CHPA

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January 26, 2007

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

Re: Docket No. 2005N-0403 / RIN 0910-AA49
"Requirements for Foreign and Domestic Establishment Registration and Listing for Human Drugs, Including Drugs that are Regulated Under a Biologics License Application, and Animal Drugs"
71 Federal Register 51276 (August 29, 2006) (Proposed rule)

Dear Sir or Madam:

On August 29, 2006, the U.S. Food and Drug Administration (FDA) published in the Federal Register a proposed rule that would amend its regulations governing establishment registration and drug listing.[1] The proposed revisions are extensive[2] and include (among others) a requirement to use an electronic registration and listing system; changes to the assignment and use of National Drug Code (NDC) numbers; changes in the regulation of private label distributors; and new rules governing which registration and listing information would be available for public disclosure.

FDA invited interested parties to submit written or electronic comments on the proposed rule by November 27, 2006. This deadline was subsequently extended by the agency to January 26, 2007, based (in part) on a letter submitted by the Consumer Healthcare Products Association (CHPA), requesting a 60-day extension of the comment period.[3] The agency also held a public meeting on December 11, 2006, to discuss the proposed changes to the NDC number system, at which CHPA was a registered presenter.[4]

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[1] 71 Fed. Reg. 51276 (August 29, 2006) (to be codified at 21 C.F.R. parts 20, 201, 207, *et al.*) (Proposed rule).

[2] The proposed revisions would "reorganize, consolidate, clarify, and modify current regulations..." *Id.*

[3] 71 Fed. Reg. 63726 (October 31, 2006) (Proposed rule; notice of public meeting and extension of comment period).

[4] *Id.* The transcript of CHPA's statement at the December 11th public meeting has been added to the docket for this matter – i.e., Docket No. 2005N-0403 / RIN 0910-AA49.

Consumer Healthcare Products Association
900 19th Street, NW, Suite 700
Washington, DC 20006
T 202.429.9260 F 202.223.6835
www.chpa-info.org

If the revisions that have been proposed by FDA are implemented in a final rule, a significant impact on the ability of CHPA member companies to conduct their business operations efficiently and in a cost-effective manner would result. CHPA, founded in 1881, is the trade association representing manufacturers and distributors of nonprescription or over-the-counter (OTC) medicines and dietary supplements in the United States. Currently, CHPA member companies account for over ninety (90) percent of the domestic retail sales of OTC drugs.

Collectively, CHPA and its member companies have carefully examined the proposed rule and, based on this coordinated assessment, have prepared these written comments for consideration by FDA. At the outset, we would like to commend the agency for engaging in a process the overriding purpose of which is to further protect the public health. The preamble of the proposed rule articulates a wide range of statutory and regulatory objectives that the proposed rule is intended to accomplish.[5] As CHPA has continually done in the past, we support the agency's efforts to devise new and innovative ways to effectively serve these goals.

We would also like to register our appreciation for FDA's willingness to exercise flexibility. As the viewpoints expressed at the December 11th public meeting confirmed, this is a very complex and difficult undertaking, not only because of the scope of the project, but also because of its potential impact on the regulated community. To ensure that this effort will be a success, maintaining an open stakeholder dialogue will be of the utmost importance during this process. To this point, we are especially appreciative of Dr. John Gardner's opening remarks at the December 11th public meeting that the agency will only issue a final rule once the concerns with the proposal have been adequately resolved – clear evidence of a flexible approach.

Our written comments will focus on four major points. First, CHPA supports the development and implementation of an electronic registration and listing system that meets the needs of FDA and the regulated community. Second, CHPA supports retention of the current NDC number system. Third, the proposed rule does not adequately distinguish the regulatory requirements for drug products in commercial distribution in the United States from drug products intended for export only or those imported-for-export. Fourth, the proposed periods for implementation of an electronic system and the transition to placement of NDC numbers on labels are unrealistic.

To address these points, we believe a step-wise strategy which enhances the integrity of the current paper system while concurrently developing an electronic system would be the most appropriate means of meeting the needs of FDA and the regulated community. In sum, we look forward to working with FDA on this important matter. A brief summary of our principal arguments in support of these specific measures follows.

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[5] 71 Fed. Reg. at 51277-51278, 51280.

EXECUTIVE SUMMARY

I. CHPA supports the development and implementation of an electronic registration and listing system that meets the needs of FDA and the regulated community

CHPA and its member companies generally support FDA's proposal to develop and implement an electronic system for registration and listing. The potential benefits of such a system include increased efficiency, greater accuracy, and enhanced compliance opportunities.

We believe, however, that there are additional conceptual, regulatory, technological and economic issues that should be considered by the agency prior to implementation of an electronic system. These issues are exemplified by our more detailed comments on the proposed data submission requirements and certifications, as well as the resources and time required to develop and validate appropriate software applications.

The development of an electronic system should include educational and compliance-building tools that could ease the transition to an electronic system and enhance the functionality of the system as a whole, operationally, as well as in terms of regulatory adherence. These tools should include those which will enhance the integrity of the current paper system while concurrently developing the electronic system.

Certainly, the most effective means to improve the electronic system and obtain the insight of industry is to share the draft specifications of a *beta* version of this system before it has been finalized. The reciprocal benefits of this collaborative approach are clear – stakeholders would develop a greater understanding of the technology, and FDA could obtain additional input on actual or potential problems from an industry perspective. The exchange of this information could be accomplished in a controlled environment through in-person meetings, demonstrations, or tutorial-like ("Webinars") training sessions. These could be held at FDA or in the field, or wherever the agency would prefer.

Moreover, once an electronic system is operational, these educational or compliance-building opportunities could continue. In addition, the Center for Drug Evaluation and Research (CDER) should look to other systems within FDA (e.g., those implemented by the Center for Food Safety and Applied Nutrition (CFSAN) for cosmetics and imported foods, and the Center for Devices and Radiological Health (CDRH) for device listings) for guidance.

II. CHPA supports retention of the current NDC number system

Our member companies believe that the current NDC number system is a well-established and effective regulatory framework. In particular, the current system is an intricate part of the OTC industry's activities, such as research and development; manufacturing; internal corporate recordkeeping and business development; distribution; and, marketing. Under current law, the marketing of monograph OTC drugs does not require marketing pre-

clearance, and the current NDC number system is consistent with and supports this go-to-market structure of the monograph system.

Re-allocation of the responsibility for assignment of NDC numbers from industry to FDA will significantly disrupt the efficient marketing of effective and safe OTC drug products without corresponding regulatory benefits for the agency and health benefits for consumers. As discussed in more detail below, FDA assignment of NDC numbers and the proposed rule's framework for obtaining and utilizing NDC numbers will undo needed flexibility and will impact product "ownership" and associated regulatory obligations, as well as packaging and labeling operations.

III. The proposed rule does not adequately distinguish the regulatory requirements for drug products in commercial distribution in the United States from drug products intended for export only or those imported-for-export

In the preamble to the proposed rule,[6] FDA indicated its intent to revoke certain provisions of the current sections 207.40(a) and (b). FDA cites the Bioterrorism Act[7] as one basis for this proposed revocation. We note that with regard to drug products, the Bioterrorism Act does require establishment registration, prior notice of importation, statements of activities/plans, certificates of analysis, and recordkeeping; however, the Bioterrorism Act does not require listing of drugs or drug components intended for subsequent export. In this regard, the proposed rule does not clearly address whether drug components and drug products intended for export or imported-for-export are exempt from the various provisions related to obtaining an NDC number, drug listing and updating of drug listings.

IV. The proposed implementation dates for a final rule and the transition period for adding the NDC number to all OTC drug labels, are unrealistic

The complexity of the proposed NDC number requirements, the currency of FDA's drug listing database and an effective date of nine (9) months for a final rule adds an enormous time burden on entities required to have an NDC number and to list. It is unlikely entities could complete a review and update of all their listings in the FDA database within the time allowed (nine (9) months), or change all of their labeling to comply with this rule within five (5) or seven (7) years. This is especially true of entities that would need to coordinate efforts within a complex supply chain.

Our detailed comments for consideration by FDA are set forth below.

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[6] 71 Fed. Reg. 51276.
[7] 71 Fed. Reg. at 51283-51284.

DETAILED COMMENTS

I. CHPA supports the development and implementation of an electronic registration and listing system that meets the needs of FDA and the regulated community

One of the principal innovations in the proposed rule is that registration and listing information would be submitted electronically, rather than utilizing paper forms.[8] The electronic submission of this information, as well as information required for an NDC number, would generally need to comply with 21 C.F.R. part 11 (Part 11).[9]

CHPA and its member companies generally support FDA's proposal to develop and implement an electronic system for registration and listing. The potential benefits of such a system are wide-ranging and include increased efficiency, greater accuracy, and enhanced compliance opportunities.[10] We also concur with the recommendation of the Office of Inspector General, Department of Health and Human Services (OIG) – and agreed to by FDA – that "[e]lectronic filing of drug registration and listing information will facilitate the timely exchange of information between FDA and firms."[11]

Although we generally support FDA's proposal to develop and implement an electronic system for registration and listing, we believe there are additional issues, technical and otherwise, that should be considered by the agency prior to its implementation. We have highlighted these recommendations in this section of our written comments, in no particular order of importance.

We urge that the development of an electronic system should include educational and compliance-building tools that could ease the transition to an electronic system and enhance the functionality of the system as a whole, operationally, as well as in terms of regulatory adherence. These tools should include those which will enhance the integrity of the current paper system while concurrently developing the electronic system.

Certainly, the most effective means to improve the electronic system and obtain the insight of industry is to share the draft specifications of a *beta* version of this system before it has been finalized. The reciprocal benefits of this collaborative approach are clear – stakeholders would develop a greater understanding of the technology, and FDA could obtain additional input on actual or potential problems from an industry perspective. We urge that the exchange of this information could be accomplished in a controlled environment through in-person meetings, demonstrations, or even tutorial-like ("Webinars") training sessions. These could be held at FDA or in the field, or wherever the agency would prefer.[12]

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[8] Proposed 21 C.F.R. § 207.61(a).
[9] *Id.*
[10] 71 Fed. Reg. at 51277-51278, 51314-51316.
[11] "The Food and Drug Administration's National Drug Code Directory" at 14 (August 2006) .
[12] The time may be ripe for this review to occur based on Dr. Gardner's status report on the electronic drug registration and listing system (e-DRLS) at the December 11th public meeting.

