After extensive industry debate, the US FDA has proposed a new rule to amend its prescription drug and biological product labeling regulations that will take effect in 2015. The rule applies to the electronic distribution of the package insert (PI) which is currently provided in paper form with drug packaging for the benefit of health care professionals (HCPs). When pharmaceutical companies market their products in the US, they will be required to provide the PI in an electronic file and no longer permitted to distribute it in paper form with packages. FDA has proposed an effective date of six months after the publication date of the final rule in the Federal Register and a compliance date of two years after the date of publication of the final rule.

There are many pros and cons regarding the proposed rule, and there are probable benefits to electronic labels reflecting the most up-to-date safety risks and efficacy information. While other literature aimed at patients, including promotional labeling, are excluded from the electronic distribution requirement, opponents argue that many patients still rely on paper PIs to get critical drug information. It is estimated that the proposed rule will save the biopharmaceutical industry between $52 to $164 million annually.
This change has brought to light the need for life science organizations to avoid reduced operational efficiency and profitability, and to not delay product time-to-market due to new and complex processes. FDA’s initiative to institute electronic labels in the US is aimed at ensuring the most current information is made available, and also has the potential additional benefits of reducing time and enhancing accuracy of labeling information. However, the rule will be applicable only in the US; for other highly regulated (e.g., European Union and Japan) and non-regulated/emerging markets (e.g., rest of the world countries), paper-based PIs will continue to be the norm. As other regulatory agencies continue to implement an evolving set of rules regarding the format and presentation of labeling requirements, life sciences companies have a double challenge: In the short term, they must establish systems and processes to ensure compliance with emerging standards; in the long term, they must make strategic decisions to reduce the complexity and cost of managing their global labeling content.

YEARS IN THE MAKING

The proposed rule comes after years of development at the FDA and is applicable only to pharmaceutical products marketed in the US. Under Section 1140 of the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA), legislators called on the Government Accountability Office (GAO) to study the advantages and disadvantages of largely doing away with paper-based labeling for drug products and moving to an electronic system.

The findings found both likely benefits and potential downsides to an electronic-based labeling system. Electronic labeling would ensure that all labeling reflected the most up-to-date safety risks. At present, paper-based drug labels may not contain the most current safety and efficacy information because they may have been printed and distributed prior to more recent labeling changes, while the electronic form of prescribing information can be updated in real-time. In addition, unlike many types of communications, which may have a single intended audience, FDA approved labeling typically serves two audiences simultaneously: Patients and health care providers. Switching to an electronic-based system could allow both groups to view information in a more user-friendly format. For example, patients might see information presented in one way (such as with options to increase font size or hyperlinks to definitions of complex terms), while health care professionals might see a version with a search function to facilitate the discovery of potential safety risks.

But the proposal also has its downsides. For example, elderly consumers might not have internet access or know how to access the drug label online. Counseling patients might become more difficult for doctors who no longer have access to printed PIs. And if patients do get a printed PI from their doctor the first time they are prescribed a medicine, they may continue to go by it even if the label has been updated with new information in electronic format.

FDA must also amend the language that currently requires PIs to be located “on or within” the drug packaging, another significant change: other forms of prescribing safety information, such as medication guides (MedGuides), are already allowed to be sent electronically.

FDA’S PROPOSED LABELING RULE

The proposed rule would apply to manufacturers, applicants (including holders of NDAs, ANDAs, and BLAs), and persons who market prescription drugs that they regard as not subject to section 505 of the Federal Food, Drug, and Cosmetic Act (FD & C Act) (21 U.S.C. 355). It looks to avoid the vast majority of the potential downsides identified in GAO’s report by focusing on prescribing
information intended for healthcare professionals. FDA is proposing that such prescribing information with few exceptions (e.g., when compliance could adversely affect the safety, effectiveness, purity, or potency of the drug, is not technologically feasible, or is otherwise inappropriate) “will no longer be permitted to be distributed in paper form with the package from which a prescription drug or biological product is dispensed.”

