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cGMP Radiosynthesis for Early Phase Clinical Trials: A Unique Challenge and Development of a Standard Process

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Abstract

Purpose
Radiolabeled drugs are used in human ADME and bioavailability studies. While the regulatory requirements for traditional "cold" clinical trial materials are well understood, the regulatory requirements for radiolabeled are much less understood by the industry. The synthesis of radiolabeled compounds sometimes requires development of new synthetic pathways which can be significantly different from the traditional synthetic pathway. The radiolabeled drug can have different stability and impurity profiles from the non-labeled drug and thus require special considerations. These special considerations may pose challenges in ensuring cGMP compliance and safety for the patient during the clinical trial.

This presentation discusses the challenges associated with radiolabeled synthesis coupled with maintaining CGMP compliance for the synthesis and analytical portions of the program.

Methods
A standardized process has been developed for implementing cGMP requirements for early phase clinical compounds to radiolabeled drugs for human studies. The typical procedure for generation of the final compound for dosing requires blending the radiolabeled drug with the nonlabeled drug to meet a certain radioactivity (specific activity). Both the labeled and nonlabeled drugs need to be manufactured under cGMP requirements prior to the blending process. The release testing, under cGMP, is complicated by the need to determine not only the chemical purity, but also the radiochemical purity of the drug substances or drug products. Our standardized process addresses these challenges that are inherent in developing and validating specific analytical methods required for the radiolabeled drug substances and drug product.

Results
A standard process for ensuring regulatory compliance is presented and discussed. Case studies are presented for different scenarios.

Conclusions
By implementing the standard process, radiolabeled drugs are produced which meet phase appropriate cGMP compliance.

Background

Radiolabeled products are used extensively during pre-clinical studies in BA/DMPK studies. The material used for these studies is typically research grade material released under Good Laboratory Practices (GLP's). However radiolabeled drugs are also used during ADME and bio-availability studies. Since the products are now intended for use in human studies, they now must comply with cGMP regulations in its manufacture and release testing.

Definitions

Hot Material
API which is fully labeled at the determined position. This material has high specific activity.

Cold Material
API which is not labeled, i.e. no radioactivitiy.

Blended Material
Final API material which is a blend between the hot and cold material to reach the desired final specific activity.

Specific Activity
The amount of radioactivity per unit mass of the compound. Usually expressed as mCi/mmol or µCi/mg.

Challenges

Regulatory Challenges
Part of the confusion as to the regulatory expectations of cGMP radiolabeled material is a result of the manufacturing process for radiolabeled material.

Hot Synthesis
The initial step is the production of the radiolabeled material. This is most often accomplished by synthesizing a fully radiolabeled product. This material typically has significantly higher specific activity than is needed for the clinical studies.

Blending
To achieve the target activity level needed for the clinical studies, the hot material is blended with cold cGMP produced API material. The blending ratio will depend on many specifics but can range from a 1:10 blend to 1:1,000 blend. As a result the amount of radiolabeled material can typically range from 0.01% to 10%.

It is the second part which has led to some confusion on the regulatory expectations, as the level of radiolabeled material is typically at or below typical impurity levels observed. *Should the material be treated as an API or as an impurity considering the level at which it is being observed for the product?* This question was posed to the FDA, in addition to whether the level of hot material in the final product would have an impact on the regulatory expectations. The FDA replied as follows:

"As stated in the FDA guidance for industry on: cGMP for Phase 1 Investigational Drugs, "Consistent with the FD&C Act (§ 501(a) (2) (B)), cGMP must be in effect for the manufacture of each batch of investigational drug used during Phase 1 clinical trials." The guidance also states that, "For each batch of the API (or drug substance), you should perform confirmatory identity testing." Therefore, since the radiolabeled API is a component of the blended API to be used in the IND, the hot (radiolabeled) API should be produced under the same standards of cGMP as were used to manufacture the cold (non-radiolabeled) API. Further, since both APIs are used as components of the IND, each API should be tested separately to confirm its identity, as well as other critical qualities, regardless of the ratio of radiolabeled to non-radiolabeled API in the final API blend." – From Office of Compliance, Division of Manufacturing and Product Quality, FDA.

