Clinical Research Industry Whitepaper: February 2011

Risk based decision making in determining whether drug research requires an IND

Risk based decision making in determining whether drug research requires an IND

Oftentimes, academic and office based researchers wish to study an approved drug in a slightly new way. How do researchers decide whether or not they need to file an IND with the FDA? The restrictions regarding whether or not clinical research requires an IND are increasing year by year as new drugs, procedures, and devices are introduced to the market. Most questions concerning the process of INDs revolve around risk. Who should decide the "acceptable amount of risk"? As opinions of risk vary among healthcare organizations such as the medical community or an IRB, for example, how do we decide on the definition and assignment of risk?

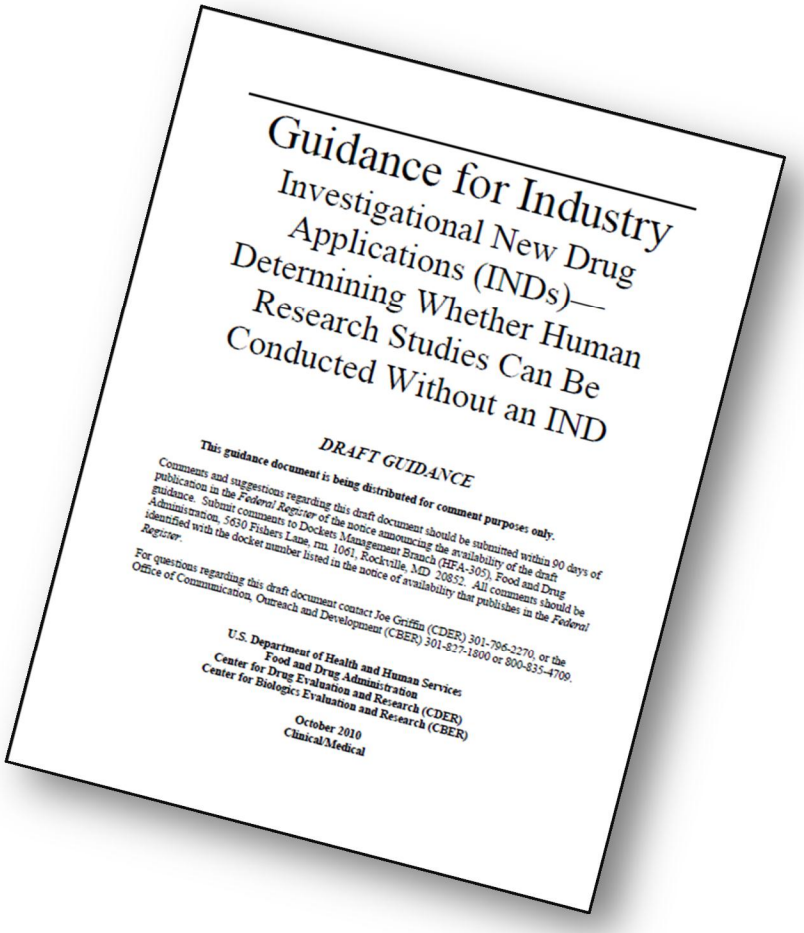
Let's begin with what we know from the FDA. There are six criteria the FDA created to help companies and investigators determine when research is exempt from an IND. Per the recent October 2010 Draft Guidance Document issued by FDA on this topic, all criteria below **must** be met and are listed here[1]:

I. The drug product is lawfully marketed in the U.S.; and,
II. There is no intent to report the investigation to FDA as a well-controlled study in support of a new indication and no intent to use it to support any other significant change in the labeling of the drug; and,
III. In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug; and,
IV. 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; and,
V. The investigation is conducted in compliance with the requirements for review by an IRB and with the requirements for informed consent
VI. 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.

Three questions arise about the above criteria that merit further discussion. Let's examine each one in detail

[1]Guidance for Industry: Investigational new Drug Applications (INDs) – Determining Whether Human Studies Can Be Conducted Without and IND. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm229175.pdf

1. *What is meant by a drug that is "lawfully marketed in the U.S."?* This guideline was created by the FDA with the intent of granting some latitude when sponsors or investigators need to slightly modify the marketed version of the drug to conduct the study. But how much can the marketed version be modified to keep it exempt from IND regulations? By making changes that are both "low-risk" and "minor," a researcher or sponsor can circumvent the IND requirement. Such modifications might include color changes, scoring, or capsule size. Major variations include complex changes within oral dosage and non-oral dosage forms as well as injectable forms. The definition of major versus minor is subjective. Often the investigator may not know if the drug will still be effective after changes that may be assumed to be a minor


Guidance for Industry
Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted Without an IND

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Joe Griffin (CDER) 301-796-2270, or the Office of Communication, Outreach and Development (CBER) 301-827-1800 or 800-835-4709.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

October 2010
Clinical/Medical

2. *Does the risk associated with the product significantly increase (or the acceptability of the risk decreases)?* In this case, investigators must carefully consider the risk implications made in the interest of the study which deviate from the original product label. This concern resides particularly in the areas associated with route of administration, dosage, and patient population. Such modifications could include a change from oral to non-oral dosage forms, changes in dosing schedule, and use in new disease

[1]Guidance for Industry: Investigational new Drug Applications (INDs) – Determining Whether Human Studies Can Be Conducted Without and IND. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm229175.pdf

states. For example, the latter two issues concerning tolerated risk are especially difficult when the clinical trial contains cancer patients. Could an investigator consider pancreatic cancer an acceptable risk as the product is approved for use in the treatment of lung cancer? Could use in stage 2 cancer be acceptable risk because the product is approved for stage 4, or vice versa?

