Demystifying Highly Potent API and Cytotoxic Drug Products

By Sharada Kolindrekar, Director of Continuous Improvement, Technology, and Validation (CITV) and Devan Patel, Senior Director, Project Management and Pharmaceutics International, Inc (Pii)

Thirteenth century philosopher Ibn Yami is credited with the origins of a design framework referred to as “Knowns and Unknowns.” He initially captured the idea in a verse, “one who knows and knows that he knows…his horse of wisdom will reach the skies.”

This framework re-emerged in the 1950s as the Johari Window, a tool used to help people better understand their relationship with themselves and others. Several decades later NASA used the same framework to develop the re-entry plan for the Space Shuttle that factored in all the known and unknown risks.

At Pii, although we aren’t involved in interplanetary navigation, we do apply the concept of the “Knowns and Unknowns” framework in drug development and process design, especially for highly potent active pharmaceutical ingredients (HPAPI) and cytoxic drug products.

Proliferation of HPAPI and Limited Industry Capacity

Cancer remains the second leading cause of death in the United States, a close second behind heart disease. This will likely sustain the already well-funded oncology segment of the pharmaceutical industry for the foreseeable future. Oncology drugs have traditionally included a significant number of highly potent compounds contributing heavily to an industry-wide average of nearly one quarter of New Chemical Entities (NCEs) being considered potent in accordance with the Biopharmaceutical Classification System (BCS).

Despite a considerable need for oncology drugs, many with a HPAPI and cytotoxic compounds, the manufacturing capacity remains surprisingly limited. The cost of developing HPAPI capabilities is high. Both the science and engineering are complex, and the human resources

needed cannot be developed quickly. Additionally, the technology required to safely manufacture highly potent and cytotoxic drug products is complex and expensive.

Spurred by an industry-wide shortage of highly potent and cytotoxic manufacturing capacity, we were motivated to pursue some solutions. We discovered that we could create additional capacity by shortening the lead time required from the initial inbound inquiry of a program to project start-time by applying the “Knowns and Unknowns” framework.

Turning the Unknowns into Knowns

The key to turning unknowns into knowns is data, and capturing the right information early demystifies the development process, especially for drugs with HPAPI components. In addition to using compound classifications to drive formulation and process development, using data to quantify risk early can be much more effective.

Pii’s clients are often positively surprised by the amount of work performed before ever signing a contractual agreement. Prior to project initiation, Pii is interested in understanding as much as possible about the drug safety and handling requirements for HPAPI and cytotoxic compounds. Pii ensures the drug sponsor is fully informed before making critical decisions to move their program forward.

Gathering, organizing, and understanding critical risk data related to HPAPIs and cytotoxic drugs, ensures appropriate controls are defined from concept to clinical batch manufacturing to commercial-scale manufacturing. At Pii, we begin the conceptual planning with a compliant, end-to-end assessment.

End-to-End Quality Assessment to Support Decision Making

A quality assessment to identify risk in drug development concept planning is not unusual. However, if the project is at the pre-Investigational New Drug (IND) stage, the unknowns far outnumber the knowns. Making critical decisions based on assumptions and unquantified risks does not reflect the level of precision that the pharmaceutical industry, and its patients deserve.

Initial quality assessments typically include the following: initial API safety assessment, API handling considerations, and toxicology reports. Projects involving drugs with HPAPI and cytotoxic drugs will also review data related to ADE, OEL, PDE and ARL.[1] All this information then shapes the Quality Risk Management Process (QRMP). However, at the pre-IND stage, some of this information may not be available to support the risk management strategy.

The pharmaceutical industry defines a potent compound as one with an OEL at or below 10 $\mu g/m^3$ of air as an 8 h time-weighted average. When combining this single data point with information gained from an investigator's report, Affygility® and Safebridge® reports, and safety data sheets (SDS), a clear path for safe handling during development and process design emerges.

As a result, Pii can communicate critical decision-making information to clients. For example, Pii can identify specific facility resources that will be used for the project, special containment procedures, resource requirements, including personal protective equipment (PPE) requirements, and additional safety considerations. Most importantly, we can even deliver cost estimates and project timelines, all within a week of beginning the technical assessment. After routinely using this process with discipline, Pii developed new standard operating procedures, and grew its high potent and cytotoxic drug product manufacturing capacity.

The concept of development, process design, and manufacturing of drugs with a HPAPI or cytotoxic compounds should not be a mystery to drug sponsors using a contract development and manufacturing organization (CDMO). Transparency ought to begin with the quality assessment and drug sponsors are entitled to fully understand the concept before they make the critical decisions to move forward.

1. ADE-Acceptable Daily Exposure, OEL-Occupational Exposure Limit, PDE-Permitted Daily Exposure, ARL-Acceptable Residue Limits

About Sharada Kolindrekar and Devan Patel

Sharada Kolindrekar is the Director of Continuous Improvement, Technology, and Validation (CITV) at Pharmaceutics International, Inc (Pii).

Sharada joined Pii in 2011 as a member of the analytical research team and has held positions of increasing responsibility including: Validation Coordinator, Supervisor of Aseptic Validation, and Associate Director of Validation and Tech Services. She assumed her current role in 2019.

In her role as Director, Sharada leads a multi-disciplinary team responsible for commissioning, validation, and technology transfer for Pii's manufacturing processes including, complex, highly potent parenterals under aseptic conditions, tablets, capsules and softgels. Additionally, she is instrumental in steering activities contributing to Pii's foundation of quality that includes product

risk assessment, cross-contamination risk assessment, qualification, cleaning, and process risk assessments.

Before joining Pii, Sharada served as an Automation Specialist for Electronic cGMP Methods and Records for VelQuest Corporation, a provider of automated Procedure Execution Management Systems (PEMS) and before that as a Project Engineer at the National Chemical Laboratory, a research, development, and consulting organization in Pune, India. Sharada received a Bachelors in Chemical Engineering from Visveswaraiah Technological University, Belgaum, India and a Masters in Engineering Management with a concentration in Chemical and Biochemical Engineering from the University of Maryland, Baltimore County.

Devan Patel is the Senior Director of Project Management at Pharmaceutics International, Inc (Pii).

Devan joined Pii in 2012 as a member of the Project Management team and he now leads that team.

Devan has held roles of increasing responsibility in Project Management leading key development and commercial programs for Pii for both the orals and injectables. With his leadership, Pii has built a world-class Project Management Organization (PMO) consistently characterized by superb customer experience. Over the years, Devan has used his knowledge and technical skills to play a vital role for the Operations team, managing key initiatives for the Parenteral/Sterile business unit, including managing the overall scheduling and planning of all Aseptic Operations. His collaborative style when working with cross-functional teams across Pii's business units and ability to anticipate problems before they occur has raised the role of project management to an artform. Devan delivers a positive, outcomes-focused experience for our client-partners, from initial contact through successful completion of each project.

Devan earned his Bachelors in Cell Biology and Molecular Genetics from the University of Maryland and a M.B.A. from Johns Hopkins University.

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 working collaboratively to complete scientific assessments quickly and effectively, resulting in providing critical decision-making information to their clients. Pii offers end-to-end development and manufacturing services including comprehensive analytical testing, formulation development, and manufacturing capabilities across a variety of dosage forms. Its Hunt Valley campus has four aseptic suites with lyophilization capabilities.