Moreover, once an electronic system is operational, these educational or compliance-building opportunities could continue, in addition to the publication of guidance, technical specifications, and on-site interactions for FDA personnel. A 'win win' outcome would be achieved.

For all of these reasons, we strongly encourage an open approach that emphasizes education and collaboration. In sum, we look forward to working with FDA on this important matter and have provided below some issues that should be considered as part of the development and implementation of an electronic system for registration and listing.

A. If FDA assumes the responsibility for assignment of NDC numbers, then the manufacturer initially should be required to submit minimal information to obtain an NDC number for a finished drug product

For the reasons discussed more fully in section II.A below, we do not believe that FDA should assume the responsibility for assignment of NDC numbers. However, should FDA assume this responsibility, the information required to obtain an NDC number should be limited.

Proposed section 207.33(c)(3) indicates the information that a manufacturer of a drug other than an active pharmaceutical ingredient must provide in order to obtain an NDC number. Currently, NDC numbers are often assigned well in advance of the actual launch of a product, sometimes as early as one year or more. At the time of assignment, formulas, packaging, imprint information, and even the manufacturing site (or sites) may not be fully known – all prerequisites for NDC number assignment under the proposed rule. Consequently, the initial information required to obtain an NDC number(s) should be limited to:

- Manufacturer's name, address, telephone number, fax number, email address, and labeler code
- Therapeutic category (e.g., upper respiratory, topical analgesic, et al)
- Drug or drug product type (human drug or animal drug)
- Marketing status (prescription or OTC)
- Private label distributor's name, address, telephone number, fax number, email address, and labeler code (if applicable)
- Estimated number of package sizes anticipated

Based on the above information, FDA can provide a labeler code (if not already designated by FDA), a product code, and a "block" of package codes which the

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According to Dr. Gardner, the Drug Facility Registration Module (DFRM) has been implemented in the FDA Uniform Registration and Listing System (FURLS), and firms logging-in to FURLS will soon be able to utilize the DFRM to enter firm and importer information. Dr. Gardner also reported that an electronic listing system (eLIST) that will eventually enable industry to provide listing information via Structured Product Labeling (SPL) is under development. In the future, eLIST will be utilized to validate listing information prior to the public posting of the SPL.

manufacturer/distributor may assign as product development proceeds. The other data requirements of proposed section 207.33(c)(3) can be updated electronically at the time of drug product listing (see also section II.D with regard to inactive ingredients).

B. FDA should eliminate or modify its drug listing proposals related to the submission of labels and labeling, at least as these proposals apply to OTC drug products

The proposed listing requirements would require that each entity (i.e., every manufacturer, repacker and relabeler, and drug product salvager) submit certain information to list a drug.[13] A manufacturer must submit, among other things, the labeling for the listed drug.[14] Under proposed section 207.49(g)(2)(i), for each OTC drug that a manufacturer regards as subject to section 505 of the Federal Food, Drug, and Cosmetic Act (FDC Act) or section 351 of the Public Health Services (PHS) Act, if the manufacturer has not provided the drug's approved application number as part of the listing information under proposed section 207.49(c), it would submit a copy of all current labeling, including the content of labeling.[15]

Under proposed section 207.49(g)(2)(ii), for an OTC drug marketed pursuant to a monograph, the manufacturer would submit a copy of the current label, the content of labeling, the package insert (if any), and a representative sampling of any other labeling.[16] Proposed section 207.1 defines the phrase "content of labeling," for human OTC drugs, as the content of the "drug facts" labeling required by section 201.66, including all texts, tables, and figures.[17] Proposed section 207.1 defines the phrase "representative sample of any other labeling" as excluding labels and package inserts but including any other materials that provide a "balanced picture of the promotional claims."

1. FDA should clearly delineate between "label" and "labeling" in the regulation, and for OTC drug products should eliminate the requirement to submit representative samples of "any other labeling"

The proposed rule does not clearly distinguish between "labeling" defined as the label on the product's packaging – versus – "labeling" as promotional information that may accompany the product. Under proposed section 207.1, the "content of labeling" for human OTC drugs means the "content of the drug facts labeling required by section 201.66..." The content requirements of section 201.66 pertain to the "outside container or wrapper of the retail package, or the immediate container label if there is no outside container or wrapper..."[18]

In contrast, the definition of the "representative sampling of any other labeling" under proposed section 207.1 concentrates on the promotional claims for a drug, including the

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[13] Proposed 21 C.F.R. §§ 207.49, 207.53 and 207.54.
[14] Proposed 21 C.F.R. §§ 207.49(g).
[15] Proposed 21 C.F.R. § 207.49(g)(2)(i).
[16] Proposed 21 C.F.R. § 207.49(g)(2)(ii).
[17] Proposed 21 C.F.R. § 207.1
[18] 21 C.F.R. § 201.66(c).

promotional material described in section 202.1(l)(2) (e.g., brochure).[19] That is, the representative sampling of any other labeling refers to "typical labeling material...that gives a balanced picture of the promotional claims used for the drug."[20] Labels and package inserts are expressly excluded from this definition. Arguably, this is a very different conception of "labeling" than that being used for the "content of labeling," yet FDA utilizes the term "labeling" interchangeably. For added precision, we believe it would be helpful for FDA, in a final regulation, to clearly delineate between "label" and "labeling" rather than using the term "labeling" generally.

In addition, FDA should eliminate the requirement to submit representative samples of any other labeling, including promotional labeling for OTC drug products. In making this recommendation, we do not overlook the fact that "content of labeling" and "representative sampling of any other labeling" both constitute "labeling" under section 201(m) of the FDC Act, and that "labeling" means (in part) "all labels."[21] However, the submission of promotional labeling goes beyond the primary purpose of the drug listing database which is intended to capture the number and types of drug products in commercial distribution in the United States.

2. FDA should eliminate the requirement to submit the "drug facts" label for monograph OTC drugs or should further limit the number of representative samples of the "drug facts" label that must be submitted

Under proposed section 207.49(g)(2)(ii), for a human OTC drug marketed pursuant to a monograph, the manufacturer would be required to submit a copy of the current label, the content of labeling, the package insert (if any), and a representative sampling of any other labeling.[22] As noted, the "content of labeling" is synonymous with the "drug facts" labeling required by section 201.66, including all texts, tables, and figures.

From a regulatory perspective, it is not clear why FDA needs manufacturers to submit "drug facts" labels for monograph OTC drug products when the agency has set much of the required content of the label in the monographs already. Section 201.66 plainly sets forth "the content...requirements for the labeling of all OTC drug products," including monograph OTC drug products.[23] These requirements include (but are not limited to) information related to the product's active and inactive ingredients, purposes, uses, warnings and directions.[24]

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[19] 21 C.F.R. § 202.1(l)(2).
[20] Proposed 21 C.F.R. § 207.1.
[21] 21 U.S.C. § 321(m); *see also* 21 U.S.C. § 321(k) (definition of "label").
[22] Proposed 21 C.F.R. § 207.49(g)(2)(ii).
[23] 21 C.F.R. § 201.66(a). Where, however, "an OTC drug product is the subject of an applicable monograph or regulation that contains content and format requirements that conflict with [section 201.66], the content and format requirements in [section 201.66] must be followed unless otherwise specifically provided in the applicable monograph or regulation." 21 C.F.R. § 201.66(a).
[24] 21 C.F.R. § 201.66(c). 21 C.F.R. part 201 also contains general labeling provisions (subpart A) and other labeling requirements for OTC drugs (subpart C).

FDA's reasoning is also unclear from an enforcement perspective. Monographs are developed by FDA for particular categories of drug products and not only list those active ingredients that are generally recognized as safe and effective (GRASE), but also establish specific label requirements for indications, directions for use, and warnings to ensure that the products are used properly. For these products, if the regulatory standards of the applicable monograph are not met, the product may be deemed "misbranded" (section 502) and/or an unapproved "new drug" (section 505).[25] Both misbranding and the marketing of an unapproved new drug are violations of the FDC Act which could result in the imposition of an enforcement action by FDA.

In light of the regulatory standards and enforcement remedies already in place, it is not clear why FDA's proposal for drug listing includes the content of labeling for monograph OTC drug products, in addition to the current label, the package insert (if any), and a representative sampling of any other labeling.

If a final rule includes a requirement to submit drug facts labels for monograph OTC drug products, then FDA should further limit the number of representative samples that must be submitted. Proposed section 207.49(g)(2)(ii) states that a manufacturer need submit only one representative container or carton label "where differences exist only in the quantity of contents statement or the bar code"; however, there are other instances in which an OTC drug product's drug facts label may differ in form and/or content between primary and secondary packaging or among differently sized shelf-keeping units (SKUs) but should not require samples of each drug facts label. FDA's final regulation on the format and content requirements for OTC drug product labeling provides at least two examples.[26]

Section 201.66(c) of the drug facts regulation states that "[t]he outside container or wrapper of the retail package, or the immediate container label if there is no outside container or wrapper, shall contain" all the information specified by the regulation. For OTC drug products with an immediate container and an outer carton, the drug facts regulation does not require identical drug facts format and content on both components. In this example, the outer carton may contain complete drug facts format and content and the immediate container may contain only drug facts content or essential drug facts content.

Section 201.66(d) of the drug facts regulation provides for modified drug facts format and content on the labels of small packages that meet this provision's criteria. In addition to format modifications, this section notes that "[i]n determining whether more than 60 percent of the total surface area available to bear labeling is required, the indications for use listed under the 'Use(s)' heading . . . shall be limited to the minimum required uses reflected in the applicable monograph." In this example, an OTC drug product may have multiple SKUs, some of which can comply with full drug facts format and content requirements, and some of which comply with the modified requirements of section 201.66(d)(10), including the provision for fewer "uses" on the SKU with modified labeling.

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[25] Under the FDC Act, a "new drug" must be the subject of a new drug application (NDA) approved by FDA prior to its marketing. 21 U.S.C. § 355.
[26] 21 C.F.R. § 201.66.

