FDAnews Webinar

Overview and Implications:
The Food and Drug Administration’s Proposal to Permit Generic Drug Manufacturers to Initiate Labeling Changes

Dan Kracov and Dan Pariser
Arnold & Porter LLP

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Media Inquiries: Sandy Walsh, 301-796-4660, sandy.walsh@fda.hhs.gov
Consumer Inquiries: 888-INFO-FDA

FDA takes action to speed safety information updates on generic drugs

A proposed U.S. Food and Drug Administration rule would speed the dissemination of new safety information about generic drugs to health professionals and patients by allowing generic drug makers to use the same process as brand drug manufacturers to update safety information in the product labeling.

Under the proposal, generic drug manufacturers would be able to independently update product labeling (also called prescribing information or package inserts) with newly-acquired safety information before the FDA’s review of the change, in the same way brand drug manufacturers do today. Generic manufacturers would also be required to inform the brand name manufacturer about the change.

The FDA would then evaluate whether the proposed change is justified and make an approval decision on the generic drug labeling change and the corresponding brand drug labeling change at the same time, so that brand and generic drug products would ultimately have the same FDA-approved prescribing information.
Current Regulatory Background

- Under the FDCA, FDA approves a New Drug Application (NDA), including drug’s labeling

- After approval, NDA holder (i.e., brand-name manufacturer) may submit supplemental labeling changes through:
  - Prior Approval Supplement (PAS): Major labeling changes require FDA’s prior approval
  - Changes Being Effected (CBE): Certain changes may be made without advance FDA approval
Changes Being Effected Supplements

- All NDA/BLA holders have an obligation to ensure that labeling is accurate and up-to-date.

- Certain labeling changes based upon newly required information about an approved drug can be implemented upon receipt by FDA of an NDA/BLA supplement that includes the change – “CBE-0” supplements (21 C.F.R. §§ 314.70(c)(6)(iii) and 601.12(f)(1))
CBE-0 Supplements

- Current regulations provide that application holders may submit CBE-0 supplements for the following types of changes to drug labeling:
  - To add or strengthen a contraindication, warning, precaution, or adverse reaction for which there is reasonable evidence of a causal association with the approved drug;
  - To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;
  - To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;
  - To delete false, misleading, or unsupported indications for use or claims for effectiveness; or
  - Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

- FDA may then accept, reject, or request modifications
Regulatory Background – Generic Labeling

- Hatch Waxman Amendments established the Abbreviated New Drug Application (ANDA) process for generic drugs
  - Requires generic to be the “bioequivalent” and therapeutically equivalent to reference listed drug (RLD)
  - Requires generic to have same labeling as brand name drug (except for certain changes permitted by FDA due to an approved suitability petition or because the generic and RLD are produced or distributed by different manufacturers)
  - Generics currently can use CBE-0 only to conform to the approved labeling for the RLD or upon FDA request – no unilateral changes
Background: Prescription Drug Preemption Cases

  - No conflict between federal and state law because brand-name manufacturers may initiate labeling changes through CBE

- **PLIVA Inc. v. Mensing**, 131 S. Ct. 2567 (2011): FDCA preempts failure-to-warn claims involving generic prescription drugs
  - Conflict because of the requirement of sameness, generic manufacturers cannot use initiate labeling changes through CBE

- **Mutual Pharm. v. Bartlett**, 133 S. Ct. 2466 (2013): Extends Mensing to design defect claims
Strong Reaction to Supreme Court’s Preemption Decisions

“[A] drug consumer’s right to compensation for inadequate warnings now turns on the happenstance of whether her pharmacist filled her prescription with the brand-name drug or a generic. If a consumer takes a brand-name drug, she can sue the manufacturer . . . . If, however, if she takes a generic drug, as occurs 75 percent of the time, she now has no right to sue. . . .” PLIVA Inc. v. Mensing, 131 S. Ct. 2567, 2592-93 (2011) (Sotomayor, J., dissenting)
Strong Reaction to Supreme Court’s Preemption Decisions

“The plaintiffs are ... caught in a classic ‘Catch 22,’ barred from all claims against Generic Manufacturers...(due to federal preemption) and from all claims against the Brand-Name Manufacturers....” Strayhorn v. Wyeth Pharm., Inc., No. 12-6195 (6th Cir. Dec. 2, 2013)
The Proposed Rule Responds To Criticism

“As a result of the decisions in Wyeth v. Levine and Pliva v. Mensing ... access to the courts is dependent on whether an individual is dispensed a brand name or generic drug. . . . We are proposing to change our regulations to . . . create parity between NDA holders and ANDA holders.” 78 Fed. Reg. at 67,988-67,989 (emphasis added)
FDA Proposed Rule

- Generic manufacturers may submit labeling changes through CBE-0, even if it temporarily results in labeling that is different from the RLD – same obligation as NDA holders
  - Can also distribute “Dear Healthcare Provider” letters

- At the same time, ANDA holder must notify brand-name manufacturer, and provide supporting information
  - Brand-name manufacturer and other ANDA holders can then submit their own supplements
    - If NDA holder does not submit, FDA may send a supplement request, including to those companies responsible for drugs containing the same active ingredient, even if approved under a different NDA

- If RLD has been withdrawn, FDA may select an ANDA-approved product as the reference standard
FDA Proposed Rule (cont’d.)

