

January 25, 2007

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



**RE: Docket No. 2005N-0403 Requirements for Foreign and Domestic
Establishment Registration and Listing for Human Drugs, Including Drugs
that are regulated under Biologics License Applications, and Animal Drugs**

Merck & Co., Inc. is a leading worldwide human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical and biological products available today. These products have saved the lives of or improved the quality of life for millions of people globally.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading biomedical research organizations. MRL tests many compounds as potential drug candidates through comprehensive, state-of-the-art R & D programs. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment.

In the course of bringing drug product candidates through developmental testing, clinical trials, and licensure, Merck encounters issues addressed by this proposed rule (PR). We have extensive experience in the registration, drug listing, and labeling of drug and biological products and we have utilized those experiences to author the comments below. As noted herein and in the attached table, we have provided recommendations that we believe will enhance the development and implementation of the Agency's proposed drug registration and listing system.

Generally speaking, Merck supports the proposed registration provisions that will require manufacturers to electronically submit information to the Agency using an electronic drug registration and listing system (i.e., the EDRLS) which the Agency intends to develop. We concur that accurate and complete drug registration information is critical in assisting the Food and Drug Administration (FDA or "the Agency") to identify the drug product handler and provide a more effective system of surveillance. We also agree that registration, listing, and National Drug Code (NDC) information should be structured and inventoried in such a manner as to provide easy access for both industry and the Agency. Merck supports the mandatory presence of the NDC on all drug labeling. This is consistent with our internal practice.

The current process for establishment registration and drug listing allows sponsors to assign NDC numbers independently. Sponsors assign new NDC Product and Package Codes on demand, at times, up to 12 months prior to NDA/BLA filings. One of our key concerns with the provisions of the Establishment Registration and Drug Listing PR is the efficiency and timeliness of the proposed process. Namely, under the provisions of the PR, the FDA will be responsible for assigning thousands of NDC numbers. We are concerned that the Agency may lack the capacity to respond in a timely fashion to sponsors' requests for new NDC numbers. Additionally, we are concerned that the PR has not provided adequate details regarding how the FDA plans to issue NDC Product and Package Codes. Further, an unknown consequence of Agency-assigned NDC numbers is how FDA assignment of the second and third segments of the NDC number, the Product Code (currently 4-digits) and Package Code (currently 2-digits), will impact internal company databases (e.g., financial, packaging, regulatory, among others) and how any negative effect will be mitigated. Over time, the PR could potentially impart a huge financial and resource strain on industry.

We support the proposal to provide electronic portable document format (PDF) copies of the printed packaging components (to include labels, unit cells, folding cartons, etc.) along with the drug listing submission. This reduces the burden of having to separately send paper copies which could inadvertently be separated from the electronic drug listing submission. Regarding the inclusion of a PDF copy for the "content of labeling", this appears to be a redundancy since the content of labeling already exists in Structured Product Labeling (SPL) format for pharmaceutical products. We therefore propose consideration of a process that would reference the existing SPL and only require inclusion of PDF copies in those instances where SPL does not exist (e.g., biologics and over-the-counter (OTC) products).

We recommend that the FDA consider a phased-in approach to implement the new regulation such that the electronic registration and listing system is developed prior to any changes in the NDC numbering system. By implementing the electronic registration and listing system first, the FDA would have on record all the currently assigned and in-use NDC Labeler, Product, and Package Codes. This would allow the Agency to ascertain to what degree inaccuracies, duplication, or other overlaps exist that may warrant a complete overhaul of the NDC numbering system. A phased-in approach would allow the Agency and Sponsors to optimize resources more effectively by initially dedicating resources to ensure the success of the EDRLS before redeploying resources to focus on a new NDC numbering system which will undoubtedly require considerably more attention. Additionally, a phased-in approach will allow sponsors to adequately plan funding and resources to implement changes to internal processes and databases made necessary by the Proposed Rule as well as afford sponsors adequate time to become compliant with the Final Rule within the 3-year proposed implementation period.

Additionally, we believe it is important for the Agency to align the provisions of this PR with ongoing projects and other initiatives in development. We believe it is important for the FDA to communicate how this initiative will impact other Agency priorities, such

as SPL and the Barcode Final Rule. Specifically, we believe the FDA should ensure that the requirements for the drug listing data elements (DLDE) included with SPL will be aligned with the requirements set forth in the Establishment Registration and Listing Final Rule to leverage areas of synergy and reduce any possible redundancies. We would like to note that there are several proposed changes in the Proposed Rule that represent significant process changes for industry, requiring sufficient time to implement (specifically, any changes related to an expansion of, or revision to, existing SPL requirements). Additionally, the technical nature of these changes and relationship with an existing standard will require detailed criteria for implementation of these changes. Therefore, we recommend advanced notice and comment period prior to the implementation of these process changes in accordance with FDA's good guidance practices under (21 CFR10.115).

