal Register*, 929-930,  
January 7, 2004]

Dear Sir or Madam,

Millennium Pharmaceuticals, Inc., (Millennium), a leading biopharmaceutical company based in Cambridge, Mass., co-promotes INTEGRILIN<sup>®</sup> (eptifibatide) Injection, a market-leading cardiovascular product, markets VELCADE<sup>®</sup> (bortezomib) for Injection, a novel cancer product, and has a robust clinical development pipeline of product candidates. The Company's research, development and commercialization activities are focused in three disease areas: cardiovascular, oncology and inflammation. By applying its knowledge of the human genome, its understanding of disease mechanisms, and its industrialized technology platform, Millennium is seeking to develop breakthrough personalized medicine products.

Millennium recognizes the extensive effort that has gone into the preparation of the draft guidance. We are pleased to have the opportunity to comment on it, as follows.

Starting Materials for Synthetic Drug Substances

The goal, during the development of a new drug substance, is to develop a process that affords control over and reproducibility for the production of a drug substance with a defined purity profile. This purity profile must meet the specifications that have been set based on the levels of impurities that have been qualified and the experience with the process.

We endorse the position that the agency articulates on page 55, lines 1976 to 1982 related to having the ability to change the process being used to manufacture the starting material without reporting these changes to the Agency, as long as no commitment has been made

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and the specifications of the starting material are not changed. This, of course, requires the sponsor company to ensure that analytical methods are appropriate for demonstrating that no changes in the purity profile has occurred.

#### Recommendation 1

A starting material should be defined by whether control of its purity profile affords effective control of the quality of the finished drug substance. Whether the starting material is novel, an item of commerce, an existing drug, or used outside the pharmaceutical industry is not relevant to whether it has specifications that are appropriate to ensure control of the quality of the drug substance. Thus, these factors should not be used to define whether or not a material is suitable for use as a starting material.

#### Recommendation 2

The level of impurities present in the starting material should not impact whether or not that material is considered suitable for use as a starting material. For example is an impurity is present at 1% in the starting material (an enantiomer or a regioisomer for example) and appears in drug substance at 0.3%, this material should still be considered suitable for use as a starting material as long as the impurity has been suitably qualified and the specification for this material can be achieved reproducibly based on the process being proposed.

#### Recommendation 3

Complex materials may be used as starting materials as long as the specifications developed ensure that the drug substance can be produced that meets its specifications. To ensure control, the specifications for a complex starting material should be related to the route or routes that have been demonstrated to afford the starting material that meet the defined specifications (and include specifications for impurities that are specifically derived from a defined synthetic route if appropriate).

#### Recommendation 4

The use of advanced analytical technologies, especially for structurally more complex starting materials) should be encouraged (not discouraged) as long as they can be used effectively in a production environment. This decision should be left to the sponsor company. To restrict the use of new technologies will in the end lead to less control of the quality of the drug substance.

#### Recommendation 5

The closeness of a starting material to the finished drug substance should be defined by the whether or not the quality of the finished drug substance can effectively be controlled by the specifications that have been established for the starting materials. There should not be a requirement that dictates that the starting material must be a certain number of steps removed from the drug substance since there are multiple factors that impact the selection of the starting material such as crystallinity, stability, and ability to define specifications that afford control of its quality. Justification should be provided by the sponsoring company regarding reasons the selected starting materials were selected.

The following additional comments are aligned with each section of the draft guidance document:

