Regulatory Agency Relations

Merck & Co., Inc
Two Bethesda Metro Center
Suite 700
Bethesda MD 20814
Tel 301 941 1400
Fax 301 941 1406

0596 '03 FEB 14 P1:59

February 14, 2003

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

RE: Docket No. 02N-0516
Agency Information Collection Activities; Proposed Collection; Comment Request; Request for Samples and Protocols

Merck & Co., Inc, is a leading worldwide, human health product company that has produced many of the most important pharmaceutical products on the market today. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment. It is incumbent upon regulators and upon industry to see that important therapeutic breakthroughs reach patients without unnecessary or unusual regulatory delays.

Merck's extensive experience in vaccine development has provided its scientists and regulatory affairs professionals with an important understanding of the laws and regulations governing biologics. Therefore, Merck is well qualified to respond to this request for input regarding information collection requirements relating to lot release samples and protocols (21 CFR 610.2) and whether the collection of information is necessary for the proper performance of FDA's functions, whether the information collected has practical utility, ways to enhance the quality, utility, and clarity of information, and ways to minimize the burden on respondents.

A similar comment was presented by PhRMA to the HHS Secretary's Advisory Committee on Regulatory Reform on February 13, 2002, and by Merck to the Food and Drug Administration on April 9, 2002, as submitted to Docket No. 01N-0587, and is repeated here for emphasis.

Per 21 CFR 610.2(a), CBER may require samples of any lot of any licensed product, together with the protocols showing results of applicable tests, to be submitted to CBER and the manufacturer may not distribute a lot of a product until the lot is released by CBER. CBER has interpreted this statement as a requirement for most products.

Merck recommends that CBER modernize the requirements for batch certification. Requirements for lot release should reflect the current state of technology within the many types of biologics. Advances in product characterization and biotechnology have progressed to a point where manufacturers should not be subjected to prolonged periods where CBER lot release is routinely required. When a manufacturer has demonstrated the ability to consistently product acceptable lots and has procedures in place that prevent the release of lots that do not meet release specifications, it is no longer necessary for CBER to routinely verify that the lots are acceptable for release.

02N-0516

C 1

We suggest that a process consistent with that used for specified biologics[1] could be applied more widely as an expectation rather than an exception. CBER consideration of any or all of the following components could serve to improve the current lot release requirements. A modern system could operate as follows.

For new products:
In the licensure/approval letter, CBER requires a manufacturer to submit lot release protocols and samples until a specified number of lots have been produced; the number of lots may differ by product type, but would be generally known to manufacturers of that product type (e.g. # lots for X vaccine). When the specified number of lots is reached, the manufacturer may request an exemption from routine lot release requirements by submitting a summary of data compiled for the specified number of lots produced since licensure, accompanied by a proposal to submit samples less frequently in the future (e.g. annually). CBER reviews the exemption submission and provides feedback to the sponsor within a reasonable time (e.g. within 6 months of receipt). If CBER agrees with the sponsor's proposal, the Agency exempts the sponsor from the requirement to submit lots for release by CBER, provided the manufacturer complies with the agreed-upon schedule to submit samples, and data continue to support the decision. Thereafter, CBER reviews less frequent (e.g. yearly) submissions.

For older products, where CBER has already released many lots:
The manufacturer may request an exemption from routine lot release requirements by submitting a summary of data compiled for lots produced in the last three years (not to exceed a specified number of lots) accompanied by a proposal to submit samples less frequently in the future (e.g. annually). The number of lots may differ by product type, but would be generally known to manufacturers of that product type (e.g. # lots for X vaccine). Due to the extensive lot release history with the product, CBER reviews the exemption submission and provides feedback to the sponsor on an expedited schedule (e.g. within 3 months of receipt). If CBER agrees with the sponsor's proposal, the Agency exempts the sponsor from the requirement to submit lots for release by CBER, provided the manufacturer complies with the agreed-upon schedule to submit samples and data continue to support the decision. Thereafter, CBER reviews less frequent (e.g. yearly) submissions.

Prior to implementation of FDA's cGMP standards, there may have been scientific legitimacy in having CBER repeat release testing to confirm results submitted by the manufacturer. However, this is clearly no longer the case, as biologics are produced under strict adherence to cGMPs and CBER Compliance staff regularly inspect manufacturing facilities to ensure that cGMPs are followed. Greater control has been achieved by manufacturers over the production of biological products through in-process controls, process validation, and advances in analytical techniques. Therefore, the assumption that for most products, lot release testing by CBER is justified and will improve the quality of biologics is outdated. Routinely subjecting biologics manufacturers to testing of product lots for prolonged periods adds little to improving the quality of biologics, drains healthcare resources, and unnecessarily extends the cycle time required to release product to market. In an age when pharmaceutical shortages are common, particularly for vaccines, the extended cycle time required to release product to market has public health implications. Although CBER recognizes alternatives to the lot release requirements[1], the alternatives are not widely applied.

---

[1] *Federal Register* notices 58:38771-38773 and 60:63048

Merck encourages FDA to review the regulations concerning lot release and consider modifications to reflect current manufacturing technology standards in light of industry's ability to control and test products to ensure identity, purity, and potency.

We thank the FDA for the opportunity to comment. As always, we may be called upon to provide further insight on this issue.

Sincerely,

Lauren M. Ketrick

for David Blois, Ph.D.
Senior Vice President
Global Regulatory Policy