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A Proven Approach to Impurity Control Across API and RSM Synthesis

An Interview with Robert Hughes,
Research and Development (R&D) Fellow, W. R. Grace & Co.

Controlling impurities during manufacturing is critical to ensuring high-quality, safe therapeutics for patients. To help manage impurities and mitigate risk across all stages of your process, consider the benefits of working with a contract development and manufacturing organization (CDMO) that has robust chemistry understanding and extensive manufacturing experience. At Grace, our Fine Chemical Manufacturing Services (FCMS) experts across all stages of development collaborate to establish a thorough impurity profile control strategy that assures a high-quality product.

In the following Q&A with Robert Hughes, Research and Development (R&D) Fellow at Grace, Hughes explores the importance of a consistent project team, strategies for identifying and controlling impurities, and steps for securing a reliable supply chain.

At the beginning of a project, how does Grace approach onboarding and collaborating with a new client to understand their product? Which Grace team members will a client rely on over the course of their project?

Robert Hughes: At the start, a program manager is assigned who oversees a project's full scope and scheduling and ensures continuous communication between sponsor and CDMO teams. From there, the project team is assembled, which includes process R&D, analytical services, and engineering. If the program is in clinical trials, a member from the quality assurance group will also be assigned to the team.

Once that team is in place, we review the program deliverables internally. When we first engage with the sponsor, a key topic that is discussed is impurity identification and control, and we need to leverage their expertise as much as possible, including learning more about what impurities have been identified. This gets us off to a strong start.

Throughout a program, we do everything we can to keep the project team together to mitigate knowledge loss. While we may add more team members as we approach the commercial launch, we'll always try to maintain the same R&D lead on the project, which helps ensure overall process knowledge is maintained.

Could you speak to the integration of R&D, analytical, engineering, quality, and regulatory groups to achieve process optimization and control to improve active pharmaceutical ingredient (API) quality?

RH: Process R&D, analytical, engineering, and quality departments are represented on our project teams. We typically have weekly meetings with the sponsor, and each of these departments provides an update. This routine communication ensures that the sponsor is up to speed on the status of the program from all Grace departments that are involved.

Aside from that, there is a lot of daily interaction at the site. In the early stages of a program, information sharing between R&D and analytical services starts immediately. These two groups work closely to identify impurities. The relationship goes beyond R&D sending a sample to analytical services for data collection; the analytical services group has enough experience and chemistry knowledge to make suggestions on the structure of an impurity based on the data collected. Close collaboration between these two groups typically results in a timely identification of the structure of an impurity.

Our R&D team takes a lot of pride in understanding reaction mechanisms and our ability to propose structures of impurities, which we pass on to the analytical services chemist. In one recent example, there was a three-step sequence where the impurity structures were proposed at each step and the high-performance liquid chromatography-mass spectrometry (HPLC-MS) data aligned perfectly. The impurities were then synthesized, which further confirmed the structures.

Once we identify an impurity, the next step is to determine how it can be controlled. Ideally, control is through process improvements, but there are cases where it requires assistance from the engineering and quality groups. For example, if an impurity is the result of overheating the reaction mixture and this generates the impurity at a higher level, it can be difficult to purge it to an acceptable level. The upper end of a prescribed temperature range becomes a critical process parameter (CPP). This is where

engineering and quality become important. We must build instructions into the batch record around that CPP so that when it's being run in a plant, the operators running the process understand the consequences of overheating a batch. Operators go through training before starting a new batch to ensure they understand those CPPs.

From a regulatory perspective, the regulatory team typically becomes involved when we reach commercialization. However, we have at times brought regulatory into the development phase. For example, some small organizations may not have their own in-house regulatory expertise. We can bring our dedicated regulatory folks into discussions to offer guidance on acceptable limits in the API. When we get to the pre-validation stage, there's a lot of documentation that's generated and regulatory is involved quite extensively at that point.

How does Grace work to secure regulatory compliance for APIs from the very beginning?

RH: We have a very experienced process R&D group, many of whom have over 20 years of experience in API process development, including previous work with large pharma companies. With this experience comes a mindset where quality and regulatory considerations are built into our programs from the start.

When R&D begins working on a project, the impurity profile is one of the first things we consider. At every step, we look at impurity formation because we know that individual impurities can affect the purity of the final product and potentially contribute to lower API purity levels. The objective is to identify all impurities and understand their concentration in the final API, keeping in mind worldwide regulatory agency expectations for specifications on impurity content. Engaging in this level of process understanding in the early phase helps to ensure success as a program advances to commercial approval.

When we approach commercialization, we execute a Quality by Design (QbD) program to support process validation. A significant component of the QbD program is a formal spike, purge, and fate study, which is a key piece of the regulatory package. Prior to the spike, purge, and fate studies, impurities are identified and synthesized to run reactions spiked with elevated impurity levels to see how well they purge throughout the synthesis of the API. This data is reviewed in detail with the sponsor to ensure that regulatory compliance is a team effort.

What are the key technologies and strategies leveraged for impurity control for APIs?

RH: The primary analytical tool we use to evaluate impurities in APIs and regulatory starting materials (RSMs) is HPLC. If the molecule is not suitable for HPLC — for example, if it is volatile and lacking a suitable chromophore — we might leverage gas chromatography (GC). We also use nuclear magnetic resonance (NMR) spectroscopy routinely to collect data for APIs, intermediates, and RSMs. The acquisition of NMR data on RSMs from different suppliers gives us the opportunity to do a quick comparison by overlaying chromatograms, which shows subtle, but in many cases, important differences.

