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FDA Rule and Companion Guidance Regarding Manufacturing of Phase 1 Investigational Products

In July 2008, the Food and Drug Administration (FDA) amended the current good manufacturing practice (CGMP) regulations to exempt most phase 1 investigational drugs from complying with the regulatory CGMP (21CFR part 211) requirements (http://www.fda.gov/OHRMS/DOCKETS/98fr/oc07114.pdf). The amendment applies to small-molecule drugs and biologics, including vaccines and gene therapy products. However, the exemption does not apply to an investigational drug for use in a phase 1 study once the investigational drug has been made available for use by or for the sponsor in phase 2 or phase 3 trials, or the drug has been lawfully marketed.
At the same time FDA has published a companion guidance document that provides recommendations on applying CGMP that is appropriate and meaningful for the manufacture of the earliest stage investigational drug products intended for use in phase 1 clinical trials while ensuring safety and quality (http://www.fda.gov/cder/guidance/GMP%20Phase1IND61608.pdf). The recommendations and expectations contained in this new guidance utilize an approach to CGMP similar to that outlined in ICH Q7A (http://www.fda.gov/CDER/guidance/4286fnl.pdf) where it addresses the manufacture of drug substances for use in clinical trials.

Additional insight into FDA's thinking has been published in the Final Rule in which FDA announced these changes and discusses the comments it received from our industry (http://www.fda.gov/OHRMS/DOCKETS/98fr/oc07114.pdf).

This and other FDA initiatives stem from the 2002 congressional mandate (from PDUFA III) that FDA adopt a risk-based approach in interpreting and implementing CGMP that was consistent with good scientific methodology. Accordingly, FDA recognizes that certain CGMP requirements were directed at the commercial manufacture of products typically characterized by large, repetitive, commercial batch production, which may not be appropriate to the manufacture of most investigational drugs used for a phase 1 clinical trial. For example, requirements for fully validated manufacturing processes, rotation of stock for drug product containers, repackaging and relabeling of drug products, separate packaging and production areas are generally not concerns for limited production investigational drug products used in Phase 1 clinical trials.

The new guidance conveys that adherence to CGMP during manufacture of phase 1 investigational drugs occurs mostly through well-defined written procedures, adequately controlled equipment and manufacturing environment and accurately and consistently recorded data from manufacturing (including testing).

With regard to an appropriate manufacturing environment for phase 1 investigational drugs FDA expects us to "eliminate or mitigate potential hazards to safeguard the quality of the phase 1 investigational drug" and goes on to provide some basic considerations to meet this goal.

The guidance emphasizes the importance of the role played by the "QC function" (QA and/or QC groups) and recommends that every manufacturer establish a written plan that describes the roles and responsibilities for QC functions. FDA goes on to say "Although quality is the responsibility of all personnel involved in manufacturing, we recommend that you assign an individual(s) to perform QC functions independent of manufacturing responsibilities, especially for the cumulative review and release of phase 1 investigational drug batches." It does allow (under limited circumstances) the same individual who performed production to also release or reject the batch. However, in such circumstances, FDA strongly recommends that another qualified individual not involved in the manufacturing operation conduct an additional *periodic* review of manufacturing records and other QC activities.

The risk-based approach advocated by FDA is evident when, in lieu of process validation they state "You should have in place appropriate equipment and controls in manufacturing to ensure that unit operations with safety-related functions (e.g., viral clearance, virus/toxin attenuation, pasteurization) perform their function with a high degree of assurance."

Historically, through the IND process, FDA has reviewed the manufacture and testing of new investigational drugs on a case-by-case basis and to many of us these changes are not necessarily news. However this new guidance provides a concise overview of the minimal requirements for written SOPs, production records, facilities, equipment, in-process controls, final release testing and an independent QA/QC group which help take some of the guess work out of the early stages of drug development. FDA points out that it does not diminish sponsor's responsibility to ensure that the phase 1 investigational drug meets appropriate standards of safety, identity, strength, quality, and purity.