In these examples, the requirement to submit representative samples of the immediate container label or the modified label for small packages does not provide any additional, useful information over that provided by submission of representative samples of labels from a carton or immediate container that complies with full drug facts format and content. Additionally, the submission of drug facts labels for promotional SKUs that may contain two or more OTC drug products that are already drug listed (including submission of drug facts labels) would seem to be redundant.

C. The proposed rule would expose confidential information that must be protected from public disclosure

Under proposed section 207.81(a), the following information would be made available for public disclosure upon request or at the agency's discretion: (1) all registration information; (2) after a drug is listed, all information submitted under proposed section 207.33 for that drug to receive an NDC number; and (3) after a drug is listed, all information submitted under the drug listing regulations – proposed sections 207.49 (manufacturers), 207.53 (repackers and relabelers), and 207.54 (salvagers).[27]

Certain information would be automatically exempt, including the NDC number assigned to the drug immediately before the drug was received by a repacker, relabeler, or drug product salvager.[28] FDA has proposed to exempt this information because it might disclose a business relationship between the manufacturer, repacker, relabeler, or drug product salvager and the business from which it obtained the drug, and may constitute commercial or financial information that is exempt from public disclosure under 21 C.F.R. § 20.61(c). Also exempt would be information submitted as the basis upon which it has been determined that the drug product is not subject to sections 505 or 512 of the FDCA.[29] *CHPA strongly supports these exemptions.*

For other types of information, FDA might decide on a "case-by-case basis" not to disclose the information, if to do so would be "consistent with the protection of the public health and the Freedom of Information Act." In this case, the burden would lie on the manufacturer, repacker, relabeler, or drug product salvager to demonstrate that the information was "exempt" or its disclosure was "otherwise prohibited by law."[30]

We believe that providing the public with all the information in the registration and listing database does not provide health-related, useful information to the consumer (patient) and will divulge commercially sensitive and trade secret information. Publicly available information should be limited to the information similar to that found in the prescription and non-prescription Physician's Desk Reference – typically the information contained in drug product labels, package inserts, and patient medication guides. Additionally, this information should only be available after the drug product has been drug listed.

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[27] Proposed 21 C.F.R. § 207.81(a).
[28] Proposed 21 C.F.R. § 207.81(a)(2).
[29] Proposed 21 C.F.R. § 207.81(b). This exemption would be lifted if the information is publicly available or its non-disclosure would be inconsistent with the protection of the public health.
[30] Proposed 21 C.F.R. § 207.81(c).

1. FDA would likely lack the resources necessary to render a "case-by-case" determination

FDA would likely lack the resources necessary to decide on a case-by-case basis not to disclose certain information, and do so on a timely basis. This could translate into serious delays in the assignment of NDC numbers if the request for an exemption is placed in advance of the actual assignment. (The request for an exemption would logically precede the assignment in order to preserve confidentiality.) In this situation, the efficiencies of an electronic system would be at risk of being totally negated. To counteract these concerns, we encourage the agency to adhere to the disclosure criteria set forth in these written comments (see section I.C.5. below).

We also request a clarification of the criteria FDA will employ in deciding whether or not to render a case-by-case determination. If a request is submitted and the requisite burden of proof has been met, then (we contend) the agency *must* act by granting the request.

2. The submission of "a list of every drug *in commercial distribution at that time*" should be re-inserted in a final rule

Under the proposed rule, "initial listing information" would be provided at the time of "initial registration" of an establishment. Specifically, the manufacturer, repacker, relabeler, or drug product salvager "must list any drug being manufactured, repacked, relabeled, [or] salvaged *for commercial distribution* at that establishment."[31]

Similarly, proposed section 207.41(a) requires manufacturers, repackers, relabelers, and drug product salvagers who are subject to the registration requirements to "list their drugs being manufactured, repacked, relabeled, or salvaged *for commercial distribution*."[32] Initial registration of each establishment must be accomplished by the domestic manufacturer, domestic repacker, domestic relabeler, or domestic drug product salvager "no later than 5 calendar days *after beginning to manufacture, repack, relabel, or salvage a drug*."[33]

The proposal modifies the current regulation with respect to the timing of registration and listing in that the current regulation requires that "the owner or operator...register the establishment within 5 days after the beginning of the operation and shall submit a list of every drug *in commercial distribution at that time*."[34] In other words, "[d]omestic manufacturers, domestic repackers, domestic relabelers, and domestic drug product salvagers who are subject to the registration requirements under [proposed] § 207.17

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[31] Proposed 21 C.F.R. § 207.45 (emphasis supplied).
[32] Proposed 21 C.F.R. § 207.41(a) (emphasis supplied).
[33] Proposed 21 C.F.R. § 207.21 (emphasis supplied). The initial registration for foreign manufacturers, foreign repackers, foreign relabelers, and foreign drug product salvagers is subject to a different schedule. *Id.*
[34] 21 C.F.R. § 207.21 (emphasis supplied).

[would be required to] list such drugs *regardless of whether the drugs enter interstate commerce.*"[35]

The deletion of this "in commercial distribution at that time" language from the proposed rule is problematic because it would make the information available for public disclosure under proposed section 207.81(a) available prior to the launch of a product. Our member companies have warned that the premature release of this information could compromise future developmental projects, chill innovation, and result in a competitive disadvantage. A needless administrative hurdle for a product that is listed but never actually launched would also result, because the manufacturer, repacker, relabeler, or drug product salvager would have to update this information pursuant to proposed section 207.57(b)(2).[36]

Retaining this language in a final rule is also important because it harmonizes with the stated purpose of drug listing, which is to provide "FDA with a current inventory of *marketed* drugs."[37] It would also (indirectly) reinforce the exemption for manufacturers, repackers, relabelers, or drug product salvagers who manufacture, repack, relabel, or salvage drugs solely for use in research, teaching, or chemical analysis - *and not for sale*.[38]

For all of these reasons, we ask that the language respecting "a list of every drug in commercial distribution at that time" be re-inserted by FDA in a final rule.

3. Submission of inactive ingredient information should not be required at the time of requesting an NDC number

Because proposed section 207.81(a) would allow the disclosure of information submitted under proposed sections 207.33(c) and (d) to obtain an NDC number, the new regulations would in some situations make available for public disclosure a drug product's inactive ingredients.[39] This information would be provided to obtain an NDC number, although a manufacturer with an NDA would have the option of instead providing the approved U.S. application number.[40]

Proposed section 207.33(c)(2)(ii) would allow a manufacturer, at the time it requests an NDC number, to identify the inactive ingredients that it considers trade secret.[41] Information identified by the applicant as trade secret would not be routinely posted on the Internet. Rather, FDA would evaluate claims of trade secret protection based on the definition of "trade secret" in section 20.61(a) of its regulations, when making disclosure decisions in response to requests made under the Freedom of Information Act.

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[35] Proposed 21 C.F.R. § 207.41(a) (emphasis supplied). This language respecting 'regardless of whether a drug enters interstate commerce' appears elsewhere in the proposed regulation as well.
[36] Proposed 21 C.F.R. § 207.57(b)(2) (discontinuation of a listed drug for commercial distribution).
[37] Proposed 21 C.F.R. § 207.5 (emphasis supplied).
[38] Proposed 21 C.F.R. § 207.13(d).
[39] Proposed 21 C.F.R. § 207.81(a).
[40] Proposed 21 C.F.R. § 207.33(c)(2)(ii).
[41] *Id.* Public disclosure of inactive ingredients not designated as trade secret at the time of listing would be authorized by the proposed regulations. 71 Fed. Reg. at 51320-51321.

CHPA urges that the submission of inactive ingredient information should not be required for an NDC number. As a threshold matter, the evaluation of claims of trade secret protection FDA would receive (e.g., a claim for the subcomponent of proprietary mixtures such as fragrances) would put a strain on its (FDA's) already scarce resources. Claims not evaluated on a timely basis could translate into product launch delays or delays in the fulfillment of requests for an NDC number.

Moreover, as we explain in section II.D below, requiring this information runs counter to FDA's policy on over-inclusive inactive ingredient labeling;[42] opens the NDC number to being changed many more times than it is subject to change under the current system; and overlooks existing regulatory requirements that effectively address the agency's concerns.

Should the agency require the submission of this information in a final rule, we request that this information be categorically exempt from public disclosure. The underlying justification would mirror the exemption for the NDC number assigned to a drug immediately before it was received by a repacker, relabeler, or drug product salvager.[43]

4. Batch number and size should not be required

FDA has invited comment on whether the agency should require manufacturers, repackers, relabelers, and drug product salvagers to provide the number of batches and batch size for each drug subject to the listing requirements.[44] We appreciate the opportunity to comment on this important issue.

Manufacturers, repackers, relabelers, and drug product salvagers should not be required to provide this information which may be commercially sensitive and should be confidential. If the number of batches and batch size are provided to FDA for drug listing, and this information is subsequently disclosed pursuant to proposed §207.81(a), agreements with suppliers could be jeopardized; e.g., knowledge of this information may

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[42] FDA's policy on inactive ingredient labeling provides (in part) that "OTC drug product labeling may include certain ingredients in the inactive ingredient listing that may be contained in the product. This can be accomplished by placing an asterisk next to the ingredients that may or may not be in the product and inserting the phrase 'contains one or more of these ingredients' at the bottom or end of the inactive ingredients section in the 'Drug Facts' box." *See* Docket No. 00P-1297.

[43] Proposed 21 C.F.R. § 207.81(a)(2); 71 Fed. Reg. at 51320 ("...this information may disclose a business relationship between the manufacturer, repacker, relabeler, or drug product salvager and the business from which they obtained the drug, and may constitute commercial or financial information that is exempt from public disclosure under § 20.61(c).").

[44] 71 Fed. Reg. at 51312. According to FDA, having better estimates of manufacturing volume "would improve a more risk-based approach to manufacturing quality oversight activities." *Id.* That is, "[b]y requiring establishments to provide the number of batches and batch size for each drug subject to the listing requirements, we would have objective data regarding production volume and be better able to find and address CGMP violations that may have the most impact on public health." *Id.*

provide competitors with information on supply chain processes, as well as potential inventory and product distribution.

