

UPS - Overnight



Berlex, Inc.

June 1, 2004

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Dockets Management Branch (HFA-305)  
U.S. Food and Drug Administration  
**Room 1061**  
5630 Fishers Lane  
Rockville, Maryland 20852

**Re: Docket No. 2003D-0571**  
**Draft Guidance for Industry on Drug Substance**  
**Chemistry, Manufacturing and Controls Information**

To Whom It May Concern:

Berlex, Inc. is a wholly owned US subsidiary of Schering AG of Berlin, Germany. Schering AG is a global, research-based pharmaceutical company that aims for leading positions in specialized markets worldwide. Our activities are focused on four business areas: Gynecology & Andrology, Diagnostics & Radiopharmaceuticals, Dermatology as well as Specialized Therapeutics for disabling diseases in the fields of the central nervous system, oncology and cardiovascular system.

Schering AG/Berlex Inc. has reviewed and are providing comments on the recently available "Draft Guidance for Industry entitled **Drug Substance - Chemistry, Manufacturing, and Controls Information**". We commend the Agency on announcing this draft guidance as it revises the "Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances - February 1987" and adopts the requirements of the CTD. In support and further improvement of the guidance, we are offering the comments in the manner described in the guidance by identifying the specific comment by the line number of the PDF version. We are providing comments by two categories; highest and high priority. The highest priority comments are concentrated on critical issues and the high priority comments are related to the complexity of the Manufacture and Documentation e.g. Flow diagram, Description of the

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Manufacturing Process and Process controls; Controls of Materials, Critical Steps and Intermediates; Characterization; Control of Drug Substance; Container Closure System. Documentation required is generally more detailed than described in the EU regulations.

In addition, we are providing the three general comments:

1. Attachment 1: Starting materials for synthetic drug substances

We recommend that this Attachment should be reviewed focussing on a risk and science based approach. From our perspective criteria for definition of Starting Material (SM) are defined in a very detailed manner that leads to a significantly increased regulatory burden. In a science based approach SM's should be defined at a step where these are fully characterized to ascertain suitability for the intended use. A more detailed analysis if the SM is properly defined should be conducted in a case to case assessment. Therefore a broad definition of the SM should be developed in accordance with the ICH-requirements (e.g. M4Q, Q7A)

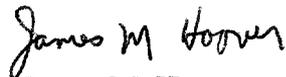
2. Attachment 1: Include pharmaceutical market. Our understanding is that the definition of further (non-science based) criteria (significant non-pharmaceutical market) shall secure a SM with a high quality being under Control by the market. We appreciate this approach and would suggest to also include SM's with a significant pharmaceutical market as these are even more under control (e.g. in terms of changes in the manufacturing process of a SM) and therefore also secure a safe SM.

3. We recommend adapting the requirements of semisynthetic drug substance to those of synthetic drug substance. A broad interpretation of the requirements regarding semisynthetic drug substances may cause problems in any synthesis in which - at any point - material of plant/biological origin has been used.

An electronic copy of this submission in "Word" will be sent to [cummingsd@cder.fda.gov](mailto:cummingsd@cder.fda.gov). as requested in the draft guidance.

Please contact me at (973) 487-2208 if you have any questions concerning our comments.

Sincerely,  
BERLEX, Inc.



James M. Hoover  
Director  
Drug Regulatory Affairs

**Comments on the  
Guidance for Industry on Drug Substance: Chemistry, Manufacturing, and Controls Information  
Draft Guidance - January 2004**

**Docket No. 2003D-0571**

**Berlex Inc./Schering AG**

**Guidance for Industry – Drug Substance [Docket No. 2003D-0571]  
Highest Priority Comments**

<b>Comment Number</b>	<b>Line # of PDF Document Section/Title</b>	<b>Comment/Recommendation for Revision</b>	<b>Comments regarding text</b>
1.	488 2. Description 1520-1528	Change ...“A statement should be provided...are not used in the same facility.”... to <i>A risk assessment to prevent BSE contamination should be provided.</i>	As the BSE risk is determined by the material, the process and the risk of cross contamination conducting a specific risk assessment in any case of animal origin material would ensure low BSE risk. Therefore, focussing on BSE countries only would not be sufficient.
2.	780-781  785-787 C. Control of Materials D. Controls of Critical Steps and Intermediates	Change...“Any experimental data...as well.” to <i>Justification should be based on experimental data.</i>  Change...“critical process...justification.” to <i>critical process controls values from batches should be provided as part of the justification, if necessary.</i>	Only representative batches can support the justification. Production process from earlier development stages may differ from the finalized process. See section IV.F. Development report .
3.	905-910 F. Manufacturing Process Development	Please clarify <u>primary stability batches</u>	Are these the batches for early stability testing in the clinical trial faces or are these initial ICH stability testing ?
4.	1059-1060 B. Impurities	...“Summary of the route of synthesis or method of preparation...”	This is not typical. Usually, proof of structure is provided and should be sufficient.
5.	434-435 1. Flow Diagram	Change...“each component“... to <i>main components of the mixture should be indicated in the flow diagram.</i>	Impurities are discussed in Chapter V.B. Main component would indicate e.g. those reflecting stereochemistry.

