Complex Drug Development and Manufacturing —Steroids, Peptides, and Hormones

By Dr. Thomas S. Ingallinera, R.Ph., Ph.D.

There are pharmaceutical therapies that are growing in their application and importance in patient care, and they occupy a scientific space between small molecules and biologics. They include steroids, natural and synthetic peptides, and hormones. They are complex, often pose solubility and stability challenges, and combine microbiological and chemical processes. They are also highly potent per dose and expensive--$3000-$4000 per gram.

When developing and manufacturing these complex drugs, the risks are significant in terms of product quality, cost, safety, and mistakes can place delivering results to patients in jeopardy. However, risks can be greatly mitigated by the following: preventing cross contamination, employing single-use technology, and using non-destructive testing procedures.

Cross Contamination Prevention Plan

According to both FDA and EMA, cross-contamination is defined as the adulteration of a starting material, intermediate or finished product with another starting material or product. When not managed properly, cross-contamination poses significant risk to the quality and integrity of a drug product. Whether manufacturing your own product or using a contract development and manufacturing organization (CDMO), cross contamination must be prevented and should be a special focus when working with complex drugs like the ones described above.

The Initial Safety Assessment (ASI) of a drug under development contains critical information for preventing cross contamination. A toxicology report is derived from the ASIs and identifies Allowable Daily Exposure (ADE) and defines Acceptable Residue Limits (ARLs). This data informs the Cross-Contamination Risk Assessment which enables the manufacturer to develop the cross-contamination prevention plan. All of this critical data and the processes developed for preventing cross-contamination must be calculated, documented, and measured throughout the manufacturing process.

When working with complex formulations in which cross-contamination poses a significant risk to quality, developing the prevention plan is a leadership function and operational leaders must be intimately knowledgeable of the critical details.

Single-Use Technology

One way to reduce the time-consuming process of extensively cleaning manufacturing suites is to employ single-use equipment. As disposable technology has gained in popularity, it has also been improved and can handle the complex formulations containing proteins, steroids, and hormones.

Easy to handle disposable bags as small as 1 liter is ideal for the expensive, often highly potent batches noted above. Single-use bags are specially designed to mix, hold, and store batches before and after filtration. Additionally, the material used to manufacture the bags poses no risk related to extractables and leachables.

Non-Destructive Testing

Every fill-finish operation will incorporate testing to ensure precise dosage amounts and critical quality attributes (CQA), and this is especially important when handling small amounts of highly potent medicines. Over-filling wastes expensive drug product and under-filling impacts quality and patient results. Randomly sampling finished product is less precise and wastes product.

Non-destructive testing can save time and money, can ensure quality with precision, and can be performed on an entire batch. A variety of non-destructive means of testing finished product are available to the pharmaceutical industry and the best inspection solution should be driven by the product's critical quality attributes (CQA). Testing can be as straight-forward as a final check-weighing of finished product to complex visual automated inspection systems to detect particulates in the product, check residual seal force (RSF), or the integrity of a prefilled syringe.

Summary

Developing and manufacturing complex formulations that fall somewhere between small molecule and biologics can be full of challenges: risks that can jeopardize quality, processes that waste costly drug product, and safety concerns for staff and patients. Preventing cross-contamination, employing single-use technology, and conducting non-destructive testing of the finished product will produce higher quality medicines and deliver better results to patients.

About Dr. Tom Ingallinera

Dr. Thomas Ingallinera is the Vice President of Technical Support at Pharmaceutics International, Inc (Pii) and one of Pii's talented subject matter experts whose purpose is to solve problems. Dr. Tom has over 40 years of experience in pharmaceutical development, with an expertise in complex dosage forms. He has advised on product development programs across the continuum, from pre-formulation through commercial production. He has worked at several leading pharmaceutical companies including BioCryst Pharmaceuticals, Parenta Pharmaceuticals, AAI Pharma, Genzyme, Burroughs Welcome, and A.H. Robins. Dr. Ingallinera has a B.S. in Pharmacy with a Ph.D. in Pharmaceutics from Virginia Commonwealth University. Dr. Tom also serves as a member of the Technical Advisory Group for the Bill and Melinda Gates Foundation.

About Pii

Pharmaceutics International, Inc. (Pii) is a US-based contract development and manufacturing organization (CDMO) with a passion for solving problems efficiently with the highest quality standards.

Pii's Hunt Valley, Maryland campus includes 70 manufacturing suites with 4 integrated aseptic filling lines delivering quality, safety, and efficiency. Our professionals have extensive experience with small and large molecule compounds, developing and manufacturing complex parenteral drugs, extended-release formulations, non-aqueous injectable drug products, and lyophilization. Learn more at https://www.pharm-int.com/