There is also the issue of accuracy. One batch may be produced for multiple customers, and the reporting FDA would receive may be duplicative.

This information is also not relevant to the primary purpose of drug listing. To our knowledge, the production of batches is already subject to adequate regulation under the current good manufacturing practice (cGMP) regulation (Part 211)[45] and is available to FDA upon cGMP inspection.

Finally, in light of the "product," "process" and additional "facility" components of the "prioritization of drug manufacturing establishments for routine inspection,"[46] the additional burden of reporting the number of batches and batch size – which fluctuates according to market activity – would be unlikely to achieve a corresponding benefit.

5. Public disclosure of registration and listing information should be limited to the information provided in drug product labels, package inserts and medication guides

FDA has invited comment on which specific registration and listing information should be available for public disclosure.[47] As noted above, the proposal would make available for public disclosure an extensive amount of information including, for example, the following about a domestic manufacturer of a human OTC drug product:

Registration

Name of the owner or operator of each establishment
Name of each establishment
Any trade (or other) name(s) of the establishment
Address of each establishment
Registration number of each establishment
Type of operations performed at each establishment
Name, address, telephone and fax numbers, and e-mail address of the official contact

NDC number

Manufacturer's name, address, telephone number, fax number, e-mail address, and labeler code
Drug's established name and proprietary name (if any)
Name and quantity of each active pharmaceutical ingredient or the approved U.S. application number

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[45] *See* 21 C.F.R. part 211.
[46] "Risk-Based Method for Prioritizing CGMP Inspections of Pharmaceutical Manufacturing Sites – A Pilot Risk Ranking Model" at http://www.fda.gov/cder/gmp/gmp2004/risk_based_method.htm.).
[47] 71 Fed. Reg. at 51321.

Name of each inactive ingredient (or approved U.S. application number) for certain drugs
Dosage form
Package size and type, including immediate unit-of-use container
Marketing status
Drug or drug product type
Imprinting information
Private label distributor's name, address, telephone number, fax number, e-mail address, and labeler code
Drug's proprietary name (if any) as assigned by the private label distributor

Listing

The NDC number
Route of administration of the drug
The approved U.S. application number, if any
The registration number of each establishment where the manufacturing is performed for the drug
The schedule of the drug
Labeling information
The name, address, labeler code, telephone and fax numbers, and e-mail address of the private label distributor, if any

We believe that providing the public with all the information in the registration and listing database does not provide health-related, useful information to the consumer (patient) and will divulge commercially sensitive information; e.g., supplier relationships. Publicly available information should be limited to the information similar to that found in the prescription and non-prescription Physician's Desk Reference – typically the information contained in drug product labels, package inserts, and patient medication guides; e.g., proprietary name, generic name, active ingredients, purpose, indications, warnings, directions for use, inactive ingredients, storage conditions, how supplied, imprint (if applicable), and manufacturer/distributor information (as it appears on the label). Additionally, this information should only be available after the drug product has been drug listed.

D. Development and implementation of an electronic registration and listing system that meets the needs of FDA and the regulated community will require significant time and resources

Electronic submission of the "content of labeling" raises issues of technological capability and cost. In the economic impact analysis of the preamble of the proposed rule, FDA states that, most, but not all, manufacturers of human prescription drug products are already required to submit content of labeling in an electronic format, but manufacturers of monograph OTC drug products are not currently subject to these label requirements and

may not have the software necessary to submit labeling electronically.[48] This observation raises issues of technological capability as well as cost.

1. Many manufacturers of monograph OTC drug products lack the software capability to submit the "content of labeling" electronically

CHPA concurs with the agency's assessment that many manufacturers of monograph OTC drug products lack the software capability to submit the content of labeling electronically in accordance with the proposed regulation. The time and cost needed to develop this capability by (in FDA's own estimation) seventy-five (75) percent of drug product manufacturers that market only monograph OTC drug products could be considerable.[49]

In addition, we note that the agency's estimation of the total cost per firm for software acquisition and training (approximately $1,000)[50] does not factor in the additional – and certainly relevant – costs related to the conversion to SPL or the creation and/or maintenance of a Part 11-compliant system (see sections I.D.2 and I.D.3 below). Rather, FDA's estimation is based solely on its discussions with "industry IT personnel" and a survey of prices for software such as the Adobe Acrobat Standard ($250).

2. The currently available software to facilitate a change from PDF to SPL for monograph OTC drugs may be cost-prohibitive for smaller firms

In the preamble of the proposed rule, FDA indicates that it is prepared to receive the content of labeling as a PDF file that is searchable.[51] It also goes on to say, however, that "to be responsive to technological advances, we may recommend in the future that new file formats such as extensive markup language and software applications be used to submit labeling electronically."[52] The agency specifically cites SPL as an appropriate substitute for PDF.

CHPA is cognizant of the agency's assurances that it will provide "advance notice, in accordance with FDA's good guidance practice regulations...so that affected parties will have adequate time to convert to any new format or software" and that any "such format or software will be widely available before [switching] to a new technology."[53]

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[48] 71 Fed. Reg. at 51334. In addition, active pharmaceutical manufacturers producing ingredients for OTC drug products may not have the correct software to submit registration and listing information electronically. *Id.*

[49] 71 Fed. Reg. at 51334.

[50] *Id.* FDA estimated the price of software to be $250; the training of 2 employees is expected to cost $150 per employee and require 6 hours for each employee at a cost of $51.73 per hour. The total cost per firm is about $1,000, and the total cost to the OTC monograph industry for software acquisition and training is about $0.6 million. *Id.*

[51] 71 Fed. Reg. at 51316.

[52] *Id.*

[53] *Id.*

As discussed in section I.B.2 above, we believe FDA should eliminate the proposed requirement to submit drug facts labels for monograph OTC drug products. However, should a final rule include FDA's proposal, we believe submission of a searchable PDF file of the drug facts label is adequate for purposes of drug listing. Unlike the labels of prescription drug products, the labels of monograph (and, non-monograph) OTC drug products employ a simple, non-iterative format. Additionally, the available conversion software has not been validated with OTC drug labels and may be cost-prohibitive for smaller manufacturers.

We note that this topic was also addressed at the December 11th public meeting during one of the "open discussion" periods. We encourage FDA to carefully review this portion of the transcript for additional insight and guidance on this important issue.

3. CHPA requests a ruling on a pending citizen petition prior to the issuance of a final rule on electronic registration and listing

Currently pending before FDA is a citizen petition submitted by the self-named "Industry Coalition on 21 CFR Part 11" on September 17, 2004 (Docket No. 2004P-0429/CP1), requesting that FDA revoke Part 11 in its entirety because the provisions are largely superseded by the Government Paperwork Elimination Act.[54] To our knowledge, the only action taken by the agency with respect to this petition is an interim response dated March 15, 2005, which states that it "has been unable to reach a decision on [the] petition because it raises issues that require additional review..."[55]

FDA should issue a merits-based ruling on the citizen petition prior to the issuance of a final rule and grant this request. This recommendation is based in large measure on the integral role of the Part 11 regulation in the proposal itself. As noted, the electronic submission of registration and listing information, including the "content of labeling," would generally need to comply with Part 11.[56]

A resolution of the citizen petition is also important due to the inherent complexity and substantial cost associated with creating and/or maintaining a Part 11-compliant database that could handle the transfer of information that is required under the proposed rule, including the transfer of information between FDA, manufacturers, repackers, relabelers, drug product salvagers, and private label distributors.[57] To this point, we note that the software estimates generated by FDA in the preamble of the proposed rule do not reflect

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[54] CHPA is a member of this coalition.

[55] Letter correspondence dated March 15, 2005, from Jane A. Axelrad to Mr. Alan Goldhammer and Mr. Frederick Razzaghi (Docket No. 2004P-0429/CP1).

[56] Proposed 21 C.F.R. § 207.61(a).

[57] For example, under the proposal, to list a drug that is manufactured, repacked, relabeled, or salvaged for a private label distributor, manufacturers, repackers, relabelers, and drug product salvagers would have to obtain any existing NDC number from the private label distributor or would have to obtain the NDC number from FDA for a drug distributed by a private label distributor and would then have to place the NDC number assigned to the private label distributor's drug on the label. 71 Fed. Reg. at 51307.

these additional costs (e.g., creation of firewalls), although they are clearly relevant and should be factored in.

For all of these reasons, we formally request a ruling from FDA on the citizen petition prior to the issuance of a final rule.

4. Request for additional analysis related to the security of information submitted electronically

As noted, proposed section 207.61(a) requires manufacturers, repackers, relabelers, and drug product salvagers that are subject to the registration and listing requirements to adhere to Part 11. Although Part 11 requirements would apply, the agency states in the preamble of the proposed rule "[b]ecause we control the electronic drug registration and listing system, certain controls for systems would not apply...[such as the] use of secure, computer-generated, time-stamped audit trails..."[58]

In light of recent breaches in electronic security, CHPA requests additional analysis from FDA on the protections (or firewalls) that will be in place to protect the security of information and to prevent the co-mingling of information that has been entered into the agency's electronic system. Additionally, we note that FDA's economic analysis did not address the cost implications of implementing and maintaining adequate protections.

E. CHPA proposes that the requirement that a registrant certify electronically that "no changes have occurred" in registration and listing information be removed

Under the proposed rule, manufacturers, repackers, relabelers, and drug product salvagers would utilize the electronic system to *review and update* their registration and listing information.[59] For registration information, certain changes would be reported as "expedited updates" (i.e., no later than 30 calendar days after the changes).[60] Other registration information would be reviewed and updated annually.[61] Drug listing information would be reviewed and updated in June and December of every year.[62] If none of the registration or listing information has changed since the last review and update, the registrant would certify electronically for each listed drug product that "no changes have occurred."[63] Current regulations do not require an affirmative certification of

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[58] 71 Fed. Reg. at 51317.

[59] Proposed 21 C.F.R. §§ 207.29 and 207.57.

[60] Proposed 21 C.F.R. § 207.29(a). The changes to be reported as expedited updates are: the close or sale of an establishment; any change in the name or address of an establishment; and any change in the contact information of the official contact or the United States agent.

