



May 18, 2015

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

**Re: Docket No. FDA-2007-N-0363 Electronic Distribution of Prescribing Information for Human Prescription Drugs, Including Biological Products Proposed Rule**

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the Proposed Rule entitled "Electronic Distribution of Prescribing Information for Human Prescription Drugs, Including Biological Products."

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products.

BIO would like to thank the FDA for issuing this Proposed Rule requiring the electronic distribution of prescribing information (PI) for human drugs and biologics. We believe that once implemented, the rule will provide health care providers (HCPs) with the most recent FDA-approved PI, detailing a medicine's safety, efficacy, and conditions of use, in a format that can be updated in a matter of days rather than weeks or months. As the Proposed Rule notes, under the current paper labeling system when the PI is revised to include new safety information, there may be substantial lag time before the HCP has access to the new information because of the existing inventory of product with the old labeling in the supply chain. In this modern era of ubiquitous information technology and real-time communication, the current paper-based approach to the dissemination of important new medical information is wasteful, uneconomical, and inefficient. As such, BIO fully supports replacing the paper PI with electronic distribution, with paper copies available upon request. In light of the evolution of information technology over the last thirty years, 21<sup>st</sup> century health care professionals have a growing expectation to access digital healthcare information. E-labeling is much more user friendly given the use of hyperlinks for navigation and the ability to adjust font size for legibility, and is a proven solution that will have meaningful advantages for the public health.

On the whole, BIO finds the Proposed Rule to be well-written and a positive step forward to ensure HCPs have accurate information and improve patient safety. We fully support the underlying principles of the Proposed Rule and offer the below suggestions to ensure the distribution of electronic prescribing information is effective for all involved stakeholders and protects patient safety.

## A. Other Labeling

Since patient labeling, including Medication Guides (MedGuide) and Patient Package Inserts (PPIs), are outside of the scope of the Proposed Rule there inevitably will be some inconsistencies for a period of time between the PI when it is updated electronically and the information contained in printed patient labeling. Such inconsistencies will exist, for example for those limited products required to be packaged with a patient package insert (see 21 CFR 310.510, 310.515), while the patient labeling is being updated, printed, packaged, and distributed, and until product inventories that include the previous paper version of patient labeling become depleted. We ask FDA to recognize that this will occur and continue to allow for a reasonable period of time for manufacturers to exhaust their inventory of product containing the previous version of patient labeling.

While we understand that the Proposed Rule is only applicable to the PI, and there are other FDA initiatives examining improving other labeling such as patient labeling, BIO would like to suggest that FDA consider applying the same rationale to patient and promotional labeling. In the era of patient transparency, it is important that patients receive the most up-to-date safety information about the products that they take. We recommend that patient labeling should be electronically accessible on a public website or database such as the National Library of Medicine's DailyMed website and that the electronic patient interface be user friendly and follow the usability principles outlined below in Section B. Website. Additionally, as mentioned above, as distribution of patient labeling will not be able to be updated in real time there will be differences between the PI and patient labeling while the current paper patient labeling in the market is depleted. Moving patient labeling to an electronic version will help avoid confusion and potential harm that could come from these differences. Paper copies of the patient labeling could be available upon request of the patient at the pharmacy.

We understand that inclusion of patient labeling in particular in the Final Rule may not be welcome by all stakeholders. However, this model is currently under consideration by FDA (with the patient medication information (PMI) initiative) and is already successfully implemented elsewhere (*e.g.*, Australia). However, if inclusion of patient labeling in this action would delay the overall implementation of the Final Rule then we suggest a phased-in approach beginning with PI and expanding to patient labeling in the near future.

Similarly, as promotional labelling must include the most up-to-date labeling, it would be more effective for all promotional materials to include a statement similar to that on container and package labels to obtain a copy of the most recent professional package insert labeling. Requiring paper copies of the PI to accompany promotional labeling would create a dual system, which FDA states is undesirable. However, if this requirement is retained, FDA needs to ensure that it does not inadvertently impact electronic promotional materials, in that any promotion done electronically should not be required to provide "hard" copies of PIs; companies would continue to provide links to the most recent PI.

