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Food and Drug Administration
Dockets Management Branch (HFA_305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**RE: Docket No. 01N-0587
Agency Information Collection Activities; Proposed Collection; Comment Request;
General Licensing Provisions: Biologics License Application, Changes to an Approved
Application, Labeling Forms FDA 356h and 2567; and Revocation and Suspension**

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 under the Federal Food, Drug, and Cosmetic (FD&C), and the Public Health Service (PHS) Acts, which are the subject of this notice. Therefore, Merck is well qualified to respond to this request for input regarding information collection requirements relating to the licensing of biologics.

Many of the comments that follow were presented by PhRMA to the HHS Secretary's Advisory Committee on Regulatory Reform on February 13, 2002, and are repeated here for completeness. Part 600 of the Code of Federal Regulations (CFR) requires thoughtful revision in the following areas in order to harmonize regulations between CBER and CDER; address outdated safety reporting regulations; and permit multiproduct operations involving spore-bearing (pathogenic) and nonspore-bearing (nonpathogenic) organisms.

HARMONIZE REGULATIONS BETWEEN CBER AND CDER

Regulatory reform is needed in the following areas in order to harmonize standards with CDER. The regulations under 21 CFR Part 600 are derived from two principle statutes, Part 351 of the PHS Act, and the FD&C Act. The following regulations, derived from the same statute, are significantly different when applied under 21 CFR Part 600 (biologics) compared to Part 300 (drugs). In fact, Congress recognized the differences in the relative parts of the regulations when they crafted Section 123 of the Food and Drug Administration Modernization Act (FDAMA) citing the need "to minimize differences in the review and approval of products required to have BLAs under the PHS Act (42 U.S.C. 262) and products required to have NDAs under section 505(b)(1) of the FD&C Act (21 U.S.C. 355(b)(1))."

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Sterility (21 CFR 610.12)

Section 610.12 provides for the demonstration of sterility of each lot of each product by the performance of the tests prescribed in paragraphs (a) and (b) for both bulk and final container materials. In essence, this rule establishes a standard for sterile bulk substances. Sterility testing on bulk samples of biological products is unnecessary, costly, and conflicts with other requirements, particularly, when one understands that parenteral products are generally rendered sterile at the drug product stage.

RECOMMENDATION: Delete Section 610.12, as manufacturing of biological products should be performed under environmentally controlled conditions. Sterility testing should be required for final products only to ensure consistency with drugs (nonbiological products).

General Safety (21 CFR 610.11, 610.11a, 610.12, 610.13 and 610.30)

These Sections of 610 provide specific assay methodologies for assessing safety, sterility, purity, and mycoplasma contamination of bulk and/or final product. Additional methodologies for assessing these parameters also exist in recognized compendia (e.g. United States Pharmacopeial Convention [USP]). As methodologies evolve and improve, the methodologies provided in 21 CFR 610 become obsolete. In order to update these methodologies, the cumbersome process of amending the CFR must be undertaken. Frequently, by the time the regulations are updated, the technology may have evolved rendering the methodology obsolete once more.

RECOMMENDATION: Revise 21 CFR 610.11, 610.11a, 610.12, 610.13 and 610.30 by deleting all references to specific tests. Utilize general wording to allow manufacturers to use currently accepted tests as defined in the USP, or as agreed upon as part of the licensing process.

Definition of Manufacturer (21 CFR 600.3[t])

Section 600.3(t) states, "*Manufacturer* means any legal person or entity engaged in the manufacture of a product subject to license under the Act."

At the time the regulation was written, the complex multinational corporate structures of today's industry were not anticipated. Today, U.S. corporations frequently find it important commercially to have a variety of corporate structures within the U.S. and abroad. At times, it is preferable to establish divisions within a single corporation and at other times it may be preferable to have wholly-owned subsidiaries as separate corporate entities.

RECOMMENDATION: Eliminate 21 CFR 600.3(t) to reflect today's corporate environment. Alternatively, revise 600.3(t) to be consistent with 21 CFR 201.1(c)(4), so that it reads:

"Manufacturer means any legal person engaged in the manufacture of a product subject to license under the Act. For the purposes of this paragraph, person, when it identifies a corporation, includes a parent, subsidiary or affiliate company, where the related companies are under common ownership and control."

Such a change will permit transfer of manufacturing and/or testing of biological products via supplements to the parent company's existing product and establishment licenses.

Reporting Errors (21 CFR 600.14)

Section 600.14 provides for prompt notification of errors or accidents in the manufacture of products that may affect the safety, purity, or potency of any product. The recently revised Biological Products Deviation Reporting System provides a greater degree of clarity and specificity concerning what, when, and how to report. Although easier to follow, it is different than the reporting requirement for drugs. There does not seem to be any reason why one system (e.g. Field Alerts filed under 21 CFR 314.81[b][1]) could not be utilized by both Centers.