[61] Proposed 21 C.F.R. § 207.29(b).

[62] Proposed 21 C.F.R. § 207.57(b). FDA has also indicated, however, that "we are requesting that manufacturers, repackers, relabelers, and drug product salvagers provide all updates to listing information *within 30 calendar days of a change*," rather than in June and December. 71 Fed. Reg. at 51314 (emphasis supplied). It is, therefore, unclear what FDA will actually require in this regard. We request a clarification on this issue.

[63] Proposed 21 C.F.R. §§ 207.29(b)(3) and 207.57(b)(5).

each drug product, but only require the responsible entity to amend those listings for which a change has occurred.

In response to FDA's request for comment,[64] CHPA proposes that the requirement that a registrant certify electronically that "no changes have occurred" in registration and listing information be removed from a final rule.[65] Requiring this certification – in addition to a contemporary review of this information[66] – would arguably undercut the very efficiencies that an electronic system is designed to provide.

In essence, the certifying entity would have to manually verify (or "touch") every piece of unchanged information that has been individually logged. Clearly, identifying and communicating any changes that have occurred in registration or listing information would be a better use of time and resources, and would better serve the purpose of part 207.

We also underscore that the requirement to "review and update" listing information under the proposed rule would be enough of a burden alone without this additional layer of a certification.[67] This is especially the case for smaller companies or for firms with thousands of listings to maintain. One CHPA member company, for example, has approximately 7000 listings and further adds another 1200 per year.

On this point, our member companies anticipate the burden of reviewing and updating listing information for any "material change" to increase substantially under the proposed rule. This is primarily due to the volume of information associated with this requirement[68] as well as the exclusion of private label distributors from listing.[69] (e.g., see the discussions in sections II.A and II.D below)

In section I.G below, we suggest a variety of "educational" or compliance-building tools to help ensure that the electronic system functions as fully as it is intended and that the restrictions on the use of the system are followed.[70] We offer these (in part) as an alternative to the institution of a burdensome certification requirement.

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[64] 71 Fed. Reg. at 51314.

[65] As a threshold matter, it is unclear what this obligation to certify electronically that "no changes have occurred" would entail. For example, in order for a registrant to fulfill this responsibility, would the registrant electronically select a message that "no changes have occurred," or would something else be required? Even assuming that the demands of this process are kept to a minimum, CHPA proposes that it be removed from a final rule.

[66] Proposed 21 C.F.R. § 207.29(b)(3) states that the certification would be "accomplished *through* the review and update of registration information") (emphasis supplied).

[67] Proposed 21 C.F.R. § 207.57(b).

[68] Proposed 21 C.F.R. § 207.57(b)(4); *see also* 71 Fed. Reg. at 51313 ("Under the proposed definition of 'material change', the number of changes in listing information that are considered 'material' would include more than five types of changes considered 'material' in the current definition."). The agency's assumption, therefore, that only two employees per company would be needed to submit the content of labeling seems somewhat low. 71 Fed. Reg. at 51334.

[69] Proposed 21 C.F.R. § 207.41(c).

[70] *See* proposed 21 C.F.R. § 207.37.

F. Establishment registration fee

No fee is currently required for establishment registration.[71] FDA should repeat this requirement in a final rule.

G. There are a variety of educational or compliance-building tools that could ease the transition to an electronic system and enhance the functionality of the system as a whole

There are a variety of educational or compliance-building tools that could be used both prior to and following the implementation of an electronic registration and listing system. These tools could ease the transition to an electronic system and enhance the functionality of the system as a whole, operationally as well as in terms of regulatory adherence. As explained below, they could also be utilized to address the perceived "shortcomings" of the current NDC number system, as set forth by FDA in the preamble of the proposed rule.[72] In short, we regard this as a sensible step-wise strategy.[73]

1. Tools to be employed prior to the implementation of an electronic system

The adoption of educational or compliance-building tools prior to the implementation of an electronic system would serve several important objectives. Most notably, stakeholders would develop a greater understanding of the technology and FDA could obtain additional input on actual or potential problems from an industry perspective. Indeed, sharing with stakeholders the draft specifications of a *beta* version of this system before it has been finalized would be the preferred medium in this regard.

We also urge that a forum for the exchange of this information is readily available. The exchange of this information could be accomplished in a controlled environment through in-person meetings, demonstrations, or even tutorial-like ("Webinars") training sessions. These could be held at FDA or in the field, or wherever the agency would prefer.

We appreciate your consideration of this open approach.

2. Tools to be employed subsequent to the implementation of an electronic system

The report released by the OIG in August 2006 articulates seven recommendations in relation to the NDC number system as well as registration and listing generally. Although the findings of the OIG concentrate on, and are therefore limited to, prescription drug product listings in the National Drug Code Directory, we nonetheless find six (6) (out of

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[71] 21 C.F.R. § 207.20(d).
[72] 71 Fed. Reg. at 51296.
[73] As previously noted, CDER should also look to other systems within the various centers, i.e., CDRH and CFSAN.

seven (7))[74] of the recommendations in the OIG's report to be extremely persuasive in terms of their educational or compliance-building value. Accordingly, we recommend their implementation as well, specifically as tools to be employed following institution of an electronic system.[75]

They are:

a. Finalize guidance documents for submission of forms to list drug product (page 14).

Not unrelated to this recommendation, we agree with the proposal that FDA should "periodically issue guidance on how to provide registration and listing information in electronic format (for example, method of transmission, media, file formats, preparation and organization files)."[76]

b. Continue efforts to implement electronic submission of list forms by firms (page 14).

c. Implement a mechanism to routinely identify drug product omissions and inaccuracies in the drug registration and listing system (pages 14-15).

d. Resolve the status of drug product listings in the drug registration and listing system pending file (page 15).

e. Enhance communication with drug firms to facilitate accurate and complete reporting of drug product listings (page 15).

We would also encourage in-person meetings, demonstrations, and tutorial-like ("Webinars") training sessions.

f. Identify and take appropriate action against drug firms that consistently fail to list drug products and update information (page 15).

We believe that these tools would also be effective in addressing the perceived "shortcomings" of the current NDC number system, since the problems they were designed to address are essentially the same.[77]

In sum, we encourage FDA to adopt a step-wise strategy which emphasizes education and compliance-building opportunities. The development and implementation of an electronic registration and listing system in this fashion not only would ease the transition

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[74] We do not believe FDA should assume greater control over the assignment of NDC numbers for all of the reasons articulated herein.
[75] We note that FDA concurred with all of the recommendations in the OIG's report.
[76] Proposed 21 C.F.R. §207.61(a)(4); *see also* 71 Fed. Reg. at 51317 ("We plan to publish draft guidance and technical specifications on the electronic submission of registration and listing information...").
[77] *See* 71 Fed. Reg. at 51296.

to such a system, but would enhance the functionality of the system as a whole, operationally, as well as in terms of regulatory adherence.

II. CHPA supports retention of the current NDC number system

Our member companies believe that the current NDC number system is a well-established and effective regulatory framework. In particular, the current system is an intricate part of the OTC industry's activities, such as research and development; manufacturing; internal corporate recordkeeping and business development; distribution; and, marketing. Under current law, the marketing of monograph OTC drugs does not require marketing pre-clearance, and the current NDC number system is consistent with and supports this go-to-market structure of the monograph system.

Citing certain perceived "shortcomings" in the current NDC number system, and supposedly to create an "accurate, up-to-date NDC number system,"[78] FDA has proposed to revise the NDC number system. Specifically, in order "to ensure that the numbers are unique and unambiguous,"[79] FDA will assign all three segments of the NDC number – rather than assigning the labeler code and allowing the registered party to select its own product and package codes within certain parameters.[80] The submission for the NDC number would be separate from drug listing.[81]

Re-allocation of the responsibility for assignment of NDC numbers from industry to FDA will significantly disrupt the efficient marketing of effective and safe OTC drug products without corresponding regulatory benefits for the agency and health benefits for consumers. As discussed in more detail below, FDA assignment of NDC numbers and the proposed rule's framework for obtaining and utilizing NDC numbers will undo needed flexibility and will impact product "ownership" and associated regulatory obligations, as well as packaging and labeling operations.

A. The proposal to designate the responsibility of assigning the NDC number to FDA would undo needed flexibility

One of the agency's goals in designating the responsibility of assigning the NDC number to FDA is that manufacturers, repackers, and relabelers (and drug product salvagers who obtain NDC numbers for private label distributors) would be able to obtain their NDC numbers quickly and, as a result, prepare product labels[82] and marketing plans earlier.[83] But, as we at CHPA have learned from our member companies, FDA assignment of the NDC number, even if done electronically, would have the opposite effect.

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[78] 71 Fed. Reg. at 51296.
[79] *Id.*
[80] Proposed 21 C.F.R. § 207.33(a); 21 C.F.R. § 207.35.
[81] FDA would require the manufacturer, repacker, or relabeler to provide the information for an NDC number either before or at the time of drug listing. Proposed 21 C.F.R. § 207.33(g).
[82] 21 C.F.R. § 201.2(a).
[83] 71 Fed. Reg. at 51302.

1. Agency assignment of the NDC number would undermine the go-to-market structure of the monograph system

For manufacturers of monograph OTC drugs, the proposal would cause a fundamental shift in the go-to-market structure of the monograph system. Under current law, marketing pre-clearance of monograph OTC drugs is not required if the standards of the applicable monograph are met.

Having to obtain an NDC number from FDA would subject these products to a form of pre-market evaluation by the agency. (As noted, the submission for the NDC number is separate from drug listing, and FDA would require the manufacturer, repacker, or relabeler to provide the information for an NDC number either before or at the time of drug listing.[84])

Timely consumer access to a wide range of safe and effective products could be negatively impacted, especially in consideration of the fact that the vast majority of OTC drugs on the market today are monograph-based. The preparation of labeling could also not be completed until FDA has issued the number.

In response to manufacturer concerns about potential time lags due to FDA's assignment of product codes and packages codes, FDA states in its economic impact analysis that the electronic process should provide for "prompt" responses to requests for NDC numbers from FDA.[85] But it remains to be seen whether this can be accomplished, particularly if the NDC number is needed very quickly. In any case, the mere possibility that a response will not be prompt would present an unacceptable level of risk to the regulated community, and we do not believe the agency should assume this responsibility.