BIO notes that FDA's proposed revisions to 21 CFR 201.100(d) are at odds with the Agency's recent Revised Draft Guidance: "Brief Summary and Adequate Directions for use: Disclosing Risk information in Consumer-Directed Print Advertisements and Promotional Labeling for Human Prescription Drugs." There, FDA advises manufacturers against using the full prescribing information along with consumer-directed print promotional labeling. Should FDA proceed with any changes to 21 CFR 201.100(d) in the electronic labeling rule, the Agency should ensure that those changes are consistent with the recommendations included in its recent Revised Draft Guidance.

We would also like to request that FDA consider extending the electronic labeling rule to instructions for use (IFU) required for combination products. Electronic labeling has been available for prescription devices under specified circumstances per Section 206 of MDUFMA amended Section 502(f) of the Federal Food, Drug, and Cosmetic Act.

## **B. Website**

BIO agrees that the electronic repository should be controlled by FDA. However, the DailyMed website, which is well recognized and used by industry, physicians, and patients, is fully functional and easy to use. Manufacturers are already required to submit structured product labeling (SPL) to FDA which is then forwarded to DailyMed. We would like FDA to reconsider the use of labels.fda.gov for this initiative and instead have DailyMed as the single publicly available website.

However, if FDA chooses to use labels.fda.gov as its label repository in the implementation of this Proposed Rule we ask for clarification that the current process of a single submission of labeling to the FDA Office of the Commissioner (eLIST) will continue for posting in the FDA's labeling repository and for the DailyMed website, and request confirmation the latter will still be maintained after the Proposed Rule is finalized and implemented.

Additionally, we recommend enhancing the usability of the current labels.fda.gov website to ensure future HCPs, patients, and caregivers are able to find the information they are looking for quickly and efficiently. For example, we recommend:

- Ensuring labels.fda.gov is optimized for mobile devices, so that users can access the information via smartphones;
- Ensuring the website can account for higher levels of traffic to avoid the site being down due to capacity issues; and
- Enhancing the usability of the site by allowing for the adjustment of font size, printing PI, and downloading and emailing PIs.

Currently users are directed to DailyMed to download PIs; this function should be available from labels.fda.gov. In addition, DailyMed provides access to an archive of prior versions of SPL files and we request clarification on whether labels.fda.gov will provide this capability or if DailyMed will continue to be used for this purpose.

Finally, we have a number of additional questions to be addressed by FDA:

- Will the SPL file for submission to labels.fda.gov be the PI only or also include the PPI/MedGuide as is done for the SPL file submitted for posting on DailyMed?
- Will the SPL file for submission to labels.fda.gov include the chemistry, manufacturing, and controls (CMC) information (establishment details, etc.), be included as is done for the SPL file submitted for posting on DailyMed?

## **C. Review of Posted Labeling**

For a newly approved product the Proposed Rule indicates the labeling should be posted prior to shipment into interstate commerce. The FDA anticipates that the PI will be posted in the labeling repository within 24 hours, and the manufacturer would have 2 business days to review and verify the correctness of the posted labeling. If not correct, a manufacturer would

need to contact the FDA in 4 days if the label is not posted, or 2 days if incorrect information is posted. BIO requests FDA standardize the timeframe for notifying FDA in both situations to avoid confusion and variable interpretation of the term incorrectly; we recommend FDA consider standardizing these timeliness to 14 days as detailed below.

BIO also recommends that FDA should endeavor to make the final approved version of the labeling available electronically to the applicant a few days (*e.g.*, 3-5 days) in advance of issuance of the official approval letter as manufacturers often learn about final changes to the labeling when the approval letter is issued. This would enable the applicant to update the text as needed and prepare the labeling for submission for posting in the labeling repository with minimal loss of time after receiving the formal marketing approval. Manufacturers are typically prepared to initiate shipment of the new product as soon as possible upon approval, so the extra steps to review, revise, submit for posting, and verify the posted labeling could potentially delay the initial shipment and availability of the product to patients. Receiving an electronic version of the final approved version of the labeling a few days in advance of the official approval would minimize the potential delay of product availability to patients.

