

12 April 2006

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

Attention: Monica Caphart (CDER)
Christopher Joneckis (CBER)

**RE: Comments to the FDA's Guidance for Industry on INDs – Approaches to
Complying with cGMP During Phase 1. Docket Number 2005D- 0286**

Dear Ms. Monica Caphart and Dr. Christopher Joneckis:

ISPE (International Society for Pharmaceutical Engineering) has taken the opportunity to comment on the subject FDA Guidance. We have had our Clinical Materials Community of Practice look at the Guidance.

The following are recommendations based on our review of FDA's draft guidance for industry on the approach to complying with cGMP in phase 1 issued in the Federal Register on 17 January 2006, Volume 71, Number 10. We appreciate the opportunity to contribute to such an important document.

The guidance is well received as it delivers long sought after recommendations for complying with cGMP in clinical material manufacturing. It is recommended that you consider preparing similar guidance for clinical phases 2 and 3.

More specifically the following notes are suggestions and recommendations from a collective review of the document.

- Page 1, line 25: Recommend that document clarify whether the 1991 Guideline on the Preparation of Investigational New Drug Products (Human and Animal) will be replaced in its entirety by this guidance and future unwritten guidances for phase 2 and 3, or will this new guidance replace the 1991 Guideline only for phase 1 studies? This is not clear as written in this section.
- Page 4, line 113 speaks to drug substances. Please consider that biologic drug substances differ from small molecule drug substance, and as such, this line could be clarified as to the meaning of drug substance.
- Page 5, line 183 refers to cleaning burden. Is there specific guidance as to cleaning being verified and not necessarily validated at this phase?
- Page 5, line 184 refers to equipment qualification but in line 170 adequate control is stated. Please clarify as to the requirement for equipment qualification versus procedural control with appropriate calibration and maintenance.
- Page 5, line 200 speaks to adventitious virus, however, the document does not speak to viral segregation with regard to biologic manufacturing and the separation of downstream purification post virus inactivation for enveloped viruses. It may be worth

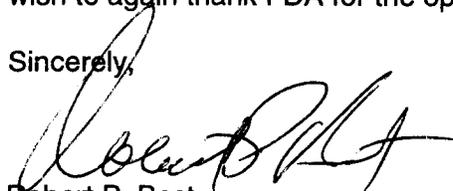
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- noting whether this sub-processes need to be segregated at this phase or could they occur in the same area.
- Page 6, line 231: We would recommend adding the prefix “pre” to the word defined in this sentence.
 - Page 6, line 234-238: We would recommend moving the fourth bullet above the third bullet and including in that third bullet that all unexpected events are concluded as to product impact prior to release.
 - Page 8, line 296: A reference here to drug substance could also use a reference to section VI.C with specifics to biologics. ID only for a biologic drug substance may not be sufficient, and appropriate viral testing may also be considered at this stage.
 - Page 9, line 347: We would recommend adding that the storage of stability samples be in the same or equivalent material as the primary packaging.
 - Page 9, 365: The industry norm for recall in clinical trials is “clinical stock recovery”; we would recommend using this terminology.
 - Page 10, line 390: Reference 5 is missing.
 - Page 11, line 454 refers to biologic manufacturing requiring qualified equipment; however, earlier it is stated that procedural control is acceptable. Please clarify if equipment is expected to be qualified for both small molecules and biologics.
 - Page 12, line 471 speaks to cleaning verification for adventitious virus removal; however, this may prove to be very difficult. Perhaps testing for the presence of virus post cleaning may be more appropriate.
 - Page 12, line 498-501: "When producing multiple batches of the same investigation product, we recommend that producers periodically conduct and document internal performance reviews... (to) ...assess the control and consistency of the production process and overall product quality." Is this an expectation for Biological and Biotechnological Products only? It only appears in this section.
 - Recommend that the terms used to refer to drug products used in clinical trials be consolidated as much as possible. In this document, those materials are referred to as: investigational new drugs; investigational drugs; IND; investigational new drug products; investigational drug products; investigational new human drug and biological products; clinical supplies, and in the EU, investigational medicinal products.
 - Recommend that the document clarify which recommendations in Section V also pertain to the Special Production Situations in Section VI.

These recommendations are based on a cross-functional review. I and the ISPE review team wish to again thank FDA for the opportunity to contribute to such an important document.

Sincerely,



Robert P. Best
President and CEO