In addition to our aforementioned comments, please find additional comments regarding specific sections of the document in the attached Table. Please contact me with questions or comments on this letter.

Sincerely,

A handwritten signature in black ink, appearing to read "Brian M. Mayhew". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Brian M. Mayhew
US Regulatory Policy

Table I. Specific Comments

Page, Section, paragraph, and Line number	Comments and Rationale	Recommendations, Clarifications, and Proposed Changes (if applicable)
<p>Page 51283-84; Section IV.A.4(d) The current exemption for FTZs and drug imported under section 801(d)(3) of the act would be revoked</p>	<p>One of the current exemptions offered to Foreign Trade Zones (FTZ) is the supply chain benefit of “Direct Delivery”. To revoke this benefit would be unnecessary when the information regarding the active pharmaceutical ingredients (APIs)/drug products could be obtained via the in-bond documents that the FTZs are required to complete and file with US Customs and Border Protection (CBP) upon merchandise admission into the FTZs. It is our contention that FTZs are more secure than most “domestic” facilities by virtue of the regulations and guidelines they must uphold. If key benefits of FTZs, such as Direct Delivery, cease, US businesses may gravitate overseas in order to remain competitive with their international competition. The provision of using Import for Export was instituted so that pharmaceutical companies would not move manufacturing overseas due to the very restrictive import and/or export laws within the US. Eliminating the Import for Export provision could potentially have a negative impact on pharmaceutical manufacturing and related jobs in the US as companies might shift their operation overseas.</p>	<p>We recommend the FDA reference CBP data regarding Foreign Trade Zone (FTZ) Admission of Merchandise such that the FDA will have a record of the merchandise (drugs and drug products) entering the FTZ. This will provide the FDA with product information while not hindering the movement of merchandise into the FTZ. (Please note that FTZs are required to tie all lots to a CBP214 Admission document and all merchandise must be accounted for.) CBP oversees the FTZ Program via regulations, Title 15 CFR, Part 400.</p>
<p>Page 51285; Section IV.A.5 What Definitions and Interpretations of Terms Would Apply</p>	<p>Reference is made to the new definition of the term “drugs” to include biologics, API, and finished dosage form (animal, human, OTC and prescription). Further reference is</p>	<p>The inclusion of other health products in the requirements for submitting electronic content of labeling (e.g., biologics, API and finished</p>

<p>to Part 207?</p>	<p>made to expanding the requirements for submission of content of labeling to all “drugs” subject to the listing requirements covered by proposed part 207.</p>	<p>dosage form - animal, human, OTC and prescription) will require major process changes for industry, similar to those required for human prescription pharmaceuticals, with a need for sufficient lead time to implement. We recommend advance notice and comment period, prior to implementation, in accordance with FDA’s good guidance regulations under 21 CFR 10.115 prior to finalization of any regulation or implementation criteria for these process changes</p> <p>Additionally, we request further clarification regarding how the proposed expansion of requirements and redefinition will impact requirements for the DLDE included with Structured SPL. Specifically, we request clarification regarding whether the current SPL DLDE requirements expand in any way to include this additional information (biologics, API, OTC, and veterinary medications), or whether this information will be provided separately to EDRLS.</p>
<p>Page 51295; Section IV.C.; The National Drug Code (NDC) Number</p>	<p>Merck & Co., Inc. fully supports the FDA’s position that the Agency-assigned Labeler Code and independent, company-assigned Product and Package Codes belongs to the manufacturer and that a repacker would not be permitted to reuse a manufacturer’s NDC number.</p>	<p>We recommend that the FDA allow sponsors to continue to assign their own Product and Package Codes. The potential for significant confusion and undue economic burden of overhauling the NDC numbering system far</p>

