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Do you know the top 5 CMC reasons that could put your program on clinical hold?

Do you know that drug substance or drug product stability is one of those reasons?

To paraphrase from the current FDA IND Guidance[1]:

"The identification of a safety concern or insufficient data to make an evaluation of safety is the only basis for a clinical hold based on the CMC section. Reasons for concern may include, for example: 1) a product made with unknown or impure components; 2) a product *possessing chemical structures of known or highly likely toxicity;* 3) a product that cannot remain stable throughout the testing program proposed; or *4) a product with an impurity profile indicative of a* potential health hazard or an impurity profile insufficiently defined to assess a potential health hazard; or 5) a poorly characterized master or working cell blank."

How do you demonstrate stability to the FDA?

Essentially you need to prove that what you dosed the animals with is the same as what you propose to give to humans. You also need to prove your compound will be stable throughout the proposed human dosing (testing) period. In your IND filing there are two ways you can demonstrate that your drug substance and drug product is stable:

1) You can refer to ICH stability data from on-going stability studies that cover the proposed testing period.
2) You can show stability or retest data before and after pivotal toxicology.

What type of stability testing is needed for Phase 1?

While it is often considered an "industry standard", you do not actually need validated analytical methods and ICH protocol-driven stability studies for a Phase 1 compound. In order to convince a reviewer your data is reliable and stability indicating you should have good quality analytical methods that are "validatable". To demonstrate drug substance stability, you need a COA issued at time of manufacture that includes the critical stability-indicating methods for your compound. A re-test using the same test methods should then be performed at the completion of the toxicity study to demonstrate stability during the testing period. For each (structure class) of drug substance the critical stability-indicating methods may be different. While a stability indicating HPLC method is always needed, other tests may be required based on the chemical structure and proposed use. A salt form may be hygroscopic thus stability issues may not show up until the salt form is hydrated. Alternatively, the opposite may be true, where "hydration" may be necessary to provide stability to your drug substance. In such a case, a water content test would be considered a critical stability-indicating test. Physical form can also play a role; micronized drug substance may behave differently on storage than unmicronized, native crystal form. Because of this, you typically would need to demonstrate stability for both unmicronized (native crystal form) as well as micronized drug substance.

Is my CRO "over-developing" my drug?

While supporting data in an IND filing needs to be sufficient to support the phase of development, far too much time and money is spent "over developing" compounds at CROs. Many companies are unaware that the FDA actually encourages us to be creative and flexible in our development approaches and *not* to provide *too* many studies. The following excerpt is taken directly from a current CMC Guidance from the FDA.[2]

"...Existing regulations allow a great deal of flexibility in the amount of data that need to be submitted with an IND application, depending on the goals of the proposed investigation, the specific human testing proposed, and expected risks. The Agency believes that sponsors have not taken full advantage of that flexibility and often provide more supporting information in INDs that is required by regulations..."

TRIPHASE Pharma Solutions

At TRIPHASE, our scientists take ownership of your CMC management and exploit this "flexibility" that is allowed, in fact encouraged, by the agency. By knowing where to "draw the line" your company will not spend additional weeks or months developing methods or performing studies that are not needed. Using this process, where science drives regulatory, will lead to untold savings and help you reach your milestones faster.

If you have any questions about the stability of your product or other CMC questions, please call TRIPHASE today.

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[1]See Guidance for Industry: *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products.* [2]See Guidance for Industry: *Investigators, and Reviewers Exploratory IND Studies.*