ANDAs Labeling Requirements for Rx to OTC Switched Products

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Learning Objectives

- Explain how a prescription (Rx) drug product may initiate the change in marketing status to over-the-counter (OTC) through the New Drug Application (NDA) process.
- Discuss the process for labeling and policy updates when a Reference Listed Drug (RLD) undergoes an Rx-to-OTC switch.
- Identify roles of the Agency and roles of the Applicant.

Polling Question

Have you sought approval for an Rx-to-OTC product?

a. Yes

b. No

Overview

- Full switch: Rx and OTC product have the same approved uses
  - Same drug product (e.g. diclofenac sodium, ivermectin, olopatadine)
- Partial switch: Rx and OTC product can have different uses
  - Can be different NDA entirely (e.g. levocetirizine solution, proton pump inhibitors)

Requirements for Full Switch

- NDA holder switches the drug product to nonprescription marketing status in its entirety by submitting efficacy supplement.
- NDA holders may submit patents within 30 days from the date of approval of efficacy supplement.
- Holders or applicants of approved and pending ANDAs referencing that NDA must submit a supplement or amendment to their ANDA relying on the RLD for OTC conditions of use and associated labeling.
  - Does not require a completely new ANDA

505(j)(2)(D)(i) of the FD&C Act; 21 CFR § 314.97(b).
21 CFR § 314.53(c)(2)(ii), (d)(2)(i), (d)(2)(ii)(C).

FDA Regulations

- After supplement is approved, FDA will continue to list the patent information for 30 days or until Form 3542 is submitted.
  - For patents already listed in the Orange Book, the patent submission date will stay the original (pre-switch) date.
- If patent information is submitted, patent submission date for patent information will reflect original date of submission in accordance with 314.53(d)(5).
  - This ensures that the new entry in the OTC section contains complete and accurate patent information for the drug following the full switch.
- If the NDA holder does not submit Form 3542 within the 30-day period, the carried-over patent information will be removed from the Orange Book at the end of the 30-day period.*

*Unless it is a qualifying patent for unexpired/unextinguished 180-day exclusivity, in which case the patent remains listed in the OTC entry, and a delist flag is added.

21 CFR 314.53(d)(2).

Durham–Humphrey Amendment of 1951

- 1940's to 1960's abuse of amphetamines and barbiturates
- Prior to this, the determination as to whether a drug was safe and effective for self-medication was left to the manufacturer.
- Distinguishes OTC and Rx drugs
- Labeling of Rx-only
  - *Caution: Federal law prohibits dispensing without prescription*
- Misbranding: Rx and OTC versions of the same drug product are not permitted to be marketed at the same time.
- The failure to maintain labeling that is consistent with that for the RLD is a basis to propose withdrawing approval of an ANDA.

Photo courtesy of Kleinert Reference Files University of Wisconsin

Former vice president and senator Hubert H. Humphrey Jr., who was a pharmacist in South Dakota before beginning his political career, co-sponsored the 1951 Durham-Humphrey Amendment.

Section 503(b) of the Federal Food, Drug, and Cosmetic Act
21 U.S.C. § 353(b)(4)(B)

Pending Applications

- Pending ANDA submits an **amendment** to conform to the labeling requirements.
- If new patent information for the OTC entry (compared to the Rx entry) is listed (i.e., newly listed patent or revised method of use), ANDA applicant must provide an appropriate certification, re-certification, or statement.
- Example: Proposed Rx to OTC switch with revised use code

314.96(d)(1)(a), 314.50(i)(6)(iii) and 314.94(a)(12)(viii)(C)

Approved Applications

- ANDAs are responsible for monitoring Orange Book for updates of RLD.
- Approved ANDA is required to submit a Prior Approval **Supplement** (PAS) to comply with the updated labeling requirements.
- Generally, an ANDA's labeling must be the same as its RLD's labeling. There are, however, limited exceptions, including an exception for differences caused by the ANDA and RLD being produced or distributed by different manufacturers.

314.94(a)(12)(viii)(C)(2), Section 505(j)(2)(A)(v) of the FD&C Act and 21 CFR 314.94(a)(8)((iv)

Division of Labeling Review (DLR)

- It is the responsibility of the ANDA holder to monitor for updates to the labeling for their Reference Listed Drug on Drugs@FDA and submit supplements/amendments accordingly.
  - Specifically for Rx to OTC switches, submit a PAS as soon as possible; otherwise, ANDA is considered misbranded.

Section 503(b) of the Federal Food, Drug, and Cosmetic Act

OGD's Next Steps

- Upon receipt of PAS, a filing review and subsequent "Acknowledgement sANDA Receipt" letter will be issued with an appropriate GDUFA goal date.

- The PAS will undergo standard review practices.
  - OGD will issue any formal communication via the Information Request(IR)/Discipline Review Letter (DRL) process.

Challenge Question #1

Which of the following statements is NOT true?

A. Rx and OTC versions of the same drug product are permitted to be marketed at the same time.

B. Pending ANDAs should submit an amendment to switch their ANDA drug products from Rx to OTC.

C. ANDA applicant is responsible to update their labeling.

D. FDA does not consider a post-full switch NDA product to be a different listed drug.

Challenge Question #2

What type of submission should approved ANDA Applicants submit for a full RX to OTC switch?

a. CBE-0

b. CBE-30

c. PAS

d. New ANDA

Summary

- Pre- and post- full switch drug products are considered to be the same drug product under section 505(j)(5)(B)(iv) of the FD&C Act.
- ANDA applicants are required to update their labeling to be consistent with the most recent approved RLD labeling.
- Pending ANDAs must recertify to any new or updated patents from the RLD.
- Monitor for RLD updates; when a Rx to OTC switch is identified, submit a PAS as soon as possible.

Questions?

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