2. FDA assignment of the NDC number would disrupt the coordination required to launch new products

Currently, NDC numbers are often assigned well in advance of the actual launch of a product, sometimes as early as one year or more. At the time of assignment, formulas, packaging, imprint information, and even the manufacturing site (or sites) may not be fully known – all prerequisites for NDC number assignment under the proposed rule.[86]

Trade customers routinely request NDC numbers for products that are scheduled to launch, but are not yet in production. The need for flexibility in providing early alerts of NDC numbers to trade channels may be affected by the requirement that FDA issue the NDC number because the information required by FDA to request the number may not be available, or because the information is for a developmental product that is not yet final. Short-term promotional SKUs could also be adversely affected or, in certain cases, altogether halted due to the intervening step of FDA assignment. In particular, the proposed rule could be interpreted as requiring a re-packager/re-labeler to have a new NDC number assigned to these promotional SKUs.

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[84] Proposed 21 C.F.R. § 207.33(g).
[85] 71 Fed. Reg. at 51332.
[86] *See* proposed 21 C.F.R. § 207.33(c)(3).

On a related note, FDA's proposal also lacks a needed mechanism to change information in the NDC number application prior to NDC number assignment or prior to the listing information being submitted.[87] Any number of changes could occur at this stage of development of the drug, from a change to the proprietary product name to replacement of the preservative system in the formulation based on stability data. Under the proposal, if a product is changed after the request for an NDC number has been submitted, there could be multiple NDC requests and numbers for a drug prior to commercialization. The risk of confusion, increased cost, possible mix-ups, inefficiency, and product launch delays in this situation would be elevated.

Similarly, if a product is changed after the product has an assigned NDC number or reached the marketplace, the company's internal records, manufacturing and control documents, and embedded Universal Product Code (UPC) carrying the first-issued NDC number would have to be revised. (On this point, an FDA-mandated change to a monograph should *not* necessitate the issuance of a new NDC number.) New labels to reflect the updated NDC number would have to be created.[88] And previously prepared labels would likely become obsolete. The burden associated with these re-workings and increased inventories is expected to be substantial. Again, the risk of confusion, increased cost, possible mix-ups, inefficiency, product launch delays, and increased potential for recalls would be elevated. It would also mean – if not guarantee – that there would be repeated instances of inaccurate information in FDA's database, and company resources would be strained to repeatedly address this problem.

It is finally unclear from FDA's proposal what will become of an NDC number that is assigned to a particular product or dosage form that is never launched. Would a manufacturer, repacker, or relabeler be required to withdraw this information? A similar question arises with respect to a product that is changed after the request for an NDC number has been submitted. What exactly becomes of this information and what are the respective parties' obligations with respect to its management?

3. The proposed rule would result in the assignment of multiple NDC numbers to the same drug product

The NDC number should relate to the ultimate owner of the drug, thus reducing complexity and the chance of error. But we anticipate that the proposal would generate numerous situations where the same product would be assigned more than one (or even multiple) NDC numbers in the FDA database and/or on shelf. Take, for example, the following hypothetical scenarios:

> **Example 1**: Bulk product is manufactured at manufacturer A (domestic or foreign) shipped to packager B (domestic or foreign). Bulk manufacturer would need an

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[87] The regulation only addresses the changes that would require a new NDC number. Proposed 21 C.F.R. § 207.33(f). In brief, the regulation would require a new NDC number for any change in information that would be required to be submitted to obtain an NDC number, except a change in certain contact information. *Id.*

[88] The time required to create a new label is approximately 5 months.

NDC number for the bulk and packager would need an NDC number for the final package.

Example 2: Bulk product is manufactured and is packaged into SKU 1 at manufacturer A. Bulk is shipped to packager B who packages into SKU 2. Manufacturer would need an NDC number for bulk and an NDC number for SKU1. Packager B would need an NDC number for SKU 2. Product would have three possible NDC numbers; one for the bulk, one for SKU 1 and one for SKU2. Both SKU 1 and SKU 2 would be on shelf.

Example 3: Bulk product is manufactured and packaged into SKU 1 at manufacturer A. The same bulk is shipped to packager B and is packaged into the same SKU 1. Product with the same size would have three possible NDC numbers (including bulk). Again, both SKU 1 and SKU 2 would be on shelf.

Example 4: Product is manufactured and packaged at more than one manufacturer. Product with the same name and same sizes would have multiple NDC numbers on shelf.

Example 5: One component of the product is manufactured at site A, which is shipped to packager A, and then on to packager B, where the entire package is completed. Each step is listed on that particular site's registration. The result would be three NDC numbers.

Example 6: A private label distributor contracts with a repacker/relabeler to repackage/relabel one or more open-stock products bearing the private label distributor's NDC number for a promotional item to be distributed by the same private label distributor – which NDC number is the most appropriate?

We also note that at the December 11th public meeting, a "supply chain scenario" involving private label distributors was presented to the FDA panel during the afternoon session. This scenario demonstrated a *4-fold increase* in the number of NDC numbers over the current process, and concomitant increase in costs. It also concluded that the proposed process would "[i]ncrease [the] frequency of changing NDC numbers" and require multiple labels of multiple sizes rather than just one.

We urge the agency to study these scenarios carefully, in addition to the feedback it has already received. Among other things, these scenarios demonstrate the propensity of the proposal to add complexity, confusion, costs, and increased possibility of error (e.g., right label on the right product). In making the revisions for a final rule, we urge FDA to take these considerations into account and not take on the responsibility of assigning NDC numbers.

4. FDA should not consolidate labeler codes

Under proposed section 207.33(a), FDA's assignment of the NDC number "will include the existing labeler code, if any."[89] However, "if a manufacturer, repacker, or relabeler uses more than one labeler code, [FDA] would prospectively assign NDC numbers that use only one labeler code for the manufacturer, repacker, or relabeler."[90]

Restricting a company to one labeler code may be inappropriate in circumstances where multiple legal entities exist under one corporate umbrella. For example, Company A is a corporate umbrella or holding company with two divisions, Company X and Company Y. Company A provides broad corporate oversight and is not directly involved in the research, development or marketing of drug products. Under the ownership of Company A, Company X and Company Y are independent operating divisions with responsibilities for its distributed products, such as research and development, manufacturing, labeling, quality and safety monitoring, and marketing. Although owned by Company A, Companies X and Y require different labeler codes which reflect their regulatory and commercial responsibilities for the products each markets independently from the other.

Accordingly, a final rule should include the possibility of a company to have more than one labeler code.

5. FDA should retain the current format of the NDC number and clarify the configuration options for the NDC number

Under proposed section 207.33(a), the NDC number is to be a unique 10-digit number with 3 segments – the labeler code, the product code, and the package code.[91] This is the sole requirement related to the format of the NDC number in the proposed regulation, but the preamble of the proposed rule and FDA's notice of public meeting raise additional issues.

a. 10 digits vs. 11, 12...digits

In the notice announcing the public meeting on December 11, 2006, the agency invites comment on "[t]he possibility of adding one or more digits to the NDC code in the future,"[92] while also indicating that it "is not proposing to change the format of the NDC number..."[93] at this time. The agency similarly provides in the preamble of the proposed rule that "[i]f we reach NDC number capacity (possibly in 30 to 50 years), we could propose to either add alphanumeric capability or expand the number of numeric digits to 11 or 12..."[94] Advances in current UPC technology would likely pre-date this need.[95]

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[89] Proposed 21 C.F.R. § 207.33(a).
[90] 71 Fed. Reg. at 51300.
[91] Proposed 21 C.F.R. § 207.33(a).
[92] 71 Fed. Reg. at 63728.
[93] 71 Fed. Reg. at 63727.
[94] 71 Fed. Reg. at 51300.
[95] *Id.*

Based on the plethora of concerns that were raised at the December 11th public meeting, FDA should retain the current 10-digit format.[96] For SKUs with a premium of space on the label, this is particularly critical.

b. Configuration

In the preamble of the proposed rule, FDA indicates that as under current regulations, the labeler code would be either four or five digits, the product code would be four or three digits, and the package code would be either two digits or one digit.[97] But the proposal does not clearly address whether the agency is planning to stay with the same convention of requiring each labeler code to use only one NDC number format (i.e., 4-4-2, 5-3-2, or 5-4-1). In addition, it is unclear whether companies will be able to choose a format (10 digits or otherwise – e.g., 5-4-2 for 11 digits) when they are first assigned a labeler code, or if one will be arbitrarily assigned, and according to what criteria.

We request a clarification on these issues.

6. Importation

Assignment of NDC numbers by FDA could also impact companies' ability to obtain admission of their products into the United States. For, until FDA has assigned an NDC number, the product cannot be listed and would likely be denied admission on this basis.

B. FDA should continue to allow private label distributors to obtain their own labeler codes

Under the proposed rule, private label distributors would not be allowed to apply for or obtain an NDC number.[98] Instead, this responsibility would rest on the shoulders of the manufacturer, repacker, relabeler, or drug product salvager.[99] This exclusion (of the private label distributor) raises a number of potential wrinkles that the proposal does not adequately address.

For example, if an entity utilizes more than one contract manufacturer in the manufacture of an individual drug product, what are the criteria for determining which contract manufacturer is responsible for obtaining the labeler code for the private label distributor, or does the private label distributor continue to request the labeler code independently? If the private label distributor does not continue to request the labeler code, would the private label distributor end up with two or more different labeler codes, a different one obtained by each contract manufacturer? How would complaint and adverse event reporting obligations be impacted, if at all?

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[96] *See* http://www.fda.gov/cder/ndc (noting the effective use of an asterisk to harmonize with the HIPAA 11-digit NDC number standard).
[97] 71 Fed. Reg. at 51299.
[98] Proposed 21 C.F.R. § 207.33(b)(3).
[99] *Id.*

In short, the inability of a private label distributor to obtain its own labeler code would create unnecessary confusion on what is the "appropriate NDC number"[100] for drug listing purposes and ought to be avoided by FDA in a final rule.