FDA is taking this action to ensure that the most current PI for a prescription drug is readily available and accessible to HCPs at the time of clinical decision-making and dispensing. The rule also requires that a product’s immediate container label and outside package bear a statement directing health care professionals to the FDA’s labeling repository to view the electronic version of prescribing information.

Under the new system, product manufacturers or applicants will be required to update the product labeling at the FDA labels.fda.gov website every time there is a labeling change. They would also be required to verify that the accurate, complete, and up-to-date labeling is posted on the FDA website, and to promptly notify the agency if it is not. Manufacturers would also be required to set up a 24x7 toll-free number where health care professionals could request paper copies of the prescribing information. This would ensure that persons without internet access — such as in an emergency or power outage — could still access prescribing information.

Any drug that an applicant or manufacturer introduces that does not have accurate, complete, and updated electronic prescribing information available on FDA’s labeling repository web site, or that continues to be accompanied by paper prescribing information, would be misbranded under section 502(f)(1) of the FD&C Act.

LABELING: THE PROCESS

Electronic PIs may change the labeling process for the US. But product labeling is a globally collaborative process, from initiation of a clinical trial to commercialization, with multiple sources of inputs and hand-offs that ultimately result in a Company Core Data Sheet (CCDS). The CCDS includes all the relevant information on the product to be labeled, and any local labeling information for different geographies are derived from this. Every CCDS could require multiple changes depending on the product formulations and geographic regions where the drug is sold. Complexity increases when these regional labeling documents must be in the local language with differing content. These regional adaptations must in turn be updated whenever there is a change in the CCDS due to availability of new safety, efficacy or product quality information, or changes in regulatory landscape.

DIA RELATED OPPORTUNITIES

Product Labeling eLearning: Includes information on components and structure of the prescription drug label and the medication guide, plus all pertinent regulatory and legal requirements with which you must comply. Part of the DIA Medical Communications Certificate Program.

DIA EuroMeeting 2015: Development, Access, Innovation and Patient Safety: Connected Health is not only about the technology. It’s about being able to actively navigate the ever evolving healthcare ecosystem holistically. DIA EuroMeeting 2015 allows you to debate the issues across the entire drug development value chain during the conference & find solutions within the exhibition with 2500+ other cross-functional thought leaders. (Paris, France, April 13 – 15)

eRegulatory & Intelligence Annual Conference 2015: Industry as a whole has been converging towards looking at regulatory as an end-to-end process. Document management, publishing and technical regulatory requirements are all subsets of regulatory information management at its broadest definition. This conference features plenary sessions on the latest industry trends plus direct updates from the FDA and other regulatory agencies. (May 11 - 13, Philadelphia, PA)
Changing regulatory requirements and numerous hand-offs make the process more complex. The existing process of developing a product label is human resource intensive and therefore requires extensive reviews and proof-reading to ensure that the printed label is error-free. All of these factors significantly add to cost and time, not to mention the possibility of introducing manual errors.

**ENSURING EFFICIENCY AND COMPLIANCE**

Biopharmaceutical product labeling is very specific in its content, especially with respect to efficacy and safety data and adverse effects. Furthermore, the label needs to comply with country-specific regulations governing the product. A product label from an innovator pharmaceutical company, prior to commercialization, is drafted by the pharmaceutical company and is reviewed and approved by the applicable regulatory agencies, based on regulations and guidelines.

On the other hand, a generic product label is based on the innovator label having already been approved by the regulatory authority. While a generic company’s portfolio may include 300 products, the Reference Listed Drug (RLD) label could be sourced from 20 to 30 different innovator companies, compounding the complexities in referencing and tracking of RLD updates. Labels are an essential part of the marketed product since they provide comprehensive information about the drug. They also represent a significant percentage of the manufacturing cost and commercialization risk.