3. The third question is three pronged: *does the sponsor intend to (1) report the investigation to FDA as a well-controlled study in support of a new indication, (2) use it to support any other significant change in the labeling of the drug, or (3) use it to support a significant change in advertising (for prescription drugs only) for the drug*. In general, it seems reasonable to infer that the intent of any well-controlled trial of a marketed drug sponsored by the manufacturer of the drug would be to influence labeling or promotion in some way. What about off-label promotion? For example, a researcher's results, particularly in the case of an investigator initiated trial (IIT), can be published in a journal article with no intent of directly affecting or changing the labeling of the drug. Since the FDA does not regulate journals, what stops a healthcare professional from using journal articles to promote a drug off-label? Often differences in interpretation of stakeholders' intentions make it difficult to determine the acceptability of a clinical trial conducted without an IND.

While the FDA's guidance document does offer some specific criteria for INDs, a few other scenarios require some clarification. The first is bioavailability or bioequivalence studies in humans where FDA regulations seem to facilitate the development of generic drugs. A planned bioavailability/bioequivalence (BA/BE) study using the generic equivalent of a particular drug, whether capsule or tablet, does not require an IND if all the following requirements are met: *(1) the drug product does not contain a new chemical entity, it is not radioactively labeled, and is not cytotoxic. (2) the dose (single dose or total daily dose) does not exceed the dose specified in the labeling of the approved version of the drug product. (3) the investigation is conducted in compliance with the requirements for review by an IRB and the requirements for informed consent. (4) The sponsor meets the requirements for retention of test article samples.* This specific section of the guidance document is clear and do seem to expedite the approval path for the generic drug market players.

[1]Guidance for Industry: Investigational new Drug Applications (INDs) – Determining Whether Human Studies Can Be Conducted Without and IND. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm229175.pdf

Another area where it is clearly defined that the researcher does not need an IND is in the case of clinical investigations using cold isotopes to obtain basic information regarding metabolism, human physiology, pathophysiology, or biochemistry. When conducting research with cold isotopes an IND is not required as long as the results are not intended for immediate therapeutic, diagnostic, or preventive benefit.

Finally, we should review the area of testing the effectiveness of dietary supplements. Dietary supplements are defined as "a product taken by mouth that is intended to supplement the diet and that contains a dietary ingredient.[1]" Ingredients can include vitamins, minerals, herbs, and other botanicals, amino acids, other dietary substances intended to supplement the diet, and concentrates, metabolites, constituents, extracts, or combinations of the preceding items. IND requirements are determined based on the intent of the clinical investigation. As long as the dietary supplement is not intended for immediate therapeutic, diagnostic, or preventive benefit, an IND is not required.

Unfortunately, there is no perfect algorithm or decision tree to follow when navigating the research pathway and regulatory requirements for researching existing compounds that are available on the market or existing dietary supplements. But by understanding the FDA guidance and examples presented in this Whitepaper, researchers should be able to consider carefully the parameters they need to consider as they design research studies. Also, don't hesitate to reach out and ask FDA their opinion. Oftentimes when the path is not clear, consulting FDA is the best route. And remember, all research that meets OHRP's definition of research still requires an IRB review. And be prepared for the questions your IRB will ask regarding a secured IND or FDA waiver. Most commercial IRB's will not accept a review without an IND or at least a communication from the FDA stating it is acceptable to conduct the study without obtaining an IND.

For more information, click here to review FDA guidance document issued October 2010 entitled *Guidance for Industry: Investigational New Drug Applications (INDs) – Determining Whether Human Studies Can Be Conducted Without an IND.*

About Pearl IRB

Pearl IRB is an independent Institutional Review Board that provides comprehensive IRB services for institutions, principal investigators, sponsors, and CROs nationwide. We deliver quality and timely

[1]Guidance for Industry: Investigational new Drug Applications (INDs) – Determining Whether Human Studies Can Be Conducted Without and IND. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm229175.pdf

reviews that balance the interests of human subjects, sponsors, sites, and institutions. Together, we will drive enhanced efficiency and value in clinical research. To learn more, please visit us at www.pearlirb.com, call us at 317.278.4100, or email info@pearlirb.com.

[1]Guidance for Industry: Investigational new Drug Applications (INDs) – Determining Whether Human Studies Can Be Conducted Without and IND. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm229175.pdf