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6.	466-467 2. Description 630 3. Recovery	Delete this sentence..."Identification of manufacturing steps..."  Delete this sentence... "The use of recovered solvents ...of the manufacturing process."	This requirement indicates that we should distinguish between recovered and other solvents. As recovered solvents and auxiliary materials can be used according to their adequate specification we would recommend not to make this differentiation.
7.	471-472 2. Description	Delete this sentence..." Identification of processes..."	Due to the submitted ranges of in- and out-coming material of each manufacturing process there are different batch sizes which have to be combined according to production conditions. It is common understanding that all batches can be combined if these are in specification. (see ICH Q7A Chapter 8.4)
8.	611-616 Reworking	In general,...postapproval...	If the reworking is not a single event the application is updated.  It is not necessary to submit reworking which has been used only once in the life cycle of product. In case of unique reworking the procedure is part of the failure investigation which is not relevant for submission.
9.	630-636 Recovery	Delete this sentence..."The use of recovered solvents..."	The quality of virgin solvent or recovered solvent must be the same and appropriate for intended use. It is a general issue in ICH Q7A Chapter 14.4

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10.	1229 – 1230 C. Validation of Analytical Procedures	Change...“This information...for all analytical procedures...” to <i>This information should be provided for all non-pharmacopoeial, quantitative analytical procedures listed....</i>	Otherwise this could be interpreted that validation data need to be submitted for pharmacopoeial test procedures.
11.	1244 – 1246 D. Batch Analysis	Delete this part...“evaluate consistency in manufacturing.”	This leaves too much room for interpretation; in the worst case this could mean to deliver data from the very early phase of development; those data may have been gathered with completely different analytical methods which raises other questions such as the one for validation.
12.	1264 Batch Analysis Report	Change...“including tests that are not part...” to <i>including tests that were previously but are no longer part of the proposed specification.</i>	It is practically impossible to report any test procedures, which might have been tested, on a batch.
13.	1414-1418 <b>VIII. Container Closure System</b>	Change...“The suitability of the container Closure System...and referenced in S.6 .” to <i>if the container closure system is critical for protecting and assuring the quality of the active substance the choice of the primary and secondary packaging material should be justified.</i>	A description including specifications and detail of the materials of construction should be sufficient (see CTD EU requirements)
14.	1490 Stress Studies	Delete...“Any”	In early development orientating stress testing is performed. Only stress tests performed according to ICH Q1 are relevant for this section.
15.	1859-1867 C. Specification	Delete this part...Moreover, FDA recommend...	See Carryover: Higher impurity levels should be allowed as long as those are controlled during the synthesis and qualified on the drug substance level.

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16.	1924-1937 1945ff 2. Starting materials c. Carryover of Impurities  This applies also to lines 1777 to 1790	Delete this sentence and examples	Accept impurities in the API on an acceptable level even when they are derived from the starting material, as long as those are controlled during the synthesis and qualified on the drug substance level.  Compare also to chapter 3.2.S 2.4 of EU-CTD requirements (CPMP/QWP/130/96).

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17.	384 f <b>IV. Manufacture</b> A Manufactures	Delete...“Building numbers...”	Too much detail for Manufacturers.
18.	410 1. Flow Diagram	General: Flow diagram must be simple  Delete... “release testing”	This is not a production step.

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19.	417 1. Flow Diagram	Delete...“drug substance release testing”	This is not a production step. Therefore it is not necessary to indicate that as a single step in the flow diagram. Redundancy with Chapter VI
20.	425 1. Flow Diagram	Delete...“auxiliary materials”...	Redundancy with B. Description of Manufacturing Process and Process Controls
21.	426 1. Flow Diagram	Delete...“critical process control”...	Please clarify <u>critical process control</u> and the points at which they are conducted. It is not a requirement in the EU CTD. CPMP/QWP/130/96 <Guideline on Chemistry of the New Active Substance> Redundancy with Chapter IV.B.2
22.	443, 457 2. Description of the Manufacturing Process and Process controls  521-522 2. Description	Change ...“all process controls”... to <i>operating parameters and process tests</i>  Delete ...”and the associated numeric ranges, limits, or acceptance criteria... Furthermore, any process controls...highlighted.”  Change ..”All process controls...should be included in the description of the manufacturing”... to <i>operating parameters and process tests</i> .	It is not necessary to describe the intermediate test, postsynthesis material test, unfinished drug substance tests and the associated numeric ranges, limits or acceptance criteria, because all this is described in chapter IV.D. (according CTD requirements)
23.	459 2. Description	Delete this sentence “Type...(e.g. HPLC) used for each process test...”	The full description of in-process material tests is given in Chapter IV.D. that includes process tests, which are critical.