C. FDA should include product formulators who market the final product under their own label in the definition of "manufacturer"

The proposal segments the current definition of manufacturing into four functional types: (1) manufacturer; (2) repacker; (3) relabeler; and (4) drug product salvager.[101] Under the proposed rule, only manufacturers, repackers, relabelers, and (in certain cases) drug product salvagers would be able to obtain an NDC number from FDA and register and list. Private label distributors would not.

An entity that develops a new proprietary formula as part of its research and development for an OTC drug product and then utilizes a contract manufacturer for commercial production of that drug product, does not meet the definition of a manufacturer, repacker, relabeler, or drug product salvager under the proposal. As a result, the entity arguably with the most product knowledge – i.e., the formulator company who will also market the product under its label, would be unable to obtain an NDC number and list the drug, and (in effect) would be incorrectly classified as a private label distributor. The formulator company, in essence, would lose control of its own drug, and the NDC number assigned to the contract manufacturer would be deemed the "appropriate NDC number."[102] (We also note the possible assignment of multiple NDC numbers to the same product if the specification developer engages multiple contract manufacturers, each of which would have a different NDC number.)

To avoid this situation, the definition of manufacturer should be expanded to include an entity that is a formulator company that markets the final product under its label. FDA has adopted a similar policy with regard to prescription drug pedigrees in its November 2006 guidance on the requirements of the Prescription Drug Marketing Act (PDMA).[103] Within FDA, CDRH's assignment of manufacturer responsibilities to the "specification developer"[104] of a medical device provides a similar approach.

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[100] Proposed 21 C.F.R. § 201.2(b).

[101] *See* proposed 21 C.F.R. § 207.1. The definition of "manufacturer" includes, but is not limited to, contract manufacturers.

[102] Under the proposed rule, the "appropriate NDC number" is "the NDC number of the last manufacturer, repacker or relabeler (including drug product salvager who repacks or relabels the drug), or private label distributor, as defined in section 207.1, that is the last manufacturer, repacker, relabeler, or private label distributor responsible for the drug immediately before it is received by the wholesaler or retailer." Proposed 21 C.F.R. § 201.2(b).

[103] Guidance for Industry; Prescription Drug Marketing Act (PDMA): Questions and Answers. November 2006. In section 13 of the guidance, FDA notes that an NDA-holder who does not perform manufacturing operations would not be considered a "manufacturer" under sections 203.3(s) and 201.1, but that for purposes of the PDMA pedigree requirements, FDA will exercise its enforcement discretion to allow an NDA-holder to be treated as a manufacturer with regard to certain pedigree responsibilities.

[104] *See* 21 C.F.R. part 807.

Alternatively, the definitions and associated responsibilities should distinguish a "distributor" (i.e., product formulator who markets the final product under its label) from a "private label distributor," and allow the distributor to obtain an NDC number and perform its own drug listing.

D. The proposal that the name of each inactive ingredient must be submitted in order to obtain an NDC number from FDA

Inactive ingredient changes in a product, whether qualitative or quantitative, can occur with regular frequency, both before and after the product is launched, for any number of reasons. The inactive ingredient may be replaced because it is unavailable or has become too expensive. Or, a new raw material vendor may have acceptable specifications with no effect on the product, but vary from those of the previous supplier. Where a product has more than one manufacturing site, especially between a domestic and foreign site, there is a possibility that an inactive ingredient may be different, but equal within the formula. As explained below, each of these changes would necessitate a new NDC number and would greatly complicate the current system.

Notably, the proposed rule does not provide a definition for "material change" as related to inactive ingredients.

1. Submission of this information would result in multiple inefficiencies, such as confusion and product launch delays

The required submission of inactive ingredient information is ill-advised because every time an inactive ingredient change occurs – for any of the reasons enumerated above – unless the approved U.S. application number is provided, a new NDC number from FDA would be required.[105] This opens the NDC number to being changed many more times than it is subject to change under the current system. It also opens the door to multiple NDC numbers being issued for the same product. This could result in unnecessary confusion, product launch delays, and the potential for recalls. And, changing the NDC number is not an insignificant undertaking, in light of the changes to the label and other records and documentation that must also occur, including UPC re-application. An update to drug listing information would also be triggered.[106]

2. Requiring a new NDC number based on a variance in inactive ingredients runs counter to FDA's policy on "over-inclusive inactive ingredient labeling"

On September 8, 2000, CHPA submitted a citizen petition to Docket No. 00P-1297/CP3, requesting that FDA "amend 21 CFR 201.66 to allow an OTC drug manufacturer or distributor to use a phrase 'may contain,' 'may also contain,' or 'and/or' in the inactive ingredient section of the finished drug product labeling to list those inactive ingredients

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[105] Proposed 21 C.F.R. § 207.33(c)(2)(ii) and (f)(1). We note that the exclusive reference to certain human prescription and animal drugs in proposed section 207.33(f)(2) is confusing at best, and we seek clarification from FDA on this provision.

[106] Proposed 21 C.F.R. § 207.57(b)(4).

that are different when a finished OTC drug product is obtained from multiple suppliers." CHPA requested this action "so that manufacturers and distributors can fulfill the requirement to disclose product ingredients, but have the needed flexibility to source ingredients and product from more than one supplier without the expense of separate inventories and costly label changes."

In November 2001, FDA issued a favorable letter in response to the CHPA citizen petition. Based on an examination of the statutory and regulatory language, the agency concluded that –

> [N]othing in 502(e)(1)(A)(iii), or FDA's OTC labeling rule, prohibits use of over-inclusive OTC drug inactive ingredient labeling. Although there is nothing related to such labeling in the legislative history for § 502(e)(1)(A)(iii), the agency has located no evidence that Congress intended to affect the preexisting voluntary common industry practice of listing inactive ingredient information for OTC drug products in alphabetical order, and utilizing over-inclusive inactive ingredient labeling, as appropriate. Indeed, FDA recognizes that some OTC drug manufacturers used 'may contain' or similar language on OTC drug labeling without objection from FDA for nearly 15 years. The agency is not aware of any adverse consequences occurring as a result of over-inclusive inactive ingredient listing. Consequently, there is no reason to believe that over-inclusive inactive ingredient listing was meant to be prohibited by § 502(e) of the Act, as amended by FDAMA.

Although the agency stopped short of amending section 201.66 as requested by CHPA, it found as a practical matter that over-inclusive inactive ingredient labeling "may be accomplished, consistent with the Federal Food, Drug, and Cosmetic Act, by placing those ingredients that may or may not be contained in the OTC drug product in the inactive ingredient listing with an asterisk placed next to those ingredients. The asterisk would then be reprinted at the end or bottom of the inactive section of the 'Drug Facts' box, with the notation 'contains one or more of these ingredients.'"[107]

3. The agency's concerns related to the disclosure of inactive ingredient information can be adequately addressed under current regulatory controls

CHPA strongly agrees with the agency's statement that consumers must be aware of "the inactive ingredients of the drugs they might be taking..."[108] We also believe, however, that individuals and their caregivers already have the tools necessary to "prevent potentially serious reactions" from occurring based on current regulatory controls.[109] FDA's investigative powers are also sufficiently robust.

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[107] The agency also cautioned against "overzealous use of over-inclusive inactive ingredient labeling" and also noted that it "intends to issue guidance to the industry listing suggested parameters for the use" of such listing.

[108] 71 Fed. Reg. at 51321.

[109] *Id.*

Specifically:

- The label of all OTC drug products must specify the identity of active and inactive ingredients they contain.[110] Therefore, individuals and their caregivers can quickly know in advance whether or not a specific product can be taken safely.

- Regulations specifically require disclosure of certain ingredients that for public health reasons regulations are affirmatively listed in the labeling (e.g., ingredients with specific allergenic or dietary concerns).[111] These controls help ensure that detailed warnings about a specific ingredient are communicated clearly.

- By regulation, monograph OTC drugs may only contain "suitable inactive ingredients which are safe in the amounts administered and do not interfere with the effectiveness of the preparation or with suitable tests or assays to determine if the product meets its professed standards of identity, strength, quality, and purity."[112]

And finally:

- Because the current labeling is available to FDA at the time of drug listing,[113] the agency has a repository of information to enable an effective investigation of "possible drug contamination, counterfeiting, or adulteration"[114]

E. FDA should not require the labels of OTC drug products to include human-readable NDC numbers with the prefix "NDC"

Currently, FDA requests, but does not require, that the NDC number appear on all drug labels and labeling.[115] Proposed section 201.2(a) would require the "appropriate NDC number," in human-readable form, to appear on the labels of all drugs subject to the drug listing requirements.[116] The "appropriate NDC number" is described as the NDC number assigned by FDA to the last manufacturer, repacker or relabeler, or private label distributor responsible for the drug immediately before it is received by the wholesaler or retailer.[117]

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[110] 21 C.F.R. § 201.66(c).
[111] *See, e.g.*, 21 C.F.R. § 201.64 (sodium); 21 C.F.R. § 201.21(b) (aspartame); 21 C.F.R. § 201.70 (calcium); 21 C.F.R. § 201.71 (magnesium); and 21 C.F.R. § 201.72 (potassium).
[112] 21 C.F.R. § 330.1(e).
[113] 21 C.F.R. § 207.25(b).
[114] 71 Fed. Reg. at 51321.
[115] 21 C.F.R. §§ 201.2, 207.35(b)(3). Drug products described in the current section 201.25(b) must also have on the label a bar code that contains, at a minimum, the appropriate NDC number in a linear bar code that meets the specified standards.
[116] Proposed 21 C.F.R. § 201.2(a).
[117] Proposed 21 C.F.R. § 201.2(b).

As discussed below, the mandatory inclusion of human-readable NDC numbers on the labels of OTC drug products creates a burden without providing clear and consistent benefits.

