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

Re: [Docket No. 99D-0674] INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products; Chemistry, Manufacturing, and Controls Content and Format. (Published in Federal Register: April 21, 1999)

Dear Madam or Sir:

Eli Lilly and Company is pleased to have the opportunity to provide comments on the Draft Guidance for Industry on INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products; Chemistry, Manufacturing, and Controls Content and Format.

We commend FDA's efforts to address the comments raised by industry in response to the initial draft guidance (12/97). However, we believe that the information required by the guidance for phase 3/pivotal studies is more appropriately provided in the NDA/BLA. We suggest that information submitted to the IND should focus on the safety of material, regardless of the phase of clinical studies.

Attached please find our comments on the draft guidance. The attachment includes general comments as well as comments about specific sections in the guidance where Lilly has concerns about the information required. We hope that these comments will result in revisions in the guidance to keep the focus of IND information on safety.

Please feel free to contact me at (317) 276-0368 for clarification of any comments.

Sincerely,

Tobias Massa

Tobias Massa, Ph.D.
Director, Global Regulatory Affairs
Chemistry Manufacturing and Control

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99D-0674

General Comments:

1. Submitting NDA-level CMC information during phase 3 would require a change in the way sponsors develop drugs. Under current practices, much of the data requested for phase 3 is not available until late in phase 3 or just prior to submission. Requiring this information in phase 3 is not consistent with the Agency's goal of facilitating drug discovery and development and expediting the entry of new drugs into the marketplace.

The supplementary data and information required at phase 3/pivotal studies is the level of information expected at the NDA/BLA. Submitting this level of information during phase 3/pivotal studies increases the regulatory burden on industry.

Normally, sponsors do not invest in commercial development until there is evidence that the project may lead to a successful NDA. This evidence is often not available until the end of phase 2. To expedite development, the sponsor may initiate phase 3 studies with drug substance and drug product made by an earlier manufacturing process. Commercial material may either be introduced later in phase 3 studies or be qualified with bioequivalence studies. Sponsors do not wish to duplicate efforts by developing and submitting full CMC data for both the material used to start phase 3 studies and the commercial material. Therefore, the phase 3 data requested would likely not be available for the commercial material until late in the trial, or just prior to submission of the marketing application.

Lilly believes that the CMC information submitted in support of clinical trials <u>should be focused on safety</u> of the clinical trial material. Submitting NDA-level CMC data during phase 3 places an extra and unnecessary burden on the sponsors. There is no clear safety benefit to be gained by submitting this information to an IND in late phase 3.

2. Submitting NDA-level CMC information during phase 3 would require the Agency to review additional information that is not relevant to the commercial process. It is unclear how the Agency intends to use the supplementary data and information requested for phase 3.

If sponsors submit the supplementary data and information requested during phase 3/pivotal studies, the Agency will have the burden of reviewing the additional information in both the phase 3 IND and the NDA. Because changes in the detailed CMC information will likely occur as the process is refined or scaled up, the first review during phase 3 will be of information that may not be relevant to the commercial process.

Because the supplementary data and information required may be generated and submitted during phase 3/pivotal studies, this information is apparently not necessary to evaluate the safety of patients entering phase 3 trials. Therefore, it is unclear why this information should be submitted during the phase 3 trials in addition to the NDA/BLA.

Lilly believes that information that impacts the safety of the product in clinical trials should be submitted to the IND, and that the supplementary information should be submitted in the NDA/BLA.

3. The guidance is unclear about when information is required during phase 3.

The guidance specifies that "safety updates" should be submitted during IND clinical trials as information amendments, and that the information that is not related to safety should be submitted as summary annual reports. There is not a clear definition of "safety updates." A broad definition of this term is not consistent with the goals of facilitating drug discovery and development and expediting the entry of new drugs into the marketplace.

The guidance also states that the supplementary data and information specified for phase 3/pivotal studies need not be submitted until the initiation of phase 3 studies, and may be submitted as they are generated during phase 3. This statement is open for differences in interpretation, and may be applied differently among sponsors and among chemistry review divisions. Clarification is needed as to when this information is required.

Lilly believes that sponsors should submit data and information that may impact patient safety as information amendments to the IND. The supplementary data and information should be submitted in the NDA/BLA.

4. Considering current industry practice, the guidance does not provide regulatory relief for sponsors by avoiding redundant submissions of data and information.

It is not our current practice to submit CMC information amendments at the initiation phase 2 or phase 3 studies, nor to resubmit data and information already submitted to an IND. Instead, information amendments are compiled as changes are made to the manufacturing or control methods, and the amendments are submitted prior to using materials impacted by these changes in clinical trials. Additionally, the sponsor may summarize the progress of CMC development in briefing documents submitted prior to end of phase 2 and other CMC meetings with the Agency.

