Regulatory Overview: Post-Approval Changes to Marketed Drugs

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The popularity of GLP-1s have brought post-approval changes to New Drug Applications (NDAs) to centerstage. Recently, the FDA approved Wegovy in tablet form, offering an alternative to the injection currently on the market. Whether relating to drug labeling, dosage form or containers, each change to an NDA must be reported to the FDA. But how? The exact reporting requirements can vary widely, depending on the severity of the change.

Changes to NDAs can be categorized as major changes, moderate changes or minor changes, depending on the change's potential to adversely affect the "identity, strength, quality, purity, or potency of the drug product," as adverse effects on the quality of a drug product can impact the product's safety or efficacy. For major and moderate changes, the FDA typically expects the sponsor to file a supplemental NDA, while minor changes only need to be reported in the drug's next annual report.

Changes with a substantial potential to adversely affect a drug product's safety or efficacy require *prior approval* from the FDA before implementing the change. For example, this could include:

- A change in the primary packaging components for any drug product when the primary packaging components control the dose delivered to the patient (e.g., the valve or actuator of a metered-dose inhaler)
- A change from a prefilled syringe to another container closure system for sterile drug products
- Certain efficacy supplements (i.e., new indication or patient population)
- Changes to clinical pharmacology section based on new/modified clinical data

Moderate changes—those with a moderate potential to impact a drug's safety or efficacy—can be implemented *30 days after* FDA receives the supplement (as long as the FDA does not inform the applicant that prior approval is required). Alternatively, some moderate changes can be implemented upon notification to the FDA, but if FDA disapproves of the change, the manufacturer must cease distribution.[1] This may include:

- Changes in the size or shape of a drug container
- Strengthening or adding a contraindication, warning or precaution
- Adding specifications for further assurance a manufactured drug will have its purported quality

Finally, minor changes are those likely to have only a minimal impact on a drug's safety or efficacy and only need to be included in the applicants' next *annual report*. This may include:

- Adding or changing a container closure cap (i.e., from metal to plastic)
- Changing a label's layout or making editorial changes

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- Changing the manufacturing site for product labeling

While most changes can be reported by way of a supplemental NDA or an annual report, the FDA may ask a sponsor to submit an NDA for the proposed change for certain changes.[2] For example, if a drug product changes the dosage form or route of administration of a drug, the FDA typically expects an original NDA to be filed. As such, a product changing from an injectable form to a tablet or capsule form—like Wegovy—would be expected to file an original NDA to effectuate the change. The exception is if the change in dosage form or route of administration can be accomplished with the drug remaining quantitatively and qualitatively identical in composition.[3]

Of course, this only briefly covers the long-list of potential changes to a drug product. Sponsors considering any change to a previously approved drug should fully assess the regulatory requirements for implementing the change to avoid delays in marketing the updated product.

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[1] FDA Guidance: Changes to an Approved NDA or ANDA (Apr. 2004).

[2] FDA, Webinar: So, Your NDA Was Approved – Now What?! (2020) (at 25:50).

[3] *See* FDA Guidance: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees (Dec. 2004).

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