RECOMMENDATION: 21 CFR 600.14 should be deleted and regulated under 314.81(b)(1). Specifically, 314.81(b)(1) describes field alert reports; defines the number of copies of such reports to be submitted and the timing of the report in relation to the event; and a describes the events that prompt a field alert report.

Lot Release Testing (21 CFR 610.2[a])

Per 21 CFR 610.2(a), CBER must formally release each lot of any licensed product. Prior to implementation of FDA's cGMP standards, there may have been some scientific legitimacy in having CBER repeat release testing to confirm results submitted by the manufacturer. However, this is 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. Therefore, repeat testing of batches by FDA staff adds little to improving the quality of biologics and unnecessarily extends the cycle time required to release product to market. Indeed, CBER recognizes alternatives to the lot release requirements.¹ However, the alternatives are cumbersome and unnecessary.

RECOMMENDATION: Eliminate the antiquated requirements for batch certification by CBER to be consistent with the regulations for drug products. Advances in product characterization and biotechnology have progressed to a point at which lot release is not necessary.

FDA Form 2567 (Transmittal of Labels and Circulars)

Sponsors of biological products are required to use FDA Form 2567 to submit labeling components to CBER. CDER does not use a form for this purpose. The requirement to use a form for only one Center imposes an additional burden on companies that manufacture both biologics and drugs.

RECOMMENDATION: In the spirit of harmonization, CBER and CDER should require the same form to submit labels or not use a form.

Required Components of Marketing Applications

Currently, the sections of the CFR for marketing applications for drugs (21 CFR 314) and biologics (21 CFR 601) are quite different with regard to level of detail for required components of an application.

RECOMMENDATION: With the pending implementation of the Common Technical Document (CTD) as the standard by which marketing applications are submitted to regulatory authorities worldwide and in the spirit of harmonization, there should be a single standard for the content of marketing applications.

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

ADDRESS OUTDATED SAFETY REPORTING REGULATIONS

Merck recommends that the requirements for product safety surveillance and reporting for products off patent (and on the market for more than 10 years) be simplified. Therefore, the following recommendations on post-marketing safety surveillance are varied, but practical. We understand that FDA may be willing to accept many of these changes and may have included them within its Guidance for post-marketing surveillance (21 CFR 600.80). However, that Guidance, known in the industry and at FDA as the *Safety Tome*, has not been officially released by FDA and as such, its contents are not public.

Report Non-Serious Adverse Experiences in the Aggregate

In general, the value of the information collected by an intense safety surveillance system for products that are off patent, but on the market for more than 10 years, is more than outweighed by the effort required to collect it. For example, the numbers of Adverse Experience (AE) Reports (AERs) for these products declines over time and as competition increases. If an AE is labeled as non-serious and expected (i.e., noted the approved [by FDA] product package circular because it was identified through reporting as a non-serious experience), there is no new or valuable information that would be gained through continued collection of diminishing reports.

For non-serious *expected* AEs for drugs (but not for biologics), a sponsor may file a waiver, product-by-product, to request an exemption from the requirements to file initially reported and follow-up information on individual adverse experiences. It is easier for both FDA and sponsors to review these data in the aggregate and, therefore, for a sponsor to file them, e.g., in tabular fashion. Sponsors have already committed to FDA to file drug data in this fashion.

Simplify Periodic Adverse Experience Reporting and Post-Marketing Safety Update Reporting

Periodic Adverse Experience Reports to FDA should be simplified to exclude non-serious *expected MedWatch* reports (electronic or paper), if there are: no changes to the US package circular concerning safety; no findings leading to new safety studies or investigations and the product is 10 years or older. Sponsors will be able to provide a table of adverse experiences, identified by body system, as necessary. Likewise, if a product is on the market for 10 years or longer, a simplified Post-marketing Safety Update Report (PSUR), which would not include *MedWatch* reports (electronic or paper), should be acceptable.

Modernize the Vaccines Adverse Experience Reporting System (VAERS)(21 CFR 600.80)

As noted above, a sponsor may file a waiver for drug products, on a product-by-product basis, in order to request an exemption from selected post-marketing adverse experience reporting requirements. A similar waiver should be allowed for biologics to allow sponsors to request exemption from the requirement to file individual and follow-up VAERS reports for non-serious *expected* AEs. Again, sponsors will provide these data in the aggregate, e.g., in tabular report.

In addition, if a patient recovers from an AE following vaccination, the sponsor reporting the AE should not be required to send a one year follow-up letter to the reporter (of the AE) to confirm that the patient recovered. This paperwork requirement is excessive and should be eliminated.