The Proposed Rule states that "it is expected that labeling can be posted as early as the next business day following its submission to FDA" and that manufacturers have 2 business days to review and verify that the posted labeling is correct. While it appears that "generally" labeling will be posted the next business day, we note this may not always be the case. To ensure that manufacturers can begin review of the posted labeling as soon as it is available and thus meet FDA's deadline for review, we recommend that FDA notify manufacturers when the labeling is available. We would also like FDA to reconsider the 2 business day submission requirement as there are a number of activities involved in getting the approved labeling into the SPL format such as actually preparing, formatting, proofreading and meta data review, and submitting an SPL version of the label to FDA. As such, we would like to suggest giving Sponsors the same length of time as the current standard timelines given to submit the SPL (*i.e.*, 14 days) for all submission types (PAS approvals, CBE filings, or annual reportable changes). Additionally, for consistency, we recommend 14 days for submission of labeling as a distributor/repackager as well as for unapproved drugs.

BIO agrees that it is reasonable for manufacturers to verify that the initial version of the labeling that appears in the repository is correct. However, BIO recommends that FDA provide additional clarity and definition of this responsibility. We recommend that this responsibility should not extend beyond the initial posting of the labeling on the website and that it is FDA's responsibility to catch any corruption or misplacement of the posted labeling after the initial check by the Sponsor.

#### **D. Immediate Container and Outer Container Label Statements**

The Proposed Rule does not specify the regulatory procedure to be followed for revising the immediate container and outer container labels to include the statement referring to the labeling repository for the electronic prescribing information. BIO recommends that it be clarified that this change may be implemented with notification in the annual report. We also ask FDA for confirmation that immediate container is defined as the unit of sale.

BIO recommends that the regulation does not include the exact phrasing of the statement explaining the location of the most current prescribing information along with the number to request a paper label due to the need for flexibility for small containers and the fact that as technology changes the statement may need to change. Instead, we recommend that the regulation could include language requiring a statement per FDA guidance and FDA would issue

a guidance that would provide for the details and allow flexibility. Providing the statement via FDA guidance would also allow for easier updating. Additionally, as currently written we believe the statement is too long. It should be simple: for example, "Go to [labels.fda.gov](http://labels.fda.gov) to obtain the latest prescribing information or call [toll free#]."

As FDA noted in the preamble, some products, such as single dose vials and syringes, may not have sufficient space for adding a label statement or sticker referring to the prescribing information in the electronic repository. BIO recommends that such products should be eligible for an automatic exemption from adding the label statement on the immediate container label, as long as the product is packaged in an outer container and the required statement is added to the outer container.

Furthermore we wish to point out that with the ongoing serialization initiative, and ensuing packaging/labeling requirements, available label space might be further limited on the product. Therefore, we suggest the addition of a QR code which might alleviate the lack of space on the label, and that this be applicable to all products.

## **E. Final Rule Implementation**

BIO appreciates that FDA understands industry will need to make preparations in order to comply with this rule as evidenced by the effective date of 6 months and compliance date of 2 years after the date of publication of the Final Rule. However, we note that manufacturers will have to consider potential modifications to equipment for manufacturing and that 2 years may not be sufficient time, especially for certain products, such as those with specialized labels or those requiring the development of peel-back labels to accommodate additional required text. Therefore, we would like to recommend a phased or staggered approach to compliance similar to that used for the physician labeling rule (PLR) or serialization implementation. We recommend that the staggered compliance implementation should begin no less than 3-years after the finalization of the rule, as there are a multitude of administrative and operational challenges that will need to be taken into consideration. These may include:

- Companies with a large portfolio of products will not be able to implement the required technical changes to the entire portfolio simultaneously since products cycle through their full inventories at different rates.
- For a product with a low demand relative to the minimum batch size produced, it takes longer than 2 years to exhaust the entire quantity of a single packaged batch.
- It may take a minimum of 2 years to conduct shipping studies for a company's entire portfolio of products which are necessary to ensure that the paper labeling is not providing critical cushion to the product during shipping, and then, subsequently, to redesign product cartons to eliminate the space currently in use for the paper labeling.
- In regards to the Agency's request for feedback regarding the feasibility of a multi-pane labeling, BIO believes that 2 years is not sufficient for the implementation of a peel-back label, especially for single-use vials where the labeling may already have multiple panes, thus requiring machine modifications to accommodate the increased thickness of the labeling.

