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February 21, 2012

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

Re: Docket No. FDA-2011-N-0849: Establishing Timeframes for Implementation of Product Safety Labeling Changes; Request for Comments

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments on the notice, "Establishing Timeframes for Implementation of Product Safety Labeling Changes," published in the Federal Register on December 20, 2011. BIO appreciates FDA's initiative to clarify the process and timeframes for revising and distributing product labels to reflect new safety information incorporated under section 505(o)(4) of the Federal Food, Drug, and Cosmetics Act (FFDCA). To ensure that patients and their physicians have access to timely, relevant, and science-based prescribing information to make informed decisions about their health, we encourage FDA to implement electronic labeling regulations so that revised labeling can be distributed without any unnecessary delays associated with the printing and distribution of paper labels.

BIO represents more than 1,100 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, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

PART 1: GENERAL COMMENTS

A. Revisions to Paper Labels are Not the Most Effective Means to Speed New Safety Information to Patients

It is important to recognize that implementation of FDA approved labeling through paper-based labels involves complex, labor intensive processes for the drug manufacturer and its vendors. It is a challenging task to implement product safety labeling changes made under section 505(o)(4), especially with respect to getting the newly labeled product onto the field within a reasonably short period of time. BIO supports paperless labeling initiatives to expedite the distribution of new safety information to patients, but we do not believe it is appropriate to establish fixed, inflexible timeframes to govern the implementation of paper label revisions. The complexities of implementing changes to paper labeling are described below.

After a label change, Sponsors work closely with vendors to ensure that paper labels are appropriately revised and integrated with manufacturing processes. Following FDA approval of a revised label, the agreed upon content is released to the print vendor. The vendor utilizes internal processes by which to approve, print and ship the label. Time may be required to complete translations and filings, and manage logistics. Supplies are quality checked again in storage prior to use in packaging. In the event the label has a larger footprint than the prior version, the packaging lines may need to be reconfigured. A sufficient timeframe must be allowed to ensure that all changes are being made appropriately, and no unintended changes are made, given that a number of parties will be involved.

Additionally, the number of batches manufactured per year for a specific product can affect scheduling of new manufacturing runs. When only a few batches of a particular product are manufactured in a given year, there may be existing inventory concerns that must be factored into manufacturing new batches. Fitting unscheduled manufacturing runs into an already defined manufacturing schedule can also be challenging.

These processes can vary across manufacturers, and also depend on the lifecycle of the product with respect to the time it takes a product to be manufactured, distributed, and finally reach the patient. It will take time – weeks or months – for older paper labels to move through the supply chain as the product is dispensed and replaced. Furthermore, for a product in which new safety information is added to the label frequently, paper labels can become outdated quickly.

In short, revised labeling accompanying a packaged product is not the most efficient or practical way by which to convey new safety information. Rather FDA and industry should focus attention and resources on mechanisms to speed electronic labeling to patients and providers so that new safety information is communicated as expeditiously as possible.

B. New Safety Information Should be Communicated via E-labeling

Therefore, the regulations should be directed away from the inclusion of paper labeling in packaged product to a new paradigm in which paperless labeling distributed electronically will

serve as a reliable and timely source of safety information for the healthcare community. Under this electronic system, the latest safety information could be pushed to providers and other parties who should be made aware of the revised labeling in a matter of days, rather than months under the current paper-based system.

The drug label serves as an important source of information for patients, physicians and pharmacists. It is critical that the care community at large is alerted to product safety changes in a timely manner. Transitioning to a paperless labeling system should improve information access and usability by providing the most up-to-date information via means and forms in which the reader desires to receive it. For these reasons, we strongly support FDA and industry efforts to provide labeling for all marketed prescription products via electronic means in lieu of paper.

C. Revised Labels are Regularly Posted to Government and Manufacturer Websites

To further support e-labeling initiatives, BIO recommends that the revised label be posted on appropriate websites. The FDA-approved label should continue to be posted at the National Library of Medicine's (NLM) DailyMed website, which is considered as the primary depository of the official label and provides the link for further electronic distribution of the label. Sponsors have up to 14 days to provide a copy of the Structured Product Labeling (SPL) to FDA, which FDA forwards to NLM. NLM updates DailyMed with the revised label within 24 hours of receipt from FDA.

If a manufacturer also has a product website available, it is reasonable for the Sponsor to post the revised label on that website as soon as practicable, or within 10 days as suggested by FDA. In practice, drug manufacturers are often able to post revised labeling on company websites within hours following FDA approval.

PART 2: QUESTIONS POSED BY FDA

A. Considerations Related to Drug Manufacturing and Packaging, and to Printing Labeling:

- 1. What are the considerations related to drug manufacturing and packaging, of which FDA should be aware, as they relate to implementation of revised product labeling?*

Please see our general comments.