Page	Line	Comment
2	53	...manufactured by the chemical modification of a starting material or an intermediate - add starting material.
3	111	... remove the extra "the"
4	125	It has been assumed that if no changes are being made to the process for the manufacture of an already approved drug substance the required information can be included by reference to the appropriate NDA/DMF.
11	406	Too much information is being requested to be included in the Flow Diagram that will be provided in Description of the Manufacturing Process and Process Controls section. The purpose of the flow diagram should be reviewed. In general it should be used to provide a high level visual over of the conversion of the starting materials to the drug substance. This can be supplemented by a step flow diagram in the process description section that provides a more comprehensive pictorial view of the reaction with material balance provided.
11	421	The structure of structurally complex reagents should be provided in a separate table (along with process related by-products from coupling reagents for example) rather than in the process flow sheet if desired.
11	422	<p>The introduction of the term postsynthesis materials does not appear to be required and certainly does not related to any terminology that can be linked to the way materials are considered in a synthesis. It is in fact quite confusing since the synthesis includes all steps from the starting material to the final drug substance (salt form and polymorph defined). To use a term such as postsynthesis material implies the synthesis is complete which it is not.</p> <p>Consideration should be given to modifying the definition of an intermediate to include materials that are converted to the actual form of the drug substance. For example the free base of a drug substance that is actually produced as a salt can be considered an intermediate since it is being converted from a free base to the acid addition salt which is in fact the drug substance.</p> <p>For the definition given for postsynthesis material, it is not clear how a material that differs in stereochemical identity is not an intermediate since it is undergoing further molecular change.</p>
11	434	It is recommended that the inclusion of major isomers being produced in a given step not necessarily be included in the high level overview of the synthesis provided by the flow diagram. Rather they should be included in an equation that precedes the description of each chemical step.

13	475	It is not clear why the biological source for a semisynthetic drug substance that is derived from a well characterized organic molecule that has been produced from a biological source need be considered as the starting material. Assuming that the organic molecule that is produced can be well characterized and purified then the organic molecule should be able to be considered as the starting material.
14	521	It is recommended that only those process controls that are anticipated to be used thought the life of the process and are considered critical be listed. To list all process controls, many of which will likely be dropped once enough experience is gained with the process, represents an major increase in restrictions on how the process is operated.
14	538	Remove reference to environmental conditions.
15 - 16	--	The section on reprocessing is a nice clarification of what can be left out of an application and when a reprocessing step should be included in the application.
19	713	For some starting materials, a flow diagram will not be appropriate and this option should be included in description of this section.
20	769	Eliminate environmental controls.
21	810	It has been assumed that this sentence refers only to test that are carried out as part of the final processing step leading to the drug substance and does not apply to a situation where it has been proven that control of an impurity at the starting material or at an intermediate step. This leads to the situation where no test in the drug substance is required for this impurity. It is recommended that this requirement be limited to the final processing step.
22	824	As noted on page 13 line 475, a well characterized organic compound derived from a biologic source should be considered a starting material as long as any concerns about biological contamination from biological source are addressed in its specifications.
22	893	As previously noted it is recommended that postsynthesis material not be adopted as a new definition since it lack clarity and is not a conventional term used. From a scientific perspective, the synthesis is viewed as including all steps from the starting materials to the finished drug substance. It is recommended that either the definition of an intermediate be modified to encompass materials are being processed from free base/acid to the final salt/polymorph or a different term be selected for these materials related such as pre-drug substance where the term drug substance should be used to refer to the actual entity intended for use in humans (the chemical entity plus the final salt and/or polymorph form). Pre drug substance would be defined as having the exact chemical structure as the drug substance but is not yet in the correct salt or polymorph form and thus is not yet the "drug substance". In any event stereochemical identity would be required – i.e. a racemate is not the predrug substance or drug substance unless it will be developed as a racemate.
23	879	It is not clear from this sentence why it should be necessary to include

		validation information for control of adventitious agents in the CTD in section A2. Does this refer only to viral, DNA, etc. type agents or other things as well?
23	883	This sentence is very good and helps clarify how to approach for filing reprocessing and rework operations from a validation perspective.
30	1117	It is recommended that this provision not be implemented. It should be sufficient to if an impurity or solvent or metal is controlled at an earlier point in the synthesis and can not possibly be present in the drug substance that this information should be recorded at the processing step and not duplicated in finished drug substance specifications.
36	1263	If a test is not validated and is not part of the specification and data is being collected for informational purposes only the data should not be included with the batch record information.
42	1461	"is" should be "if"
48	1666	See Section 1 for comments

Sincerely,



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 Director, Regulatory Strategy and Intelligence,  
 Millennium Pharmaceuticals, Inc.