1. Inclusion of the NDC number on the labels of OTC drug products will create unreasonable burdens for packaging, labeling and distribution

CHPA concurs with the industry feedback received by the Eastern Research Group, Inc., that the new label requirements as they apply at the OTC unit-of-use level, such as blister packs, may pose problems. As noted by FDA in the preamble, some packaging lines for unit-of-use OTC products not subject to the bar code rule might need to be retooled to accommodate human-readable NDC numbers, and these modifications are expected to be fairly challenging and costly.[118] One CHPA member company has indicated that "it could not afford to bear th[e] financial burden" of creating new labels with human-readable NDC numbers without the corresponding imposition of higher prices for consumers.[119]

Space on the label is also a concern, particularly for small immediate packages with limited label space (e.g., printing would be too small to read). Professional and promotional samples fall into this category. Having both a bar code and a human readable NDC number could mean going to a larger container with a larger label, which raises issues of increased cost and potential slack-fill. One alternative is allowing the use of "N".[120] This option would utilize less label space than "NDC" and would clearly signal the NDC number.

Requiring the NDC number on secondary packaging may create[121] additional burdens for the labeling of temporary SKUs, such as promotional SKUs (e.g., Buy One, Get One, or "BOGOs"), where two or more immediate containers are repackaged into a single carton. In this situation, each immediate container would have an open stock NDC number, but the promotional SKU may require another, different NDC number as a different packaging configuration. "New" immediate containers (rather than open-stock) with the BOGO NDC number would be required, or the open-stock immediate containers would have to be over-labeled. It is also unclear which entity would be responsible for applying for the new bonus size NDC number.

In sum, the mandatory inclusion of the NDC number on the product label should not be required for OTC drug products, especially those products or SKUs that do not require a bar code label.[122]

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[118] 71 Fed. Reg. at 51333.
[119] This CHPA member company estimated that less than 25% of its SKUs have an NDC number printed on the carton, and less than 5% have an NDC number printed on the tube or bottle label.
[120] Proposed section 201.2(d) would require the human-readable NDC number to be immediately preceded by the letters "NDC".
[121] If multiple products that have individual NDC numbers are co-packaged for promotional items, would the promotional product need a new NDC number? This is unclear under the proposal.
[122] *See* 21 C.F.R. § 201.25.

2. Inclusion of the NDC number on the labels of OTC drug products will not enhance traceability

An issue at the December 11th meeting, FDA obtained feedback regarding the role of the NDC number in the context of product recalls and the like. The recall process is a voluntary one conducted by the distributor who may or may not be the manufacturer. The distributor is in the best position to determine which tools are appropriate for ensuring the timeliness and completeness of a recall. We would like to underscore that, generally, the primary tool for conducting a product recall is the lot number, not the NDC number. Also, brand name, distributor, and the expiration date are potentially more useful than the NDC number is in executing a recall at the consumer level. This is especially the case for those products which are not subject to the bar code rule.[123]

III. The proposed rule does not adequately distinguish the regulatory requirements for drug products in commercial distribution in the United States from drug products intended for export only or those imported-for-export

In the preamble to the proposed rule,[124] FDA indicated its intent to revoke certain provisions of the current sections 207.40(a) and (b). FDA cites the Bioterrorism Act[125] as one basis for this proposed revocation. We note that with regard to drug products, the Bioterrorism Act does require establishment registration, prior notice of importation, statements of activities/plans, certificates of analysis, and recordkeeping; however, the Bioterrorism Act does not require listing of drugs or drug components intended for subsequent export. In this regard, the proposed rule does not clearly address whether drug components and drug products intended for export or imported-for-export are exempt from the various provisions related to obtaining an NDC number, drug listing and updating of drug listings. The utility of requiring compliance with these provisions of the proposed rule for such products is not evident – especially as the recipient country will have its own label requirements.

IV. The proposed implementation dates for a final rule and the transition period for adding the NDC number to all OTC drug labels, are unrealistic

The complexity of the proposed NDC number requirements, the currency of FDA's drug listing database and an effective date of nine months for a final rule adds an enormous time burden on entities required to have an NDC number and to list. It is unlikely entities could complete a review and update of all their listings in the FDA database within the time allowed (nine (9) months), or change all of their labeling to comply with this rule within five (5) or seven (7) years. This is especially true of entities that would need to coordinate efforts within a complex supply chain.

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[123] *See* 21 C.F.R. § 201.25.
[124] 71 Fed. Reg. 51276.
[125] 71 Fed. Reg. at 51283-51284.

As discussed below, both of these dates should be re-evaluated when the complexity of the final rule is known so that a realistic timeframe can be estimated.

A. FDA's proposal that all registration and listing information be updated and entered within nine months after the effective date of the final rule is unworkable

FDA proposes that its electronic system be used to "enter and update" all NDC number information, as well as all registration and listing information, no later than nine months after the effective date of a final rule.[126] Based on the issues discussed in Section I above, as well as additional issues related to assignment of NDC numbers, which are explained in Section II of these comments, this proposed timeframe is unrealistic for several reasons.

1. The validation required of FDA would likely exceed its resource capabilities and result in additional delays

NDC numbers assigned to drugs before the effective date of the final rule would remain unchanged, provided the manufacturer, repacker, or relabeler, within nine months after the effective date, reviews and updates the information in FDA's database for the NDC number.[127] FDA will "validate" that current NDC numbers comply with the new regulations as finalized. If a manufacturer, repacker, or relabeler does not review or update its information within nine months after the final rule's effective date, FDA may assign a new NDC number to the drug or take other appropriate steps.[128]

In light of the number of existing NDC numbers and complexity of the proposal, the amount of time and resources that would be needed to "validate" current NDC number compliance with the new regulations would be overwhelming. Also, until FDA has completed its validation of an NDC number, the marketing of the product would be in limbo. Delays would be inevitable.

Retaining the current NDC number system and instituting step-wise measures, such as guidance documents and technical specifications on the electronic system, would comprise a far more effective – and achievable – strategy.

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[126] 71 Fed. Reg. at 51305 and 51345.

[127] 71 Fed. Reg. at 51296-51297, 52305 and 51345.

[128] FDA explains that to retain the NDC number, a manufacturer, repacker, or relabeler may have to provide the agency with new information about the drug's characteristics. If necessary, FDA will assign a new product code and/or package code, creating a new NDC number for a drug. FDA indicates that it intends to issue guidance related to these topics, assist manufacturers, repackers, and relabelers in determining whether their NDC numbers are accurate, and address any problems with existing NDC numbers (such as duplicate or potentially duplicate NDC numbers). 71 Fed. Reg. at 51305-51306.

2. The date of compliance for reviewing and updating this information should be extended by FDA for the following reasons

OTC drugs on the market today are expected to have an NDC number.[129] Consequently, the number of affected products for some firms will be in the hundreds, if not thousands, at the time of the effective date of the final rule. As noted section I.E above, one CHPA member company has approximately 7000 listings and furthers add another 1200 per year. But even for those companies with fewer listings to manage, we have been told that this 'review and update' will "require [a] significant allocation of internal resources to accomplish" and the "possible addition of manpower."

The complexity of the proposal's NDC number requirements also supports more time to review and update this information. For example, a product with multiple inactive ingredient combinations or other minor differences may lack an NDC number for each variation of the product as required under the proposed rule. To trace and bring these products into compliance with the new regulation, in addition to adjusting internal records and documentation to enable the review and updates to occur, will take a considerable amount of time.

Under the proposal, private label distributors, including formulator companies, would lack the authority to access drug listing information and to supply any reviews and updates. Extensive information-sharing, coordination, and cross-checking between these entities would therefore be required, and this effort is expected to be time-intensive.[130]

The impracticality of achieving compliance within the nine month timeframe is also evidenced by the fact that the information entered by FDA into its drug listing database is itself not up-to-date. To our knowledge, the last such update for OTC drugs was in 2003. Until this body of information is current, a comprehensive review cannot occur. Otherwise, extensive re-tracing would be necessary, an incredibly burdensome endeavor. The date of compliance should be extended by FDA until the task of updating the FDA database has been completed and interested parties have had an opportunity to assess the registration and listing information in accordance with the applicable regulatory requirements.

B. If a final rule requires placement of the NDC number on all OTC drug labels, then FDA should not shorten the proposed transition period

FDA intends to phase in the requirement for the NDC number placement on OTC drug labels over a seven year period, starting from the effective date of the final rule, but the

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[129] 21 C.F.R. § 207.35.

[130] Under the proposal, to list a drug that is manufactured, repacked, relabeled, or salvaged for a private label distributor, manufacturers, repackers, relabelers, and drug product salvagers would have to obtain any existing NDC number from the private label distributor or would have to obtain the NDC number from FDA for a drug distributed by a private label distributor and would then have to place the NDC number assigned to the private label distributor's drug on the label. 71 Fed. Reg. at 51307.

agency stated that it is considering shortening this period to five years.[131] It has invited comment on this issue.[132]

Due to the noticeable cost increase associated with a five year implementation period[133] as well as the overall complexity of the proposed rule and its requirements, FDA should not reduce the phase-in period for NDC number placement on OTC drug labels to five years and should consider extending implementation beyond seven years if the proposed rule is finalized as written.

CONCLUSION

We would like to thank FDA for this opportunity to comment on its proposed rule on electronic registration and listing. We are encouraged by the steps taken thus far in this process and look forward to working with and advising the agency in the future.

In sum, our position consists of four principal points. First, CHPA supports the development and implementation of an electronic registration and listing system that meets the needs of FDA and the regulated community. Second, CHPA supports retention of the current NDC number system. Third, the proposed rule does not adequately distinguish the regulatory requirements for drug products in commercial distribution in the United States from drug products intended for export only or those imported-for-export. Fourth, the proposed periods for implementation of an electronic system and the transition to placement of NDC numbers on labels are unrealistic.

We believe a step-wise strategy which enhances the integrity of the current paper system while concurrently developing an electronic system would be the most appropriate means of meeting the needs of FDA and the regulated community. Joint (i.e., FDA and the regulated community) development and testing of an electronic system; the finalization of associated guidelines; and, the utilization of educational and compliance tools may obviate the need for making many of the proposed changes to the current NDC number system.

Respectfully submitted,

Paul J. Larsen, Esq.
Associate General Counsel & Secretary
Consumer Healthcare Products Association
900 19th Street, NW
Suite 700
Washington, DC 20006
Tel: (202) 429-9260
E-mail: plarsen@chpa-info.org

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[131] 71 Fed. Reg. at 51305-6.
[132] 71 Fed. Reg. at 51306.
[133] 71 Fed. Reg. at 51338.