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24.	508 f Process Controls	Operating parameters...(e.g. temperature...)  General Comment: Please replace process test by process monitoring	It is not reasonable to include <u>all</u> operating parameters, in particular for automated facilities. It should be limited to critical operating parameters among all process controls, only critical controls should be described (see also comment No. 443-445)  Clearly differentiation from process controls (all tests within the synthesis)
25.	538-543 2. Description	Delete this section..."All of the operating parameters..."	Redundancy with IV.B. It is not necessary to describe the intermediate test, postsynthesis material test, unfinished drug substance tests and the associated numeric ranges, limits or acceptance criteria, because all this is described in chapter IV.D.
26.	578-579 Reprocessing  605-607 Reworking	Delete this sentence..."Repetition of multiple reactions..."	This is in contradiction to the ICH Q7A. It is no differentiation between single or multiple reaction steps or unique or repeated use.
27.	637 Recovery	Change..."Appropriate specifications for"... to <i>Appropriate for solvents are included in S.2.3</i>	The specification must be valid for both types of solvents.

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28.	769-777 D. Controls of Critical Steps and Intermediates	Delete this section...“or unfinished drug substance“...	Only critical process controls and associated ranges/ limits should be listed in the beginning of the justification.
		Please clarify differentiation between “intermediates” and “Critical (key) intermediates”	Compare to Chapter 3.2.S 2.4 of EU-CTD requirements
	780	Delete this part...“and a brief description of the test provided.“	The name of the process control should be sufficient.
29.	818 Intermediates	Delete “assay”	Assay testing is not always feasible and/or necessary
30.	986		If there are no other solid state forms there is no need for further stability studies and therefore no requirement for a summary report. Does this apply also for APIs used in liquid dosage forms (e.g. as solutions) ?
	988 Biological and Other Relevant Characteristics	Change to: ...“A summary of these investigations should be included, if applicable”.	A summary should be dispensable in case that no interconversion was observed during stability studies.

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31.	1008-1016 1031-1035 1037-1040 <b>V. Characterization</b> B. Impurities	Revise the total chapter B Impurities to the focus on related substances.	This chapter should focus on two types of related substances (organic impurities): potential and actual found impurities. The other types of impurities (e.g. inorganic, residual solvent) are discussed in the chapter VI.E. according to ICH Q6A.
32.	1063 B. Impurities	Change...a table listing the “qualified level of expected impurities“... to qualified level of actual impurities	Delete expected: replace by “actual“ according CPMP/QWP/130/96 page 9
33.	1219 – 1220 B. Analytical Procedures	Delete...“another country’s compendium“...	These are also official compendia as described before.
34.	1241, 1246 D. Batch Analyses	Change...“(e.g., tables, certificates ...)” to Batch analysis data, Delete „reports“	It should be left to the discretion of the applicant in which format he submits the data.
35.	1254 <b>VI. Control of Drug Substance</b> D. Batch Analyses	Delete “Manufacturing process...applicable.”	Redundancy to the development report IV.F.
36.	1261 – 1278 Batch Analysis Report	The two chapters “Batch Analysis Reports“ and „Collated Batch Analysis Data“ should be united under the header „Batch Analysis Data“; the word „report“ should be avoided.	The term report may be misunderstood; as indicated previously in the text this may also be a CoA and not necessarily a formal working report .

