

PhRMA SPL Working Group Comments on Proposed Drug Listing Changes (21 CFR 20, 201, et al.)

Key Philosophical or Strategy Issues

Key issue: Patient Safety (see Item #1). Changes to current NDC codes could bring unintended consequences to patient health care and even patient safety.

Secondary issue: Business impact of any delays in establishing NDC code.

Secondary issue: Multiple submission of duplicate data to FDA: Existing Structured Product Labeling standard overlaps with proposed data listing sets.

Assumptions

Key assumption: For cases in which the content of labelling for drug and biologic products are submitted as part of the data-listing process, only an FDA-approved Structured Product Label would be submitted.

Items and references begin on next page.

References to Federal Register 71 (167)

Category	Item with Reference	Relative Importance (major or minor)	Key Concerns with Explanation of Position	Proposed change
<p align="center">Clarifying NDC Code Assignment Standards and Lifecycle</p>	<p>#1 NDC encoding, new process and systemic changes (51299, section b., col 1 and ff.; 51300, col 2, first full paragraph, last sentence; 51330, Item 1, col 1 ff.)</p>	<p align="center">Mj</p>	<p>The SPL WG agrees that the FDA should be the caretaker of the US National Drug Code (NDC) system and supports the agency’s ownership and oversight of NDC assignments.</p> <p>The SPL WG believes that the impact of changing NDC numbers would have significant financial effect on all three groups specified in <u>E. Costs, Item 1. Costs of a Single Method of Assigning NDC Numbers</u> (51330 ff).</p> <p>Of note is the agency’s notification that the product codes for drug products with the same active ingredients but different dosage forms, strengths, or routes of administration, or an existing product in which an inactive ingredient is changed, may not be consecutive under the new NDC assignment system. This change alone will have great impact on sponsor, manufacturer, payor, and other stakeholders in the current NDC system.</p> <p>Additionally, changing NDC codes for products currently available commercially may cause significant confusion in the marketplace:</p> <ul style="list-style-type: none"> • Not all existing computer systems 	<p>Recommend that, <u>prior to finalizing the rule</u>, the FDA form a task force consisting of agency, pharma, payor, poison-control and other emergency response groups, system vendors, and other stakeholders in the existing NDC code system to analyse the current state of NDC codes and define the proposed new system in such a way that legacy codes can be accommodated while enabling a robust new NDC system that can be implemented across all stakeholders with the least disruption in business and while minimizing risk to patients.</p>

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			<p>will have any mechanism currently in place or capable of being added to the system to ensure that a legacy code will be associated with an updated code from the agency.</p> <ul style="list-style-type: none"> • Literature and other printed references in common usage, including older versions of the <i>Physicians' Desk Reference</i>, will not reflect changes to NDC codes. • During the transition period, patient records and even drug products on pharmacy shelves or in patient's hands will not be immediately identifiable via the updated, FDA-ascribed NDC code. 	
<p>Clarifying NDC Code Assignment Standards and Lifecycle</p>	<p>#2 Product code assignment (51280, col 1, second bullet)</p>	<p>Mj</p>	<p>Delay in NDC code assignment or reassignment will likely impact the internal and external timelines for labelling, submission, and distribution of drug products. Currently, sponsors establish and use NDC codes for products well in advance of application submission and product launch. While the FDA's ownership of the NDC system is a positive step, the lifecycle of NDC encoding, and especially code establishment timelines, must be clearly defined to ensure limited impact on product development timelines.</p>	<p>Recommend that, <u>prior to finalizing the rule</u>, the FDA and/or HHS work with other NDC stakeholders in establishing a workflow and lifecycle plan for NDC product encoding, including a set number of days in which a request for NDC assignment or reassignment must be completed by the FDA.</p>

