The Importance of Analytical R&D To Sterile Fill/Finish

By Irinia Prudnikova

Sterile fill/finish is considered among the most critical steps in the parenteral production process, ensuring patient safety, maintaining pharmacological efficacy, and product quality. Drug product development and subsequent production rely on a number of integrated process elements operating in a systematic and coordinated environment. Without a doubt, analytical support is one of the key process elements. Its importance and uniqueness are derived from the fact that it is required at all stages of the product's life cycle, from the early development to commercialization stages.

Any successful fill/finish program starts with analytical services, more specifically with Analytical Research & Development (AR&D). AR&D groups are responsible for development and validation of the analytical methods which are accurate, precise, reliable and suitable for its intended purpose. Analytical methods are intendent to establish the identity, purity, physical characteristics and potency of drugs including various in-process testing. Therefore, the methods are essentially designed with the purpose to assist formulation scientists gaining the detailed process knowledge. The later leads to process optimization and ability to transition from small scale to large commercial scale. Timely access to accurate analytical information is fundamental for formulation development work. Extensive interactions between analytical and formulation scientists are necessary to ensure analytical methods address specific needs of each development project. Another objective of ARD group is to develop methods robust and reproducible enough to be transferred to Quality Control laboratories. ARD teams are counted upon to lead these transitional activities and guide QC teams in the process. Given the variety and complexity of today's drug therapies and delivery systems, AR&D scientific teams must be able to perform method

development for a range of sterile fill/finish projects, such as suspensions, solutions, and lyophilized products in vials, cartridges, and prefilled syringes.

Expedited and Robust Method Development

The pharmaceutical industry is constantly evolving and the number of investigated compounds increases. This leads to a higher demand for the development of new analytical methods. Every project is unique. AR&D scientists in contract development and manufacturing organizations (CDMO) must meticulously evaluate each project to determine if there is enough information for a successful tech transfer or if new methodologies need to be developed, all while adhering to the customer's project timeline.

Not all projects are straightforward and having scientists who are problems solvers and equipped with the right resources is key. For instance, we had a case when the expedited method development was required based on FDA deficiency response and it involved separation of the active ingredient and four known closely related impurities. The development work was completed in two weeks and helped the customer meet the established deadline.

Another important trait for best-in-class AR&D teams is the ability to demonstrate that the analytical method is scientifically sound--fit for purpose and could be easily adapted. In another situation, we faced a methodology that lacked adequate robustness and precision and was overly complicated, putting successful analytical transfer at risk. An assessment of the method led my team to develop entirely new chromatographic conditions with greatly improved separation, precision and simplicity to ensure understanding by the quality control (QC) team for ease of transfer.

Importance of the Right Instrumentation

For gifted scientists with a problem-solving mindset to overcome the challenges associate with sterile fill/finish projects, they must be equipped with leading-edge instrumentation in the analytical R&D lab. The specific instruments required for the testing of injectable formulations include:

- **Break-loose and glide force:** The Instron Syringe Test Fixture accommodates a variety of syringe sizes to determine the breakaway force and glide force. Break-away force represents the force required to start the syringe's fluid ejection, and glide force is the average force required to maintain an even flow of fluid out of the syringe. This equipment is essential for an AR&D lab serving drug developers advance injectable therapies to patients.
- **Dissolution testing:** Described in the United States Pharmacopeia (USP) as Sotax Apparatus 4, dissolution and drug release testing using a flow-through cell is proven to characterize the active drug release in terms of bioequivalence and *in vitro*/*in vivo* correlation (IVIVC) in clinical studies and daily QC routines alike. AR&D teams with this capability can effectively support extended-release injectables.
- **Particle size analysis:** Accurate, robust, and reliable data is a must for informed decision-making related to certain types of formulations such as injectable suspensions, oral suspensions, and soft gelatin capsules. A laser diffraction particle size analyzer, like the Malvern Analytical Mastersizer 3000 is versatile, compact, and ideal for the demanding workflows of CDMOs.

• **Nanoparticle, colloid, and biomolecular particle sizing, and particle charge measurements:** Accurately and easily characterizing particles in solutions is another essential capability for AR&D labs. Analyzing particle mobility and charge (Zeta potential) using Electrophoretic Light Scattering (ELS) and the

molecular weight of particles in solution using Static Light Scattering (SLS) help define drug product performance and manufacturability and generates vital information that will be used by the QC lab. An instrument I find ideal for the accuracy required for complex parenterals is the Malvern Analytical Zetasizer

Culture of Agility

I am fortunate to have worked in a CDMO analytical R&D group that takes pride in its ability to accommodate pharma's aggressive timelines for sterile fill/finish projects. I've learned that the best AD&R teams have the right balance of experience and expertise with senior scientists naturally taking responsibility for the development of junior scientists. Organizational and functional transparency and selfless cooperation with other departments like formulation development, QC, and manufacturing science and technology is another feature of great AR&D teams. When done well, the work of AR&D enables success across the drug development continuum and can be the difference in successfully bringing life-saving therapies to patients.

ABOUT Pii

Pharmaceutics International, Inc. (Pii) is a US-based contract development and manufacturing organization (CDMO) located in Hunt Valley, Maryland. The experienced scientists, engineers, and staff at Pii pride themselves on adroitly employing a phase appropriate method of drug development for the prudent use of their client's resources as they solve challenging problems. In addition to offering end-to-end development services, Pii manufactures a variety of dosage forms to include complex parenteral drugs and has a wealth of analytical testing capabilities. Its Hunt Valley campus has four aseptic suites with lyophilization capabilities. Our talented professionals stand ready to help!

ABOUT THE AUTHOR

Irina Prudnikova
Associate Director, Analytical Research & Development (R&D)

Irina leads the Analytical R&D team at Pii, responsible for developing chemical test methods, providing support for formulation development, and validating all methods before transferring them to Quality Control. The work of the Analytical R&D team is critical to enabling technology transfer for drug developer clients and streamlining the scaling of drug production. She has experience in supporting the development of a variety of medicines for orphan diseases, oncology, and nervous system disorders. Irina is often the catalyst that helps to transform a development candidate, be it a small or large molecule, into a viable drug formulation that improves, and even saves, the lives of patients.

Irina earned a Master of Science in Chemistry with a focus in Analytical Chemistry from Lomonosov Moscow State University.