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37.	1267 – 1276 Batch Analysis Report	Delete the paragraph, add the sentence: A summary of any critical changes in the analytical procedures should be provided in chapter S.4.2.	Analytical Development is described in S.4.2; the CTD format foresees the submission of an Analytical Development Report, which covers the issues addressed in this paragraph. See also EU CTD (CPMP/QWP/130/96).
38.	1310 – 1311 E. Justification of Specification Tests	Delete...“one that was reported in the batch analyses“; add separate sentence: „It may also be appropriate to justify exclusion of tests reported in the batch analyses (S.4.4).“	As it is the text conveys that exclusion of any test performed on a clinical or toxicological batch would have to be justified. Such a request is deemed too strict.
39.	1429 – 1434 <b>IX. Stability</b> A. Stability Summary and Conclusions and 1442 – 1447 C. Stability Data	Please include a note that the requirements of chapters A. and C. may be provided together, e.g. in a report.	Often applicants provide actual stability data and the conclusion drawn from them together in one report. It should be made clear that this practice is acceptable.
40.	1465 – 1474 Primary Stability Studies	Start the paragraph with: „If the analytical procedure listed in the stability protocol is different from the analytical procedure describe in S.4 a summary of any changes ...“	The paragraph should only be valid for cases where the analytical procedure applied for the stability studies is different from those described in S.4.
41.	1646 ff <b>XI. Regional Information</b> C. Methods Validation Package	Please revise chapter	Redundancies between R.3.S and S.4.3 should be avoided. Therefore only additional requirements should be clearly specified here.

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42.	1670 <b>Attachment 1</b> Starting materials for synthetic drug substances	Please add ...molecular structure that “significantly” contributes.	For Clarification
43.	1671 Attachment 1	Change...“(e.g. hydride ion)” in (e.g. hydrogen atom)  Change “element” to fragment	Correction  Same wording as in ICH Q7A
44.	1683-1685 Attachment 1	Please cancel this sentence. ...”A drug substance that is used to synthesize another drug substance...”	This sentence is not consistent with the selection principles of this Attachment.
45.	1742-1743 <b>I. Selection Principles</b> A. Propinquity  1743	Change...”final intermediate by “several reaction steps” to <i>final intermediate by reaction steps</i>  Delete “purified” and change to <i>well characterized or defined</i>	Delete several, because it is much more rigid approach than in the EU.  Intermediates are not necessarily a purified step
46.	1744-1748; 1773 A. Propinquity	Please delete “identity” to <i>manufacturing steps prior to the starting material would adversely the quality, purity, or potency</i>	Scientifically unlikely that there is a risk in change of identity.

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47.	1768,1770 B. Isolated and Purified	Change..."a chemical proposed as a starting material should be "isolated and purified substance" in to <i>well characterized to ascertain suitability for the intended use.</i>	Harmonization with ICH Q7A. There is no need for purification and isolation because it is only relevant to understand the influence of the SM on the API quality.
48.	1777-1778 1784ff C. Carryover of Impurities	Change requirements to accept Impurities as long as those are qualified on the drug substance level	Scientific approach Relevant is the question if an impurity is known, fully controlled and toxicologically qualified on the API level. It is not relevant if the SM of another process step is the origin of the impurity. Purification sequence is part of the synthesis. Process should be developed and optimized in order to guarantee adequate purification.
49.	1792-1797 C. Carryover of Impurities	Change to: "statement regarding absence of TSE agents in the API"	With a statement there is now need to define the starting material at or before the point where TSE agents can be introduced into the process.
50.	1799 ff D. Complexity of Structure	Delete requirements regarding Complexity	Modern techniques are capable of characterizing complex structures, hence the complexity of the structure should not be an issue. The use of advanced analytical techniques should be allowed and supported in order to confirm structure and quality (see also ICH Q3A and Q6A).
51.	1812, 1968 D. Complexity of Structure	Please add ...identification tests (e.g. ultraviolet-visible,... optical rotation)...	Optical rotation is a typical method used additionally for identity testing.

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52.	1816 D. Complexity of Structure	Delete... “chiral HPLC”	Chiral HPLC is a standard analytical method. (chiral chromatography in general)
53.	1816 D. Complexity of Structure	Delete... “mass spectrometry”	MS coupled with chromatography is a standard analytical method for the differentiation of analogs.
54.	1827 <b>II Documentation</b> A. List of proposed Starting Materials	Please add “if available” after the CAS Registry Number.	CAS Registry Number for starting material is not always available.
55.	1833-1837 <b>II Documentation</b> B. Flow Diagram of the complete Synthesis	Change ...the complete route of synthesis “of the drug substance” to <i>complete route of synthetic route to the proposed starting material of the drug substance</i> Delete 2 <sup>nd</sup> sentence	Complexity of the flow diagram
56.	1852-1853 C. Specification	Please add “...if applicable”	Counter ion testing is unnecessary for many organic substances
57.	2142 <b>Glossary</b> Final intermediate	Change...chemical reaction “that produces the molecule or ion”...to <i>that produces the chemical entity or ion</i>	The last chemical step does not necessarily lead to the desired physiological or pharmaceutical properties. It could be for e.g. stability, applicability, solubility, etc. reasons.
58.	2145 Glossary Final intermediate	Delete the bracket “(including a salt with hydrogen or coordination bonds)”	