Lilly believes that it is a more efficient use of industry and FDA resources to submit any CMC information that may impact patient safety at any point during drug development instead of at clinical milestones. Continuing to tie CMC requirements to phases of clinical development does not provide regulatory relief.

Specific Comments

Line	Issue or Guidance Text	Change to	Rationale and References
II. BACKGROUND			
80-84	The information specified in the phase 3/pivotal study section can be submitted as summary annual reports if the changes do not affect safety.	Information that does not affect safety of clinical trial materials may be deferred until the NDA.	The information in the IND should focus on safety.
III. PHASE 2 **A. Drug Substance**			
130 – 134	The structure of the starting materials and information to support the classification of a compound as a starting material should be provided. The source, methods, and test results of the starting materials should be available upon request.	The structure of the starting materials should be provided.	Providing information about classification of starting materials prior to phase 2 is an unnecessary burden. The process is still under development and starting materials for the commercial process may not be defined or finalized.
149-151	When feasible, the flow diagram for the synthesis should contain the chemical structures and configurations, including stereochemical information of the starting materials, intermediates (in situ or isolated), and significant side products.	The flow diagram should contain the chemical structures of the starting materials and intermediates.	The side products may not have been identified or characterized at this stage of development. The definition of "significant" side products is not clear.
152 - 153	Equipment used in each step should be identified.	Delete	The specific equipment used should be specified in the NDA.
180-194	Specification		A clarification that this section applies to the drug substance (not intermediates) should be added.
193-194	Test results, analytical data, and certificates of analysis of clinical trial material prepared since the filing of the original IND should be provided.	Test results, analytical data, or release data for representative lots of drug substance should be provided. Data for lots previously submitted need not be repeated.	Specifying test results, analytical data, <u>and</u> COA seems redundant. The sponsor should present the data in a concise format. The sponsor should be allowed to submit data for representative lots, instead of every lot of clinical trial material.
198-200	Changes in the container closure system should be provided.	A brief description of the container closures system should be provided.	The phase 1 guideline does not specify that information about the container closure system should be provided.

III. PHASE 2 B. Drug Product			
Line	**Issue or Guidance Text**	**Change to**	**Rationale and References**
233	Quantitative composition per unit of use should be provided (e.g., mg/tablet or mL).	Quantitative composition per unit dose should be provided (e.g., mg/tablet or mL).	The use of the term "unit of use" is not consistent with the use of the term in the USP. The USP refers to unit of use container as a specific quantity of a drug product that is intended to be dispensed as such without further modification except for the addition of appropriate labeling.
235-237	The formulation for certain drug products delivered by devices should be similar to that intended for the marketed drug product.	Reference the appropriate guideline for information about drug formulation for devices.	This guidance specifies the content and format of the IND. Guidance about formulation requirements in pivotal clinical trials belongs in a separate document.
247-249	Information for excipients not included in previously approved drug products should be equivalent to that submitted for new drug substances.	Delete sentence.	This amount of information is excessive for phase 2 trials. The emphasis for new excipients should be on safety and not complete physico-chemical characterization. The purity/impurity profile of excipients can be indirectly controlled by the overall specifications of the drug product. Requiring this information for new excipients will discourage sponsors from developing new excipients.
286-287	Data updates on the degradation profile should be provided so safety assessments can be made. A summary table of the test results, analytical data (e.g., chromatogram), and COA for lots of the drug product used in clinical studies should be provided.	A summary table of the test results, analytical data or release data for representative lots of drug product should be provided. Data for lots previously submitted need not be repeated.	It is not a current practice for all sponsors to submit chromatograms for the Agency to assess the safety of each lot. This would be an added burden. Instead, the sponsor should submit tabular data for representative lots.
304	Stress testing on the drug product should be conducted.	Delete sentence.	Routinely performing stress testing and photostability studies in phase 2 does not add value because the drug product is normally an interim formulation, not the final commercial formulation. Testing representative batches on stability studies throughout the use of the material in CTs should be sufficient to demonstrate product stability.

