

Guidance

“Off-Label” and Investigational Use of Approved Drugs and Biologics

Overview:

This guidance covers the “off-label” use of drugs and biologics which can occur either in the context of patient care or in the conduct of research. “Off-label” use occurs when an FDA-approved drug or biologic is utilized outside of its approved labeling. IRB oversight is only required when the drug or biologic is being used in a clinical investigation. The FDA has defined “clinical investigation” to be synonymous with “research.”

Description:

“Off-Label” Use of Marketed Drugs and Biologics

Good medical practice and patient interests require that physicians be able to use approved marketed drugs and biologics according to their best knowledge and judgment. If an approved drug or biologic is used for an indication that does not appear in the approved labeling for patient management, a physician has the responsibility to be well informed about the product, to base the “off-label” use on firm scientific rationale and on sound medical evidence, and to maintain records of the product’s use and effects. This type of “off-label” use of an approved drug or biologic for the “practice of medicine” does not require the submission of an Investigational New Drug (IND) application or review by the IRB.

Investigational Use of Marketed Drugs and Biologics

The investigational use of an approved, marketed product is different from the scenario described above. At a minimum, IRB review and approval is required if the intended use of the approved drug or biologic involves a “clinical investigation.” This is defined by the FDA as any experiment that involves a test article and one or more human subjects, **and** that either must meet the requirements for prior submission to the FDA of an IND application or the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

Investigators who plan to use a marketed drug or biologic in a clinical investigation must first determine whether it is necessary to apply to the FDA for an IND for the intended new use of the product.

A clinical investigation of a marketed drug is exempt from the IND requirements if all of the criteria for an exemption in § 312.2(b) are met:

1. The drug product is lawfully marketed in the United States.
2. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.
3. In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.

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4. The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).
5. The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).
6. The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

When using these criteria, it is sometimes difficult for an investigator to determine whether an IND is required. Thus, it is important to consult with the ORS/ HRPP during the planning phase of the study to assist with this decision. Investigators may be instructed 1) that an IND is not necessary based on the criteria noted above, 2) that a request for an IND exemption should be sought from the FDA, or 3) that an IND application be submitted.

It is important to note that individuals who hold an Investigator-Initiated IND are also subject to the requirements of being a sponsor. This includes additional responsibilities with respect to monitoring, accountability, and reporting to the FDA.

Consent Document:

Even though the drug being used is currently on the market, it is important to be clear that it is being used for a different purpose in the context of the research. The consent document must state that the drug is not FDA approved for the disease or condition being studied. It is not appropriate to include wording such as “not currently approved” or “not yet approved” which implies that it will become FDA approved in the future.

Under “Risks,” include the following language, since there are risks that may be unknown at this time:

“As with any research study, there may be adverse events or side effects that are currently unknown and it is possible that certain of these unknown risks could be permanent, serious or life-threatening.”

Considerations:

One of the most difficult issues in determining whether an IND is needed is the requirement that the risk associated with the product is significantly increased (or the acceptability of the risk significantly decreased).

The FDA has offered the following guidance related to this issue:

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<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm229175.pdf>

Investigators should carefully consider the risk implications of any conditions of use in the study that deviate from the conditions of use described in the drug’s labeling, with particular attention to the following:

Route of Administration- A change in the route of administration can introduce a significant new risk. For example, there could be a significant increase in risk if a drug marketed for oral administration is converted to a dosage form that is to be administered by injection or an intravenous, intrathecal, or inhalation route. These other routes of administration introduce concerns with increased local concentrations, sterility, pyrogenicity, hypersensitivity (e.g., airway reactivity), variations in metabolism, and other issues not present with oral administration that can significantly increase the risk, or decrease the acceptability of the risk, associated with use of the drug.

Dose- Increases in dose, frequency, or duration of administration, compared to labeled dosing regimens, can significantly increase the risk in a study using a marketed drug. It is also possible that a decrease in dose could significantly increase risk. For example, administering a sub-therapeutic dose of an antiviral drug to study subjects could induce resistance in the subjects, thus rendering a subsequent therapeutic dose of the drug ineffective in treating the virus. The significance of changes in dose (in particular, increases in dose) can vary across therapeutic areas. In clinical settings, use of higher doses than are recommended in labeling may be much more likely to significantly increase the risk or decrease the acceptability of the risk.

Patient Population- The acceptability of known and unknown risks can vary across different treatment populations. The population chosen for study could be at increased risk compared to the approved use population for a variety of reasons, such as increased age, different disease or stage of disease, concomitant illness, decreased renal or hepatic function, or concomitant therapy. When use of the drug in a specific patient population decreases the acceptability of the known risks, the study would have to be conducted under an IND.

FDA Information for Submitting INDs:

<http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/ucm071098.htm>

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm229175.pdf>

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Additional Information:

<http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/ucm071098.htm>

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm229175.pdf>