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<p align="center">Clarifying NDC Code Assignment Standards and Lifecycle</p>	<p>#3 Format of request for NDC (51300, col 3, last paragraph; 51300-51301, Table 1)</p>	<p align="center">Mj</p>	<p>The cited passages list required information that a sponsor must submit in order to receive an NDC for its product. As with drug-listing information discussed in Item #2a, the SPL WG finds that the data requirements for an NDC are currently captured within the SPL data elements. Therefore, three submissions to the agency cover much of the same information: labelling (in SPL), drug listing, and NDC code.</p> <p>The WG also notes that the chronology of the three submissions usually is as follows: NDC, then labelling, and finally the drug listing data.</p>	<p>Recommend that, <u>prior to finalizing the rule</u>, the FDA partner with HL7 and the SPL Working Group to establish a methodology by which the SPL XML file format is used to submit data appropriate for a product's following three submission types: NDC request, content of labelling, and drug-listing data.</p>
<p align="center">Clarifying NDC Code Assignment Standards and Lifecycle</p>	<p>#4 Example use of drug listing (51296, col 2, first full paragraph)</p>	<p align="center">Mn</p>	<p>The cited passage presents an example in which a consumer, pharmacist, or HCP uses the bar-coded NDC number to access the latest approved product labeling from the Daily Med site. The text of the example suggests that a newly added adverse drug reaction (ADR) would somehow be highlighted as a new entry in the latest product labelling from the Daily Med site. This can be misleading, given that a new ADR would be identified in the Major Changes section of labelling only if the event were captured in the Contraindications or Warnings and Precautions sections.</p>	<p>Recommend that the text simply note a computer system could pull the latest labelling information from the Daily Med site.</p> <p>If the complete example is preferred, recommend that the text be altered either to specify that the ADR in question is captured in the Contraindication and Warnings or Precautions section of the labelling and, thus, is highlighted in the Major Changes text; or that the text clarify that the consumer, pharmacist, or HCP will need to read the Adverse Events in the Daily Med-posted labelling to find the new ADR.</p>

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<p align="center">Clarifying Drug Listing Information Submission Standards and Lifecycle</p>	<p>#5 Content of Labeling submission and drug listing requirements (51286, col 2, first full paragraph; 51296, cols 1 and 2, final bullet in col 1; 51308, sections a. b, and c., cols 1 and 2)</p>	<p align="center">Mj</p>	<p>The SPL Working Group (WG) understands that a sponsor would not send content of labelling with its drug listing submissions if it submits instead the application number of the product in question. However, given the duplication of information in the SPL data elements and the required information for drug listings, the SPL WG asks the FDA whether the rule could be changed to allow submission of drug listing information as part of the SPL submission instead of as a separate drug-listing submission.</p>	<p>Recommend that, <u>prior to finalizing the rule</u>, the FDA partner with HL7 and the SPL Working Group to investigate whether the SPL data elements could be modified and appended to include all required data-listing information and, if so, that the FDA work with its vendors to determine how data-listing and SPL can be incorporated into a common submission process.</p>
<p align="center">Clarifying Drug Listing Information Submission Standards and Lifecycle</p>	<p>#6 Clarification of submission timing (51280, col 1, second bullet; 51308, sections a, b, and c, cols 1 and 2; 51313, col 3, first bullet)</p>	<p align="center">Mn</p>	<p>According to the proposed rule, the company's Drug Listing must be updated to include new required information within nine months of publication of the final rule. Also noted in the proposal, if the application number (i.e., NDA, BLA) is supplied, the content of labelling in an SPL file does not have to be included in the drug-listing submission. Finally, as noted, a significant change in product labelling (a material change) would require an update to the drug listing information within 30 days of approval. Would reference to the NDA number fulfill this final requirement and thus pre-empt the need for submitting content of labelling in SPL format? How would an updated SPL be indicated if the NDA number is referenced?</p>	<p>Recommend that the FDA clarify in the sections noted whether material changes in prescribing information would require one of the following options as part of the drug-listing submission:</p> <ul style="list-style-type: none"> • Submitting the entire SPL for the currently implemented product labelling • Submitting the application number only, with no additional information • Submitting the unique <id> value from the SPL for the currently implemented product labelling