- FDA will establish a web page to post information regarding labeling changes proposed in CBE-0 supplements and current status of FDA review of such changes
  - Supplements remain posted until FDA issues an action letter on the change

- FDA proposes to require submission of final printed labeling in structured product labeling format at the time of submission of the CBE-0 supplement so the changes can be made publicly available promptly after submission
FDA Proposed Rule (cont’d.)

- If FDA approves the CBE-0, the change must be implemented for all such products
  - Other ANDA holders have 30 days to submit conforming labeling
    - May be modified in certain circumstances (e.g., a single, shared REMS)

- Distribution of drugs with updated labeling must occur “as soon as feasible thereafter or at the time of the next printing of the product labeling for packaging”
Example of Process for Submission of CBE-0 Supplements by ANDA Holder and NDA Holder

Newly acquired safety information. ANDA Holder #1 receives or otherwise obtains new safety information regarding its generic drug, and submits an adverse drug experience report to FDA

Submit CBE-0 Supplement (ANDA): ANDA Holder #1 submits a CBE-0 supplement containing a proposed labeling change and other required information

Distribute revised labeling: Application holder uses available means to distribute revised labeling at the time of submission of the CBE-0 supplement

Send notice to NDA Holder: ANDA Holder #1 sends notice of the CBE-0 supplement to the NDA holder for the RLD (unless NDA approval has been withdrawn)

Web page posting: Information about a CBE-0 supplement is posted on an FDA Web page

Supplement Subtype Determination: FDA evaluates whether the proposed labeling change meets the regulatory criteria for a CBE-0 supplement

Meets CBE-0 Criteria: FDA reviews the various proposed labeling changes in the CBE-0 supplements

Does not Meet CBE-0 Criteria: FDA advises that a prior approval supplement is required

Approval: FDA approves the CBE-0 supplements (with or without changes), resulting in the same labeling for the RLD and generic drug #1

Complete Response: FDA does not approve the CBE-0 supplements

Return to Previous Labeling: FDA web page is updated, and application holder must take steps to make the drug product available only with the previous labeling

Conforming labeling changes: Other ANDA holders must submit a CBE-0 supplement with conforming labeling changes within 30 days of FDA’s posting of the approval letter for the RLD labeling change on FDA’s web site

Information that had been posted on FDA’s CBE-0 Supplements web page is archived
Regulatory Implications of Proposed Rule

- Greater confusion from inconsistent pending labeling, especially if multiple companies submit CBE-0 supplements with labeling changes that differ from each other and from the brand name drug.

- Generic manufacturers:
  - Will force generics to develop a much greater capacity to conduct pharmacovigilance surveillance and analyses, and submit labeling changes.
    - SOPs, experienced personnel, etc.
  - If the safety issue is not confirmed in other products, this could raise questions as to the bioequivalence and integrity of the generic product (e.g., due to different inactive ingredients)?
Regulatory Implications of Proposed Rule (cont’d.)

- Brand-Name Manufacturers
  - Increased regulatory burdens by requiring brand name manufacturers to evaluate and respond to CBE submissions from ANDA holders
    - Loss of control in product risk management
    - May be years after discontinuing marketing
  - Will require a rapid evaluation of data
    - Rebut proposed changes or seek different labeling language
    - Testing of generic to determine if the labeling change is caused by compositional differences?
    - Impact of pending changes in the context of promotional and medical affairs activities
Potential for significantly increased product liability exposure if state tort claims against generics no longer preempted

- Rationale of Mensing/Bartlett premised on generics’ inability to change labeling
- “FDA is considering a regulatory change that would allow generic manufacturers ... to change their labeling in appropriate circumstances. If ... adopted, it could eliminate preemption of failure-to-warn claims against generic-drug manufacturers.” Gov’t amicus brief in Bartlett (emphasis added)
Liability Implications of Proposed Rule: Brand-Name Manufacturers

- Undermines a key basis for “innovator liability”
  - “Innovator liability” permits recovery against a branded company for injuries from taking the corresponding generic drug
“[I]t is not fundamentally unfair to hold the brand-name manufacturer liable for warnings on a product it did not produce . . . when those alleged misrepresentations were drafted by the brand-name manufacturer and merely repeated by the generic manufacturer.” Wyeth, Inc. v. Weeks, 2013 WL 135753, at *15, *19 (Ala. 2013)
Liability Implications of Proposed Rule: Brand-Name Manufacturers

- Are there downsides for branded companies?
  - Potential fodder for plaintiffs’ lawyers
    - If a generic proposed a labeling change, arguments that branded company should have made labeling change earlier
    - Potential to make use in litigation of disagreements among companies on proper labeling
Submitting Comments

January 2014

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Comments due January 13, 2014
Effective 30 days after publication of final rule
Will FDA’s Proposal Survive A Legal Challenge If Finalized?

- FDA: “Nothing in the Hatch-Waxman Amendments or subsequent amendments to the [FDCA] limits the Agency’s authority to revise the CBE–0 supplement regulations to apply to ANDA holders.” 78 Fed. Reg. at 67,995

- But the statute requires “sameness”
  - Does “sameness” mean that generic companies cannot be required to initiate changes, even if the differences are temporary?

- As a practical matter, legal challenges may substantially delay implementation of any final rule
Questions?

Dan Kracov  
daniel.kracov@aporter.com  
(202) 942-5120

Dan Pariser  
daniel.pariser@aporter.com  
(202) 942-6216

Arnold & Porter LLP  
555 12th Street, N.W.  
Washington, D.C. 20004