	<p>We believe the FDA should continue to allow sponsors to independently assign NDC Product and Package codes. However, if the FDA finalizes the provisions in the PR that stipulate that the Agency will assign such numbers, then we support the Agency's proposal to assume such responsibility <u>only if</u> the Agency provides for the following:</p> <ol style="list-style-type: none">1. NDC codes would need to be assigned to sponsors early enough in the development process to avoid any delays in timeline commitments. Currently, these codes are assigned up to 12 months prior to application (NDA/BLA) filing.2. That manufacturers will retain their 4- or 5-digit Labeler Code (or Codes) already assigned by the Agency and by which the sponsor is already recognized internally, externally, and in electronic media.3. That the Agency should issue in conjunction with the Drug Registration and Listing Final Rule an update to the February 26, 2004 Bar Code Final Rule requiring the NDC bar code on human drug and biological products to account for the changes being proposed in this ruling so that both rulings are consistently aligned. <p>Regarding the API, further explanation is requested as to whether the NDC is required to appear on an API label and, if so, where (as there is currently no requirements for a NDC bar code). Additionally, it is unclear what triggers a request for a NDC for an API.</p>	<p>outweighs any recognizable benefit of a new numbering system. Additionally, company-assigned NDC numbers allow sponsors to maintain the flexibility, timeliness, and the "historical logic" that has been built into package size codes. This "logic" would be lost if the FDA were to assume this responsibility.</p> <p>In contrast, if the FDA moves forward with their proposal for mandating that the Agency assign NDC codes, we request that the FDA implement a system that includes the following:</p> <ol style="list-style-type: none">1) The FDA provides for the assignment of these NDC codes up to 12 months prior to BLA/NDA filing.2) The Agency agrees to assign these codes within 5 business days of receipt of sponsor's request.3) The FDA defines the mechanism that triggers a request for an NDC number for a new/revised product or package configuration.4) The FDA standardizes package codes for all types of package configurations across the board, thus recreating some "logic" to these codes.5) The FDA allows sponsors to independently retain their unique Product Numbers and Imprint Codes which are used
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		<p>extensively in product registrations worldwide and throughout the supply chain.</p> <p>With regard to APIs, there is currently no requirement for a bar coded NDC number to appear on an API label in accordance with the Bar Code Final Rule. If an NDC number is required on an API label, we recommend that it should appear in a stand-alone, human-readable format in a consistent location (such as the current regulation - top 1/3 of principle display panel (PDP)). The guidelines for placement should be consistent for all drug labels and for all related FDA guidelines and regulations.</p> <p>For imported APIs that require Drug Listing prior to importation, sponsors would need to request a NDC prior to initiating drug listing activities. For APIs that do not require drug listing, we believe sponsors should be allowed to request NDC numbers at any time prior to label development if the FDA is resolute in their position that the NDC must appear on the API label.</p>
<p>Page 51305 Section IV.C.4 How Do We Intend to Implement the NDC Number Changes</p>	<p>In the PR, reference is made to a 9-month period to review and update all NDC codes.</p>	<p>We recommend decoupling the "review" and "update" processes from the proposed 9-month period. Nine months may be adequate time for a company to review all their NDC numbers. However, should the Agency find a</p>

	<p>Additionally, the PR references a proposed implementation schedule of 3 years for prescription products and 7 years for OTC products – but suggests consideration of shortening to 2 and 5 years, respectively.</p>	<p>reason to request that a company update their NDC numbers, far more time will be necessary to update associated drug listing submissions, labeling, and printed packaging components. The full magnitude of this work is unknown. For example, labeling revisions alone could take up 12 to 18 months to implement.</p> <p>We support the inclusion of a 3-year implementation period in the Final Rule for prescription drugs and APIs. We are not in favor of shortening the proposed implementation schedule chiefly due to the fact that so many changes are connected to this ruling and that the EDLRS is not yet operational.</p>
<p>Page 51306-7 Section IV.D.1 Who Would be Required to List Drugs?</p>	<p>The PR references the submission of drug listings for private label distributors.</p>	<p>Further clarification of the Agency's expectations with reference to Private Label Distributors (PLD) is requested. In the past, manufacturers had an obligation to carry out drug listing on behalf of the PLD. Additionally, the PLD had a responsibility to submit drug listing as the distributor. In order to accomplish this activity, the manufacturer would require the NDC number and labels of the PLD to complete the drug listing submission.</p>

<p>Page 51308-9 Section IV.D.4 What Listing Information Would Be Required for Manufacturers?</p>	<p>The proposed drug listing requirements pertain to trade as well as sample packaging. Currently, SPL DLDE include some of the drug listing information for trade components, but not sample packaging.</p>	<p>We request further clarification on the requirements for the DLDE included with SPL. Specifically, we request clarification regarding whether the Agency will expand labeling requirements to include sample packaging configurations. If the intent is to expand SPL DLDE requirements to include sample packaging information in SPL, we request that FDA provide clarification as to whether sample information will be required to appear in the human-readable Content of Labeling section.</p>
<p>Page 51312 Section IV.D.7 What are the Proposed Requirements for Reviewing and Updating Listing Information?</p>	<p>The Agency is inviting comment on whether establishments should be required to provide the number of batches and batch size (size included in master production and control records) for each drug subject to listing requirements. For solid dosage forms, the number of unit dosage forms would be required. For liquids, the total batch weight/volume (before primary packaging) would be required.</p>	<p>Merck recommends that the FDA delete this requirement before issuing an Establishment Registration and Drug Listing Final Rule as batch number and size are not typically available at the time drug listing activities occur. It could also result in unnecessary updates. Data with respect to batch number and size has not been a historical function of drug listing. Drug listing was designed to monitor products introduced into interstate commerce for commercial distribution. There are other mechanisms for obtaining batch number and size as well as other types of production and control records that could be readily queried if the FDA were to contact a Sponsor with a specific question</p>

