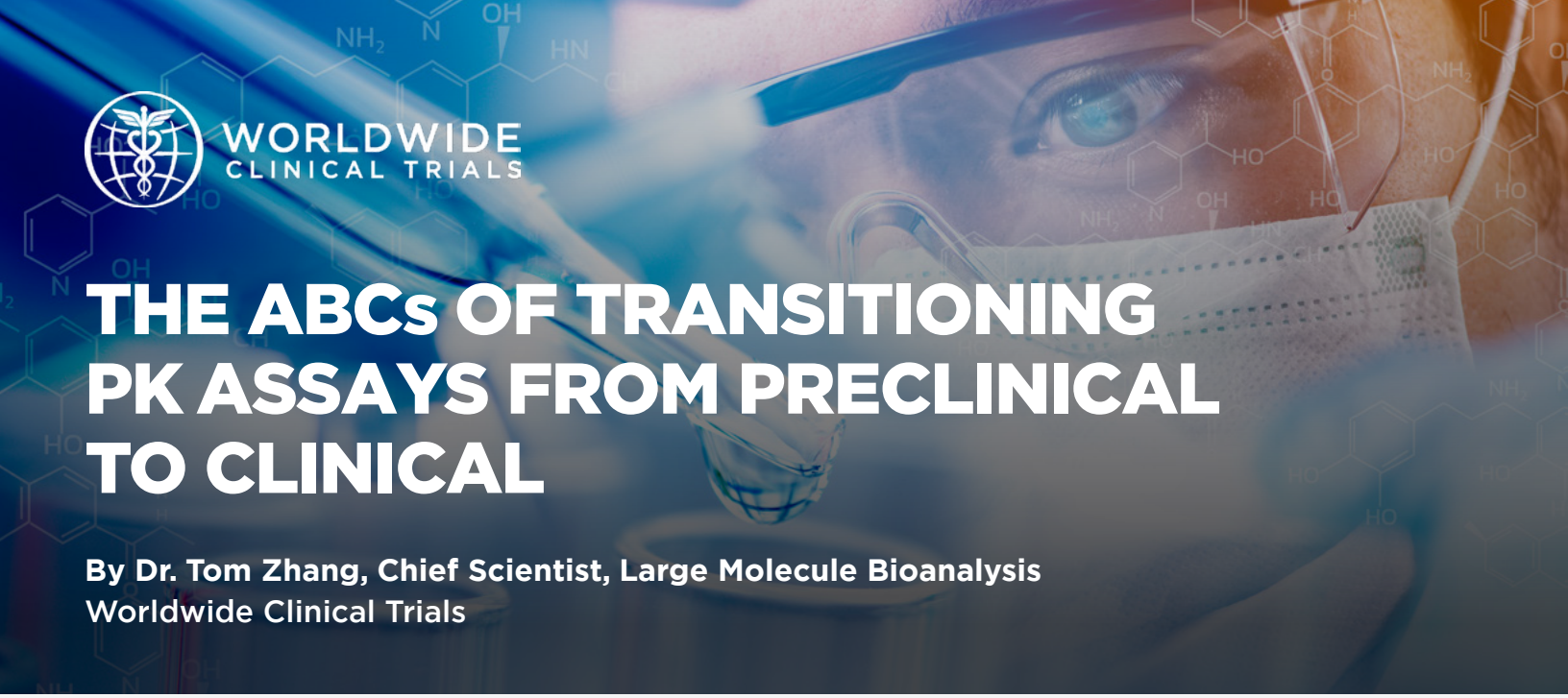

WORLDWIDE CLINICAL TRIALS

THE ABCs OF TRANSITIONING PK ASSAYS FROM PRECLINICAL TO CLINICAL

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Worldwide Clinical Trials

Ensuring a seamless transition from preclinical to clinical stages in large molecule bioanalysis will help you reach crucial trial milestones on time and within budget. However, optimizing pharmacokinetics (PK) assays to bridge the preclinical-to-clinical gap requires some finesse. This is because the stages differ both in scale (small vs. large) and focus (safety vs. safety and efficacy).

Here are a few points to jumpstart your thinking as you approach this challenge.

A Preclinical and clinical PK assay formats serve different goals

Preclinical assays designed to assess drug toxicity and safety must detect total drug. For studies of humanized therapeutics (monoclonal antibodies [mAb], fusion protein, antibody-drug conjugates [ADC], bispecific antibodies, etc.), a typical format is: receptor/target as capture with a generic binding reagent as detection (e.g., anti-human IgG).

In contrast, clinical trials focus on both safety and efficacy — the relationship between drug concentrations and pharmacological effects. That said, free drug level is the preferred measure for investigating target engagement in these studies. To measure free drug only, anti-idiotype (anti-ID) mAb testing may be the best choice. If so, it is important to plan for development of this assay within the project timeline.

B Consider matrix interference, as assays must work in both preclinical models and humans

Preclinical studies are performed in animal models, while clinical studies are performed in human subjects. While commercial anti-human IgG is a convenient assay detection tool in animals, this approach often fails in humans. Background human immunoglobulins in the clinical serum, plasma, or whole blood samples interfere with the assay by binding and saturating anti-human IgG. Special reagents must be designed that are specific for the investigational drug and will not cross-react with naturally occurring human immunoglobulins.

Differences in reactivity between biological samples from healthy volunteers and samples from diseased patients must also be considered, along with possible PK effects and drug-drug interactions (DDI).

WE'D LOVE TO TALK ABOUT HOW WE CAN SUPPORT A SMOOTH PK ASSAY TRANSITION FROM PRECLINICAL TO CLINICAL

For different scales and tolerances, assay sensitivity and range requirements are at odds

Preclinical studies are focused on assessing drug safety and maximum tolerable dose. Therefore, they employ high dosages, so most samples contain highly concentrated drug levels. The assay's range must therefore include high drug concentrations — sensitivity is less important.

In contrast, since clinical trials start with ascending doses from very low levels, highly sensitive assays are required to detect the drug concentration in samples.

Generally, an assay that can measure high concentrations is less sensitive, and a sensitive assay is typically ineffective for testing samples with high drug concentrations. For these reasons, an established preclinical assay's range is often not suitable for testing clinical samples.

Takeaways

Differences in scale and purpose make many preclinical assays unsuitable for transfer to clinical studies. Careful early planning to optimize or redevelop existing biologics PK assays — or find alternatives, if needed — will prevent unnecessary roadblocks and delays as clinical testing proceeds.

FOR FURTHER INSIGHTS, READ OUR WHITE PAPER, *LARGE MOLECULE PK ASSAYS: OPTIMIZING BIOANALYSIS FOR PRECLINICAL THROUGH FIH.*

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