IV. PHASE 3 A. Drug Substance			
Line	**Issue or Guidance Text**	**Change to**	**Rationale and References**
320-328	Guidance specifies that a complete description of the physical, chemical, and biological characteristics of the drug substance should be provided.	Updates to the information provided previously should be provided.	The level of information specified in the guidance is appropriate for an NDA, but not for the initiation of phase 3 study. Some of the specified elements (e.g., particle size and surface area) are still being refined during phase 3. These data may be reported in representative batch data, but not as drug substance characterization.
334-335	For peptides and proteins, characterization should include data on the post-translational modifications (e.g. glycosylation, gamma carboxylation).	For peptides and proteins, characterization relevant to activity should be provided.	The appropriate characterization depends on the drug substance. The examples given may not be relevant to toxicity or activity.
345-347	Acceptance criteria and analytical procedures for assessing the quality of starting materials should be provided.	The structure of the starting materials should be provided.	The additional information about starting materials is appropriate for an NDA. The sponsor may discuss starting materials during end of phase 2 meetings with the Agency.
347-350	A table listing all reagents, solvents, and catalysts should be submitted that includes (1) the grade of each material used, (2) the specific identity test performed, (3) the minimum acceptable purity level, and (4) the step of the synthesis and manufacturing process in which it is used.	A list of all reagents, solvents, and catalysts should be submitted.	The information required in points (1) through (3) is appropriate for an NDA, but an added unnecessary burden during phase 3. This information may change during scale up at the final manufacturing site.
364	Relevant information should indicate the type of reaction vessel	Delete	This information is appropriate for the NDA, not the phase 3 IND.
366 and 376	Relevant information should indicate…in process controls (compete description of the analytical procedures) And The description of the analytical procedures should be brief and appropriate validation information should be available on request	Provide a summary of in process controls, including a brief description of the analytical procedures. A complete description of the methods and appropriate validation information should be available upon request.	Lines 366 and 376 are contradictory in that line 366 requests a complete description of analytical procedures while line 376 states that the description should be brief. It is an excessive burden to require a complete description of the methods and validation at phase 3. Note that the 1987 FDA Guideline on content and format of an NDA does not require submission of analytical procedures for in-process assays. Therefore, requesting this information in the phase 3 IND represents an increase in the data required.

Line	Issue or Guidance Text	Change to	Rationale and References
367-369	For specified biotechnology-derived products, validation of the genetic stability of the cells in production, with defined passage limits, should be performed.	Delete.	While preliminary genetic stability data are usually collected early in the development program, the final genetic stability data for registration are generally gathered when the final bioreactor conditions are fully locked. The genetic stability data (and extension of the cell culture time/passage limits if warranted) should be submitted in the registration package, not the IND. ICH Q5B is a requirement for marketed products, and compliance is not required in phase 3 studies.
371-372	Controls at selected stages in the synthesis or manufacturing process to ensure reaction completion, identity, and purity or proper cell growth should be described.		A description of the control strategy is appropriate for the NDA, but not the phase 3 IND. The control strategy may change during scale-up, so information submitted during phase 3 may not apply to the commercial process.
372-374	The acceptance criteria and analytical procedures should be described for isolated intermediates that require control.	The acceptance criteria and analytical procedures should be <u>available</u> for isolated intermediates that require control	This paragraph requires submission of more detail than we currently furnish pre-NDA. Committing to in-process acceptance criteria in phase 3 may limit the sponsor's ability to develop a fully optimum process. It does not add value to furnish these if they are still under development.
386-390	The analytical procedures and calibration results for the working standard against the primary reference material should be provided. Additional analytical procedures used to characterize the working standard and the primary reference material should be updated.	If available, calibration results for the working standard against the primary reference standard should be provided.	The analytical procedures for the reference standards may not be necessary to assure safety during the IND phase. A working standard may not be established until submission.
395	Specification		A clarification that this section applies to the drug substance (not intermediates) should be added.
400-406	A complete description of the non-USP analytical procedures with appropriate validation information should be provided.	Clarify	Clarify that validation is being completed during phase 3, and ICH-level of validation is not expected at the initiation of phase 3. The referenced guideline is for NDAs, and should not be applied to phase 3 submissions. Validation needs to occur with the final material, and since the process and assays may change during phase 3, ICH-level validation is not appropriate.