- 2. What are the considerations related to printing labels and other types of labeling of which FDA should be aware, as they relate to implementation of different types of revised product labeling?*

The type of labeling that requires the change can determine the amount of time the change will take to be approved internally. Milestones needed to create or change a printed label for finishing include:

- Company provides artwork colors
- Vendor creates drawings
- Company reviews drafts as they evolve
- Company may need to run line trials on finishing equipment (if label is different size)
- Company obtains approval of the labeling/part through a change request process
- Company drafts a new recipe in accounting system
- Company signs off on vendor proof and places order
- Company obtains approvals to account for the revised labeling in packaging instructions
- Company updates electronic instructions that are used on packaging lines
- Company revises documents so that new labeling can be used in plants that package affected product

While FDA's focus is on the U.S. market, it should be noted that translations for a product insert could be considerable depending on the number of countries the product is shipped to. A product insert change will take longer than a package label or a printed carton.

B. Supply Chain Issues:

- 3. What are the supply chain factors (including storage, shipping, and distribution factors) of which FDA should be aware that limit or otherwise affect how quickly a labeling change can be implemented?*

The supply chain factors of which FDA should be aware include:

- Packaged product inventory on hand. For example, six months of inventory on hand is a realistic target for a company to strive for with all of its products
- Labeling inventory on hand and accounted for in the production schedule
- Utility of current labeling inventory to minimize waste
- Date by which vendor can deliver new labeling
- Disruption to manufacturing/supply of the product in question and other products run on the same manufacturing line.

C. Other Considerations:

- 4. What alternative labeling mechanisms (e.g., having labeling available on a product Web site) could be used to disseminate new safety information quickly to patients and health care providers?*

It is critically important for physicians to be made aware of the approved safety information so that they in turn can alert and advise patients under their care. We agree with FDA that one mechanism for quick dissemination of new safety information is to make the revised PI / labels available to patients and physicians electronically immediately after approval. As discussed in our general comments, many drug manufacturers post revised labeling on company websites within hours following FDA approval. The National Library of Medicine's DailyMed website is updated following receipt of the SPL within 1 day of receipt of labeling from FDA (refer to Part 1.C. for more details). Further, FDA and industry are considering more active ways by which to drive stakeholders to labeling updates via the paperless labeling initiative, as discussed in our general comments.

We also agree with the use of Dear Healthcare Provider Letters for the prompt dissemination of new safety information related to Warnings & Precautions and Contraindication in a manner as described in the FDA *Draft Guidance for Staff and Industry, Dear Healthcare Provider Letters: Improving Communication of Important Safety Information*.

There may also be an opportunity to leverage new technologies and social media. For example, the use of a Quick Response (QR) code or something similar could be affixed to promotional materials and/or packaging to link physical objects to the virtual world, so consumers can access the most current prescribing information online via their smart phones.

5. *How should the relative seriousness of the new safety information, or whether the new safety information describes a newly identified risk, or strengthens a risk already identified in current labeling, affect timelines for implementing revised product labeling?*

A safety label change made under 505(o)(4) is predicated upon "new safety information that the Secretary believes should be included in the labeling of the drug," which includes "a serious risk or unexpected serious risk associated with the use of the drug." Since most of these types of safety label changes will involve significant safety issues, FDA and Sponsors should take all reasonable steps to ensure that all revised label changes made under 505(o)(4) are electronically distributed to providers and patients as soon as possible.

For those changes initiated by the Sponsor such as Changes Being Effectuated (CBE) Supplements and some Prior Approval Supplements there are no mandatory timeframes for review and/or action by the Agency. In such cases, there should be no required implementation timelines.

6. *What are the implementation considerations when the safety labeling change is to prescriber versus patient labeling (or both)?*

Within most manufacturers, these changes are handled using similar change management processes. As such, we see no potential difference in the process whether the safety labeling change is directed to prescriber versus the patient. Labeling changes for either would follow the same process and external websites are updated using similar rules and timing for both prescriber and patient labeling.

7. *What would be a reasonable timeframe following approval of revised safety related labeling changes for applicants to implement the revised labeling? Please relate this timeframe to the optimal point in the supply chain (e.g., newly manufactured product, newly shipped product) and the type of labeling change.*

Please see our general comments.

8. *Are there other considerations or options related to implementing safety labeling changes of which FDA should be aware?*

As offered in our introductory comments, we recommend a transition to paperless labeling in the spirit of providing patients, providers and pharmacists with immediate access to the most current safety information and reducing paper waste in landfills.

III. CONCLUSION

BIO appreciates this opportunity to comment on the “Establishing Timeframes for Implementation of Product Safety Labeling Changes.” We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
Managing Director, Science and regulatory Affairs
Biotechnology Industry Organization (BIO)

REFERENCES

BIO Comments on FDA’s *Draft Guidance for Industry on Safety Labeling Changes; Implementation of Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act*, July 12, 2011,
http://www.bio.org/sites/default/files/20110712_labeling.pdf