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<p align="center">Clarifying Drug Listing Information Submission Standards and Lifecycle</p>	<p>#7 Variation in effective times (51280, item B in col 2)</p>	<p align="center">Mn</p>	<p>The cited text describes an electronic link between documents and data submitted as part of the drug listing submission and the DHHS health information technology environment, presumably including the National Library of Medicine’s drug information pages which contain labelling in SPL file format. The SPL WG understands that, according to the <i>SPL Implementation Guide</i> in effect, sponsors are not required to update <effectiveTime> tags in a submitted SPL file after the FDA has processed the submitted file and has posted it to the National Library of Medicine (NLM) web site. In fact, the Implementation Guide clearly states that any submitted SPL file should not contain a value for <effectiveTime> tags. (p. 8) It is not clear from the current drug-listing proposal what the result would be if a pharmaceutical company chose to supply the SPL as part of the drug listing submission and the submitted SPL file did not have the same (or excluded entirely) the <effectiveTime> values as contained within the FDA-processed SPL file.</p>	<p>Request clarification from the FDA on including content of labelling in SPL format as part of the drug-listing submission lifecycle:</p> <ul style="list-style-type: none"> From drug-listing information submitted early in product lifecycle, request clarification on whether FDA expects to receive an SPL containing the “approved” content of labelling or an SPL containing “sponsor proposed” content of labelling. For drug-listing updates submitted later in the lifecycle, request clarification on the effect of having two versions of “approved” content of labelling in SPL format – one submitted by the sponsor to FDA <u>without</u> <effectiveTime> element values and another posted by FDA / NLM <u>with</u> <effectiveTime> values. <p>FDA should be aware that most currently available vendor tools for creating SPL do not offer a direct method for including the <effectiveTime> elements within the SPL <document> and/or <section>.</p>

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<p align="center">Clarifying Drug Listing Information Submission Standards and Lifecycle</p>	<p>#8 Supplanting annual reporting (51289, col 2, second full paragraph; 51313, col 3, first bullet; 51314, col 1, third full paragraph)</p>	<p align="center">Mn</p>	<p>The cited text develops a biannual timeline for submitting drug-product listing and also notes that sponsors also have discretion to submit after any material change, including changes to content of labelling.</p> <p>The cited text also requests that “manufacturers ... provide all updates to listing information within 30 calendar days of a change.”</p> <p>The team notes that, as a component of a material change, the content of labelling provided in SPL format could be submitted within 30 days of a change in labelling as part of the drug-listing process. Thus, an SPL could be provided with the drug-listing submission, and updating the submission within 30 days after material changes are made could take the place of supplying content of labelling as SPL with the Annual Report, as well as ensuring content-of-labeling submissions for Changes Being Effected (CBEs) are received by FDA.</p>	<p>Recommend that the FDA clarify the following:</p> <ul style="list-style-type: none"> • Will the definition of “material changes” include those for CBEs and / or supplements? • Will including content-of-labeling changes as part of the drug-listing submission process also fulfil sponsors’ responsibilities for notifying the FDA of CBEs and providing labelling as part of Annual Reports?

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<p>Clarifying Drug Listing Information Submission Standards and Lifecycle</p>	<p>#9 Validating submitted SPL data with drug-listing data (51307 ff.)</p>	<p>Mn</p>	<p>As mentioned in Issue #2, above, much of the drug information required for assigning an NDC number (as listed in the cited text) is included in the data element section of the drug's corresponding SPL file. Will the drug-listing submission information be validated against the approved SPL's data elements held by the NLM when a sponsor supplies an SPL file with the drug listing? Also, will the sponsor need to provide Unique Ingredient Identifiers (UNII)s from the FDA Substance Registration system for active and inactive ingredients included with the drug-listing submission?</p>	<p>See Items #3 and #5, above. If the FDA chooses to move forward without a stakeholder evaluation of SPL as a viable method for submitting drug-listing information, then recommend that FDA restrict drug-listing submission data to include only those items that are not duplicated in SPL data elements.</p>