Moreover, a product with a wide geographical footprint would require labels in each country/region to comply with local regulatory guidelines. These multiple labels increase the risk of having non-uniform information disbursed globally for the same product. Each label update involves input from multiple stakeholders like regulatory, clinical, legal, quality and manufacturing personnel. The sheer number of reviews makes data management, version control and audit trails prerequisites to the labeling process.

In conjunction with compliance to the requirements of multiple regulatory agencies, there is a constant need to address the challenge of ensuring consistency of content across a broad portfolio of products across multiple regions.

Because FDA’s proposed rule will require prescription drug manufacturers to ensure that the electronic label is provided to the FDA each time its content is changed, pharmaceutical companies may have to globally synchronize an overwhelming number of labeling records. This could impact label accuracy and quality, as well as the ability to meet regulatory timelines. It therefore becomes even more imperative that pharmaceutical companies make fundamental operational changes to adapt to the growing complexity, minimize risk and improve efficiency of the labeling process, so that label updates are made in real time globally.

**HOW “MANAGED SERVICES” CAN HELP**

Labeling as a Managed Service is an externally managed, fully integrated platform of services, processes and technology enablers that cover the entire labeling continuum. It offers expert labeling resources that execute global labeling activities on behalf of a sponsor or generics company, best-in-class labeling processes that are monitored via key performance indicator metrics on performance, quality and compliance goals, and pre-configured, ready-to-
use technology solutions to support workflow and content management activities.

By employing a managed service model, potential clients can reap the following benefits:

### Efficiency & Scale

- **Utilize qualified external resources, best-in-class processes and integrated technology solutions to accelerate your label development, updates and implementations**
- **Quickly scale up to meet your global growth aspirations by leveraging local and regional labeling knowledge and delivery capabilities**

### Quality & Compliance

- **Gain visibility and control of the global labeling process via robust workflow management**
- **Have confidence in the overall operations through measurement and reporting of key performance, quality and compliance indicators**

### Cost Effectiveness

- **Forgo heavy investments for expensive internal resources and technology requiring optimization and customization**
- **Maintain flexibility for scale up and scale-down to manage costs**
- **Leverage tailored end-to-end solutions that optimize resource utilization and appropriate technologies aligned with client needs**

### END-TO-END LABELING WORKFLOW

Successful organizations require a streamlined workflow management model that includes document management, version control, and standardization/synchronization of processes such as labeling and artwork content across geographies.

Having a portfolio of products across multiple regions means organizations must comply with the requirements of multiple regulatory agencies. Reliance on people-intensive, paper-based processes results in errors and time-consuming quality control activities. Moreover, each version of the product label requires its own artwork for the final printed label, necessitating another series of manual processes.

Today, product labeling comprises disparate processes at different locations, based on country-specific preferences. A streamlined workflow management process, along with a document management system that allows for version control, and standardize label and artwork content, makes the task easier and more accurate, since it synchronizes content and versions across geographies.

Organizations can successfully outsource core labeling activities on a global scale by partnering with a vendor who can tailor a solution that meets their current and future needs. Vendors with a global reach will work to assess the individual organizations unique situation, build and implement a tailor-made solution, and provide support throughout the product lifecycle, ensuring quality and compliance at reduced cost. Further, the specialized vendor’s automated labelling processes produce consistent and quality documentation that promotes the accuracy required to maintain patient safety as well as brand integrity. With a reduction in manual interventions, changes can be managed much more quickly, saving significant amounts of time.

*References Available Upon Request*

**BINDU NARANG** serves as Director, Sciformix Regulatory Affairs and Scientific Writing. Bindu has over 25 years experience working with pharmaceutical companies and service organizations, and has worked in diverse platforms, including print, online, and multimedia, and has extensive medical copy and text editing experience. As head of the India regulatory writing group for Pfizer Global R&D, she helped set up a matrix regulatory writing organization in 2004. Bindu has also set up and worked closely with publishing groups using eCTD submission tools and software. Bindu holds a Masters degree in Pharmaceutical Sciences (Medicinal Chemistry).