At what stage of API development should you start to think about ICH guidelines?

Since understanding regulations is a key part of our business, this blog takes a brief look at the origins of the International Conference of Harmonization (ICH), and the implications of a unified regulatory framework. It also provides tips on how to efficiently meet ICH standards.

By Ed Price, President, PCI Synthesis

Ensuring that pharmaceuticals are safe for patients to take is the number one priority for regulatory agencies across the world. Until the 1980s, however, regulation and enforcement were local efforts. Standards differed across borders, and drug developers were left to guess which standards they needed to meet.

Things began to change in the 1980s, when European regulators started moving toward the development of a single market for pharmaceuticals, and with it initiated efforts to harmonize regulatory requirements for drugs across what was then the EC. They achieved initial success that showed it was possible to have a unified, single regulatory framework that all European countries could abide by and agree on.

But it was not until 1989, at a WHO Conference on Drug Regulatory Authorities (ICDRA) in Paris that plans began to materialize for what would eventually become today's ICH.

Soon after the WHO conference, the authorities approached the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) to discuss a joint regulatory-industry initiative on international harmonization, and ICH was conceived. The next year, in April 1990, the ICH was born, in Brussels.

Since then the ICH has provided a unified standard adhered to by the European Union, Japan, and the United States, facilitating the mutual acceptance of clinical data by the regulatory authorities in those jurisdictions.

This interesting history explains how ICH came to be and the valuable role it plays. Certainly in our industry, having a harmonized set of guidelines has made drug development and manufacturing far less fragmented. Now when we develop an Active Pharmaceutical Ingredient (API) at PCI Synthesis, we know that if it meets the set of guidelines from the ICH on safety, quality and efficacy, the drug candidate will be accepted in most of the world. It means the API will be sufficiently free of impurities and consequently safe for patients to take, starting with Phase I clinical trials.

Meeting ICH guidelines is no walk in the park. The ICH sets very high standards for impurities – a drug substance must be greater than 99% pure. With specific limits set for known, unknown, elemental and genotoxic impurities.

As readers of this blog know, developing new drug candidates is a daunting challenge to begin with. And there is no greater challenge than the identification, quantification and management of impurities. As well, the risks associated with even miniscule amounts of an impurity must be determined. It is an essential part of the drug development process and the most time-consuming.

The good news: we can always find ways to deal with impurities. It just may take some time.

How to meet ICH guidelines efficiently

Adhering to the following four conditions leads to the most efficient drug development process, one that is geared to meeting the ICH's stringent guidelines for safety, quality and efficacy:

1. Sensitive equipment
2. Wide array of instruments
3. Experienced scientists
4. An early start

Sensitive equipment

As we develop APIs, our research is only as good as the tools, equipment and expertise used to analyze the work being done every step of the way. In order to rid drug candidates of impurities,

drug developers need sensitive instruments that provide a variety of ways of filtering, isolating and identifying products, including impurities. Prep chromatography equipment is also a necessity.

Wide array of instruments

As we've previously discussed in articles about how to choose a CMO with a highly qualified R&D team, and in our article on equipment equivalencies, it's important to have instruments with different capabilities.

Good analytical instruments such as spectrophotometers are also a must.

Experienced scientists

Technical teams that can demonstrate innovative thinking will be instrumental in meeting ICH guidelines. Here's why.

Process chemistry is about solving one problem after another. You have to do hundreds of individual experiments to see how the process behaves, with tweaks and changes to process parameters along the way to get the desired end result.

The truth is that when you start your project you truly do not know what technical challenges lie ahead. A team that can think out of the box will be able to do two highly desirable things: decrease the number of process steps for a product, and increase the overall yield. They will often know whether a reaction is likely to be a mess that requires dealing with a number of side products. But they will also have good ideas on how to deal with it.

Get an early start

We begin thinking about ICH guidelines at the very earliest stages of a project. Why? Because eventually materials will go into people, and they need to be safe. And because new chemistry is rarely straightforward, meeting ICH guidelines is often time consuming and expensive—it isn't easy to get an API to 99% plus purity.

When a person learns to drive they're always told, look ahead. Look beyond the hood of the car. See what the road ahead looks like. Likewise, we begin our work by looking ahead to what the FDA

or EMA will require. We can then have a better view of what lies ahead and plan our experiments and their documentation accordingly.

In our decades of experience we have learned that the best thing to do is to take a holistic approach to a project, incorporating from the start what's likely going to be required. We think about which reagents are more efficient and which reactions will be cleaner, and what clinical steps that are better than others for purification.

Thinking ahead allows us to work as efficiently as possible to get to the end of our road, one that adheres to all ICH guidelines for faster regulatory approval.

We spend a lot of time with our sponsors, and on this blog, focused on understanding and abiding by FDA and ICH regulations. Clearly if you don't meet those guidelines and don't get approval, you can't sell your drug. We have other articles on related topics including: "Documentation for Regulatory Filings: The integration of technical, manufacturing and quality management expertise is a valuable asset in a CMO," "How to Get Your Organization Prepared for an FDA Inspection" and "Why the FDA and EMA want you to implement

Quality by Design (QbD) & 9 basics and what's in it for sponsors." If you have specific questions, please email us at info@pcisynthesis.com.