There are two key parts to the response:

1) Regardless of the level of radiolabeled material in the final product the production of the hot material should be performed to the same standards as cold cGMP API.

2) The hot material must be released prior to blending with the cold material and then the final blended material also released. Additionally, general expectations on cGMPs for API used in clinical trials are discussed in ICH Q7, Section 19.

Synthetic Challenges
The synthesis can be technically challenging using C14, tritium or other radionuclides. For C14 labeled materials, the site of labeling is specific. At this stage of development, the synthetic route for the cold material is generally worked out on a small scale. In some cases, this synthetic route can be used to synthesize the radiolabeled material. It is typically required that a unique synthetic pathway be developed using either a known radiolabeled intermediate or building the molecule up from scratch. The presence of the radionuclide can alter the synthetic pathways, such that chemistries which are known to work for the synthesis of the cold material may not work well in the presence of the radionuclide.

A unique challenge with radiolabeled materials is their stability. The radiolabeling can result in unexpected degradation as a result of radio-induced degradation. What compounds may be at risk is not predictable and in most cases cold stability cannot be used to predict stability after being radiolabeled. As a result, in many cases the compounds must be prepared relatively close to the actual clinical trial date and stored at -20/-80 °C to minimize possible degradation.

Analytical Challenges
The hot material, cold material, and final blended material all require cGMP release testing before use in clinical studies. Typically, cold material is not an issue as methods are available and have undergone at least phase appropriate validations. The same methods can be applied to the hot and final material for release testing for the chemical purity and other attributes. However, specifications for the material also require determining the radiochemical purity of the material along with the specific activity of the product under cGMP.

Determining the radiochemical purity almost exclusively involves HPLC analysis utilizing a radiochemical detector. In many cases the HPLC method utilized in determining the chemical purity is compatible with the inline radiochemical detector and can be used as is, with some validation specifically for the radiochemical analysis. However, in cases where the HPLC method is not compatible or one is not available (i.e. either not developed or the current method is GC based), then a stand-alone HPLC radiochemical method will need to be developed and validated.

As with any method utilized for cGMP release testing, the radiochemical purity method must be validated. As these studies are typically done in Phase I, a phase appropriate approach can be

utilized. The overall challenge is that while standards are typically available for the cold material, no standard material will be available for the radiolabeled material. If non-cGMP radiolabeled material is available, it can be used. Otherwise the product being synthesized will need to be used for the validation of the method, and would be performed concurrently with the release testing. This can be achieved under protocol by testing linearity, LOD/LOQ, precision of the method prior to performing the release testing on the material. By the nature of the radiochemical detector, impurities will have a direct proportional response to the parent compound (i.e. no relative response factor). The radiochemical purity method is typically performed by a simple Area Under the Curve (AUC) method.

Process

A standard process has been developed to address the specific challenges encountered during the synthesis of cGMP material.

1) Define the chemistry. This involves reviewing the target labeling position, along with the cold synthetic routes. From this, a proposed synthetic scheme is worked which may be similar to or substantially different from the cold synthetic process. Depending on the number of steps a portion of the synthesis may be performed under non-GMP conditions, with an intermediate being designated as the regulatory CGMP starting material for the process.

2) Perform proposed synthesis pathway using low level radioactivity. A low level of activity is used to determine if the proposed synthetic scheme will work and if the determination yields in the presence of radioactivity.

3) Transfer in Analytical Metods. The methods used on the cold material (if needed for the release of hot and low activity materials) are officially transferred in under protocol, if they have been previously validated.

4) Write a cGMP Master Batch Record iusing the results of the tracer study.

5) Purchase all new product contact materials (glassware, columns, etc) for the cGMP synthesis. This addresses concerns in relation to cleaning validations and cross-contamination.

6) Manufacture the cGMP. At minimum, one major bond forming step is performed under cGMP controls.

7) Validate the radiochemical purity method phase appropriately using the synthesized material.

8) Perform release testing on the hot material.

9) Perform blending of the hot and cold material under batch record to achieve the target specific activity.

10) Perform release testing of the final blended API material for adherence to pre-approved product specifications.

Summary

By establishing a standard procedure for the CGMP synthesis of radiolabeled material we have been able to streamline the synthesis process while maintaining the regulatory compliance expected for the material.