Line	Issue or Guidance Text	Change to	Rationale and References
408-409	Impurities should be identified, qualified, and quantified, as appropriate. Suitable limits based on manufacturing experience should be established.	Information about impurities should be provided if available. Suitable limits based on safety, manufacturing capability, stability, and analytical capability should be established as information becomes available.	The information is not usually completed or ready to be fully reported until the time of NDA submission. This is because sponsors do not invest in identifying and quantifying impurities until the product has a reasonable probability of success. Also, impurities may not be evident until 6-12 months of stability data are available for the commercial drug substance. Limits for phase 3 material time should be based primarily on patient safety requirements and manufacturing capability. Limits cannot be set according to manufacturing experience alone, since full-scale manufacturing experience is generally limited during phase 3.
409-411	Suitable microbial limits should be established for nonsterile products and changes in previously reported limits should be reported.	If appropriate, suitable microbial limits should be established for nonsterile products and changes in previously reported limits should be reported.	According to ICH Q6A, not all non-sterile drug substances require testing for microbial quality attributes. No routine microbial limit is necessary if the drug substance does not support microbial growth. Also, clarify that these limits should take into account the limited production history, and they are not expected to reflect final limits. Final limits will be developed when more extensive full-scale manufacturing data are available.
413-415	A summary table of updated test results, analytical data and COAs for the lots of the drug substance used in clinical trials should be provided.	A summary table of test results, analytical data, or release data for representative lots of drug substance not previously reported should be provided.	Specifying test results, analytical data, and COA seems redundant. The sponsor should present the data in a concise format. The sponsor should be allowed to submit data for representative lots, instead of every lot of clinical trial material.
419-420	The container closure system used to transport and/or store the bulk drug substance should be described in detail.	Clarify	What detail does the Agency request? The sponsor proposes a brief summary including the type of container closure system and the materials used.
425-431	Stress studies should be conducted to demonstrate the inherent stability of the drug substance, potential degradation pathways and the capability and suitability of the proposed analytical procedures.	Clarify that the information should be reported in the NDA, not the phase 3 IND.	The sponsor would normally generate this stress study data for the commercial material during the phase 3 studies, and submit a complete report at the time of the NDA.

Line	Issue or Guidance Text	Change to	Rationale and References
438-439	Each table should contain data from only one storage condition.	Delete	The value of adding pages for separate storage conditions is unclear. This will add pages unnecessarily.
439	Individual data points for each test should be reported.	Delete	The value of reporting replicates for each test is unclear.
440	Representative chromatograms and spectra should be provided, when applicable.	Delete	Reporting of chromatograms as part of stability testing is redundant of the information/data provided in the stability tables.
IV. PHASE 3 **B. Drug Product**			
457-458	The sponsor should provide updated information regarding the components, composition, and batch formula for phases 1 and 2.	The sponsor should provide updated information regarding the components, composition, and batch formula.	New information about composition and formulation should be submitted as safety updates prior to introducing the new material into clinical trials. It should not be necessary to resubmit this information at the beginning of phase 3.
460-462	The formulation for certain drug products delivered by devices should be similar to that intended for the marketed drug product.	Reference the appropriate guideline for information about formulation for devices.	This guideline specifies the content and format of the IND. Guidance about formulation requirements in pivotal clinical trials belongs in a separate guideline.
485-486	A general step-by-step description of the manufacturing method for a unit dose should be provided, including key equipment employed.	Updates in the manufacturing method should be provided.	Information about specific equipment and a step-by-step description of the manufacturing process should not be required. This information will be submitted in the NDA, but the value of submitting it in phase 3 is unclear. The specific equipment will likely change during scale-up and site changes, so information submitted in phase 3 may not apply to the commercial process.
489-490	In planning the clinical trial batch size, the sponsor should consider the post-approval production scale.	Clarify the intent of the statement.	The purpose of the statement is not clear. Is the Agency implying that phase 3 material should be manufactured at >10% scale?
508-509	A full description of the non-USP analytical procedures with appropriate validation information should be provided.	Clarify	Clarify that validation is being completed during phase 3, and ICH-level of validation is not expected at the initiation of phase 3. Validation needs to occur with the final material, and since the process and assays may change during phase 3, ICH-level validation is not appropriate.

Line	Issue or Guidance Text	Change to	Rationale and References
510-511	Degradation products should be identified and qualified.	Delete	Degradation products would be identified and qualified by the time we submit the NDA/BLA application, not at initiation of phase 3.
532-535	Stress studies should be conducted.	Clarify that the results of any stress studies should be reported in the NDA, not the IND.	Stress testing for the drug product cannot start until the final commercial form is identified. Often, this is well into phase 3 studies. Therefore, this information is more appropriately provided in the NDA.
548	Each table should contain data from only one storage condition.	Delete	The value of adding pages for separate storage conditions is unclear. This will add pages unnecessarily.
549	Individual data points for each test should be reported.	Delete	The value of reporting replicates for each test is unclear.
549-550	Representative chromatograms and spectra should be provided, when applicable.	Delete	Reporting of chromatograms as part of stability testing is redundant of the information/data provided in the stability tables.
558-562	For sterile products, the sponsor should consider the development of a container closure challenge test for future stability protocols.	For sterile products, the sponsor may develop a container closure challenge test to use in lieu of sterility testing in future stability protocols.	The FDA guidance, Container and Closure Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products provides the option for using the container closure challenge test, but does not require it.