		<p>without placing an additional burden on drug listing to become the "catch-all" for all information. Additionally, batch number and size data seem to fit more naturally into the Annual Report process for NDAs/BLAs and INDs.</p>
<p>Page 51312 Section IV.D.8 What are the Proposed Requirements for Reviewing and Updating Listing Information?</p>	<p>The Proposed Rule mandates that sponsors review and update drug listing information every June/December (discontinuations, re-entries, "material changes") and to provide drug listing information for any drug not previously listed at annual registration review and update. The PR also adds the requirement for certification of "no change" if no changes have occurred since the last review and update.</p>	<p>Merck is in favor of having flexibility for initiating drug listing. For new listings: we support the current requirement of 5 calendar days from the start of manufacturing of the product. For updates, we support the submission of updated drug listing as changes occur throughout the calendar year or every June and December.</p>
<p>Page 51314 Section IV.E.1 Electronic Format How Would Registration and Listing Information be Provided to FDA?</p>	<p>Reference is made in the PR to periodic guidance on the submission of registration and listing information in electronic format.</p>	<p>We request further clarification regarding the file format that drug listing for NDC requests will initially be submitted (XML or via web site).</p>
<p>Page 51315 IV.E.4 What are the Proposed Requirements for the Submission of Content of Labeling in Electronic format?</p>	<p>Reference is made to the proposed expansion of SPL requirements to encompass human prescription drugs (noting the proposed new definition of "drugs" to include biologics and API), OTC, and veterinary drugs. Further reference is made to the fact this change will require advanced notice of the specific requirements, in accordance with FDA's good guidance regulations under 10.115 (21CFR10.115).</p>	<p>We concur with the Agency's assessment of this impact and would like to raise awareness of the additional burden and time required to develop and implement further business process changes and the associated financial burden.</p>

<p>Page 51316 IV.E.4 What are the Proposed Requirements for the Submission of Content of Labeling in Electronic format?</p>	<p>Reference is made to the request to include NDC information in the transmittal message for listing information.</p>	<p>The Agency should further clarify as to whether this applies to those cases where NDC is included in the “Content of Labeling” section. We also seek clarification as to whether this applies in those situations when sponsors do not include “Content of Labeling” but references an approved US application number.</p>
<p>Page 51316 IV.E.4 What are the Proposed Requirements for the Submission of Content of Labeling in Electronic format?</p>	<p>Under the Proposed Rule, sponsors will need to provide certain information to request an NDC code prior to the submission of the NDA. Much of this information is included in the DLDE section that is included with the NDA submission and poses a possible area of redundancy.</p>	<p>We recommend leveraging the move to an all-electronic environment for drug listings as an opportunity to eliminate any redundancies in providing drug listing information. Therefore, further clarification is requested regarding any proposed changes in SPL DLDE requirements to reduce redundancy in the existing process.</p>
<p>Page 51316 IV.E.5 Would the proposal Require Electronic Submission of Advertisements and Other Labeling?</p>	<p>Reference is made to updating public docket 92S-0251.</p>	<p>We would like to raise awareness of the additional burden and time required to develop and implement business process changes associated with submitting advertisements and other labeling electronically as well as the associated financial burden.</p>
<p>Page 51319-20 IV.F.3 Miscellaneous</p>	<p>In the PR, the FDA requested specific comments regarding the proposal to include inactive ingredients on the</p>	<p>The FDA's proposal to change an NDC Product Code for changes in inactive</p>

<p>What registration and Listing Information Would be Made Available for Public Disclosure?</p>	<p>list of information available for public disclosure (unless it is subject to trade secret protection).</p>	<p>ingredients could: (1) disrupt supply; (2) create confusion in the supply chain downstream to the pharmacy, physician, and patient level; and (3) result in an increase in the number of labeling changes and drug listing submissions.</p> <p>As a change in an inactive ingredient would be submitted as a change to the approved application, having to submit such a change via the drug listing process is redundant.</p> <p>We request further clarification from FDA regarding its intention for “inactive ingredients”.</p>
<p>Page 51321 IV.F. 3 What registration and Listing Information Would be Made Available for Public Disclosure?</p>	<p>The Proposed Rule requests comments on the feasibility of submitting inactive ingredients for products beyond scope of proposed rule (pharmaceuticals, biologics, OTC, veterinary medicine, etc.).</p>	<p>We request clarification on how this information regarding “beyond scope” inactive ingredients would be submitted to the FDA. We are specifically requesting clarification regarding whether the FDA is proposing to require sponsors to provide this information in XML format or by other electronic means (website).</p>