PERMIT MULTIPLE PRODUCT FACILITIES (21 CFR 600.11[e][3])

Currently, 21 CFR 600.11(e)(3) states that work with spore-bearing organisms must be conducted in separate facilities with separate entrances from other licensed biologics. Similar language in 21 CFR 600.11(c)(5) requires that equipment and supplies exposed to potential pathogens shall be separated from those used for other products. Similarly, 21 CFR 600.10(c)(3) prohibits workers who have handled spore-bearing organisms or pathogenic viruses from working with other biologics without regowning. For facilities handling live vaccines (21 CFR 600.11[e][4]), no other product may be handled in the same facility at the same time as vaccine work.

The original intent of these regulations was to prevent contamination of biological products by pathogens such as *Clostridium botulinum*, *C. tetani*, and *Bacillus anthracis*, which may produce heat-resistant dormant forms described as spores. These regulations originated from manufacturing technologies involving open systems which differ significantly from those available today in several important respects. Advances in current technology have resulted in alternative methods that provide equal or better assurance of freedom from contamination than that provided by 600.11; these alternatives should be permitted.

Many companies are currently contemplating the design and construction of pilot plants for the preparation of bulk clinical supplies and of manufacturing facilities to prepare bulk ingredients for licensed products, or of single plants to achieve both tasks. In some cases, these plans involve the desire to conduct simultaneous fermentation operations for pathogenic and nonpathogenic organisms or for spore-bearing and nonspore-bearing organisms. Other companies are considering the renovation of facilities previously used to produce products from sporeformers for future preparation of clinical/market bulk supplies. Being able to implement these multiproduct design plans will result in major capital savings, usually measured in terms of millions of dollars per company. This is significant, as these high investment costs may delay the development of some potentially important products.

In addition to industrial needs and impact, public health needs are adversely affected by the current regulations. For example, during Desert Storm, the Department of Defense was unable to secure broad and rapid assistance of U.S. vaccine manufacturers in the preparation of vaccines from spore-bearing organisms. This reflected difficulties in compliance with regulations regarding dedication of equipment and facilities to products prepared from spore-bearing organisms. The Department of Defense could have met its needs more rapidly and easily if the present restrictions had been replaced by those proposed herein. Unless the regulations are modified to accommodate technological advances, this same scenario could be repeated at the time of the next military effort or civilian emergency.

EXPEDITE FOLLOW-UP ACTIONS AFTER INSPECTIONS

cGMP procedures for inspections of manufacturing sites and follow-up actions need to be reviewed and revised to establish common expectations between FDA and industry.

First, manufacturers recognize the evolution of GMPs and make significant effort to maintain compliance, especially as it pertains to older facilities and processes. It appears that field investigators rate all compliance infractions as equally important, without distinguishing between those that directly affect quality and those that may pertain to routine cGMP upgrades that may *not* affect quality parameters. FDA field inspectors should be encouraged to share the current attitude adopted by FDA headquarters

staff, which is cooperation and mutual respect toward achieving common objectives. This would result in more rapid closure of open inspection issues, which may otherwise contribute to manufacturing delays and product shortages, notably in vaccines production, where a public health crisis now exists (as reported to the National Vaccines Advisory Commission on February 11-12, 2002).

Secondly, for companies who are the sole provider or one of only a few who manufacture certain medically necessary products, timely resolution of inspectional issues can be critical to public health. However, given limited FDA resources for inspections, it appears that FDA field inspectors do not consistently prioritize completion of follow-up actions after an inspection during which infractions may be cited. Consequently, what occurs is that a facility that may have resolved inspectional issues remains idle for extended periods awaiting a required FDA re-inspection or follow-up approval, again potentially impacting availability of critical vaccines and medicines.

CONCLUSIONS

Part 600 of the CFR requires revision in the following areas in order to harmonize regulations between CBER and CDER:

- Sterility testing of final products
- Use of generally accepted general safety tests
- Definition of 'manufacturer' to reflect modern business practices
- Field alert system to report errors and accidents during manufacture
- Lot release testing
- Form to accompany submission of labels
- Content of marketing applications

The safety reporting regulations should be revised in the areas of:

- Aggregate reporting of nonserious adverse experiences
- Simple periodic adverse experiences and post-marketing safety updates
- Vaccine-related adverse experiences (VAERS)

The Agency should revise 21 CFR 600 to permit multiproduct operations involving spore-bearing and nonspore-bearing organisms and expedite follow-up actions after manufacturing site inspections.

We commend FDA for its foresight in examining these issues and providing the opportunity to comment. As always, we may be called upon to provide further insight on any or all of these issues.

Sincerely,

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