It can be tricky figuring out how and where impurities form. The first question that comes to mind is, what is the source of that impurity? Is it coming from an RSM? Is it forming from an undesired side reaction? Is it forming as a result of decomposition of the starting material, or even the product of the reaction? The Grace process R&D chemists have extensive experience in the pharmaceutical industry and, over the years, have built a broad toolkit of strategic experimental designs that allow us to pin down the sources of impurities.

The next step is identifying the impurity. If we have an enriched level of an impurity in a reaction mixture (or isolated product from that step), we get that sample into the hands of the analytical services chemist and then they utilize HPLC-MS and/or GC-MS. These technologies are essential as they give us the molecular weight of the impurity, and in many cases, a molecular formula, which helps solve the impurity puzzle.

From an RSM perspective, what are some of the obstacles to ensuring that RSMs are well-characterized and meet regulatory standards for impurities? Could you also speak to the regulatory expectations regarding RSMs?

RH: RSMs can be a source of impurities. If an impurity is structurally similar to the RSM, it can react in the downstream steps and be present at a problematic level in the final API molecule. This is why it's critical to have a complete understanding of the impurity profile of RSMs. When we're purchasing RSMs from external vendors, getting the necessary information can be an obstacle; this information includes the route of synthesis and the reaction conditions. For RSMs, we go through the same exercises as we do in the API synthesis to identify those impurities.

In terms of regulatory expectations around RSMs, methods must be validated consistent with ICHQ2. This means that a method will do what we expect it to do and provide the information we need. The methods we use for testing and approval for all RSMs are validated.

When it comes to impurity control and regulatory compliance, why is it important to have integration and transparency between Grace's different manufacturing sites?

RH: It's not unusual for the early stages of R&D and analytical development to start at our cGMP site in South Haven, Michigan. We're typically engaged with RSMs right away to understand their impurity profiles. We know how they're made and the work to identify impurities is ongoing. If we are going to self-source, we transfer that knowledge to our non-GMP site in Tyrone, Pennsylvania. A tech transfer package is generated that ensures there is strong communication between the two sites. Our Tyrone site has a lot of experience with RSM manufacturing, including a robust knowledge of their requirements.

Why is it crucial to have a reliable network of external suppliers? Why is supply chain transparency beneficial?

RH: Establishing a reliable RSM supplier network is critical to the success of our business. Our site in South Haven has been conducting API manufacturing for almost 50 years, and our approach to establishing an RSM network has evolved considerably over that time. Having open communication with our vendors has been beneficial. We might have an impurity of interest that we can only recognize by an HPLC peak; we can go back to the supplier and ask, do you know what this impurity is? In some cases, they do know what the structure is, or they put in the effort to identify it, which saves us a lot of time.

We also have examples where an RSM had potential positional isomeric impurities and with the route of synthesis knowledge that was forwarded from the supplier, we then synthesized the different impurities to make sure that our analytical method was able to detect them. This is another benefit of our supplier relationships.

Could you speak to Grace's ability to self-supply raw materials?

RH: This is always an option for every program in South Haven. When we're talking with prospective sponsors, we make it clear that we can self-supply RSMs. We often rely on our external network for RSMs in the early developmental stages of a program. However, self-supply comes into play when we have a program approaching commercial stage. If it's a high-volume, high-value product, we've had customers that were interested in securing the supply chain by bringing everything in-house.

In another example, we brought in a new clinical phase project that included eight synthetic steps from the beginning to the final product. Regulatory agencies and the sponsor must agree on which intermediate is an acceptable RSM; it can't be too structurally similar to the final molecule and there needs to be an appropriate number of steps run in the cGMP environment. We worked with the sponsor to identify steps that could be run in the non-GMP

setting and designated one of the intermediates as a proposed RSM. They took that approach to the FDA and the RSM strategy was accepted. The first three steps were completed in Tyrone and the newly designated RSM was then transferred to South Haven where the final five steps were run.

What do you think sets Grace's teams apart?

RH: We take a lot of pride in manufacturing products that help improve the quality of people's lives. The technical groups have developed a strong reputation for problem solving and developing processes that result in first-time-right when first scaled to kilo lab or pilot plant assets. Our talented and experienced group of process chemists display a high level of curiosity — we're motivated by the challenge of identifying impurities and implementing a control strategy to ensure critical quality attributes are met in a consistent manner throughout the development lifecycle to post-commercial launch. With considerable experience in API manufacturing and a strong track record for regulatory compliance, our team offers customers the opportunity to ensure a reliable, high-quality supply for their patients.

About the Author

Dr. Robert Hughes is an R&D Fellow at Grace, where he leads the custom pharma technical development effort as part of our Fine Chemicals Manufacturing Services (FCMS) business. He has worked at the South Haven, MI, site since 2007. Over his 26-year career in the pharmaceutical industry, he has held various scientific positions at Roche Colorado, Pfizer and Boehringer Ingelheim. He holds a bachelor's degree in chemistry from Northern Michigan University and a doctorate in organic chemistry from Wayne State University, which was followed by a postdoctoral position at Colorado State University.

About Grace Fine Chemical Manufacturing Services

Grace's Fine Chemicals Manufacturing Services (FCMS) is a leading North American CDMO and a full-service provider of fine chemicals to the world's leading companies across the pharmaceutical, agrochemical, and specialty materials markets. Grace FCMS helps global customers complete successful projects through a powerful combination of proven chemistry expertise, game-changing process development, high-quality custom manufacturing and exceptional service. Our strategically located facilities in South Haven, MI, and Tyrone, PA, enable us to be a fully integrated domestic partner for the development and manufacture of regulatory starting materials (RSMs), intermediates, and custom active pharmaceutical ingredients (APIs). From innovative R&D to commercial-scale production, we deliver the knowledge, experience, resources and service needed to move products to market faster and accelerate business. For more information, visit **grace.com/finechemicals**

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