## **F. Dual System**

BIO does not favor adoption of a dual system that requires both electronic distribution of prescribing information and paper copies, including the option of requiring the manufacturer to provide sufficient supplies of paper copies to one or more distributors so that a dispenser could request and obtain paper copies from a distributor. We believe such dual systems are counter to the ultimate objective of providing the most current, up-to-date version of the prescribing information to HCPs, and having both electronic and paper copies available concurrently could lead to confusion in decision making for treating patients. We recognize that a small percentage of dispensers (*e.g.*, pharmacies in remote, rural areas) might lack routine internet access, but we believe the option to call the manufacturer using a toll-free number that is in operation 24-hours/day, 7-days/week should be a sufficient mechanism to make paper copies available to these dispensers.

## **G. Providing Paper Prescribing Information on Request**

BIO agrees the telephone is the appropriate tool to request paper labeling whether internet access is unavailable or if there is a preference for paper labeling. While we assume that the 24/7 call center referenced in the Proposed Rule may be automated and is not required to be live. We ask FDA to confirm that this is the case. However, if this call center is required to be live we note that the 24/7 requirement would be onerous, especially for small companies and that an 8 am to 8 pm timeframe may be more reasonable. We also note that many some companies already have a customer service number available; in such cases we ask that this existing number may be used for requests for paper labeling and that there does not need to be a separate phone number for this purpose.

We recommend that the proposed requirement to provide paper copies upon request can be satisfied by providing an 8.5 X 11 inch or A4 sized-paper copy. Manufacturers should not be required to maintain the narrow, lengthy folded versions that are currently needed to fit with product packaging. The 8.5 X 11 inch or A4 size would satisfy the proposed requirement of providing a paper label on request and is more user-friendly and cost-effective than the current paper copies used.

## **H. Exportation Issues**

Regarding FDA's request for comment on impact to exportation, we suggest providing paper labeling outside of the carton with the shipment. This is done on occasion for Medication Guides and we believe a similar process can be adapted for export of drug product.

We would like the Agency to consider the situation with drug for export, where Sponsors have an agreement with the foreign authority to provide drug with the US label. We propose that printed US labeling be permitted for inclusion with the drug and that this not be considered 'dual' labeling since the product in question is not intended for use within the United States.

We would also like the Agency to consider that currently submission of export labeling is provided for on DailyMed. Would this labeling still need to be submitted to labels.fda.gov, given that it is not intended for use within the United States?

## **I. Other**

Regarding cell therapy products, BIO does not support a specific exemption from e-labeling requirements for cell therapy products. The language in the Exclusion section (III.D) of the Proposed Rule would allow a company to make a case for exclusion of any product, including a cell therapy, and we find this sufficient.

BIO would like the Agency to consider allowing manufacturers the option of using 4-point font rather than 6-point font where already in use on an existing product. In allowing the use of 4-point font where already in use, FDA may be able to mitigate some of the challenges associated with a multi-pane label.

FDA also asked for comments on whether the existence of two different formats of electronic labeling (per the 2006 rule) would present barriers to their value when used in the health care setting. BIO does not believe that two different formats of electronic labeling would present barriers when used in the health care setting. As such we ask FDA to retain flexibility and not force manufacturers to update labels that were not impacted by the 2006 rule. We would like confirmation from FDA that Sponsors are not required to convert older drug products to PLR as a result of this Proposed Rule.

BIO also believes that FDA should accept copies of the electronic labeling materials when issuing Certificates of Pharmaceutical Products (CPP). We suggest that FDA take a phased-in approach to this policy; accepting both printed and electronic inserts while the Proposed Rule is being finalized, while planning to phase-out the printed insert once the rule is final, as well as outlining the updated CPP labeling submission requirements for Sponsors.

Finally, BIO would like to learn about FDA's plan for communicating this new model of disseminating drug labeling to all stakeholders, including dispensing professionals, prescribers, and patients.

## **J. Conclusion**

We would like to reiterate that e-labeling will have a clear benefit for the public health by providing timely access to new safety information and fully support the underlying principles of the Proposed Rule. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

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Biotechnology Industry Organization (BIO)