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Control API Impurities to Achieve Therapeutic Safety and Efficacy for Patients

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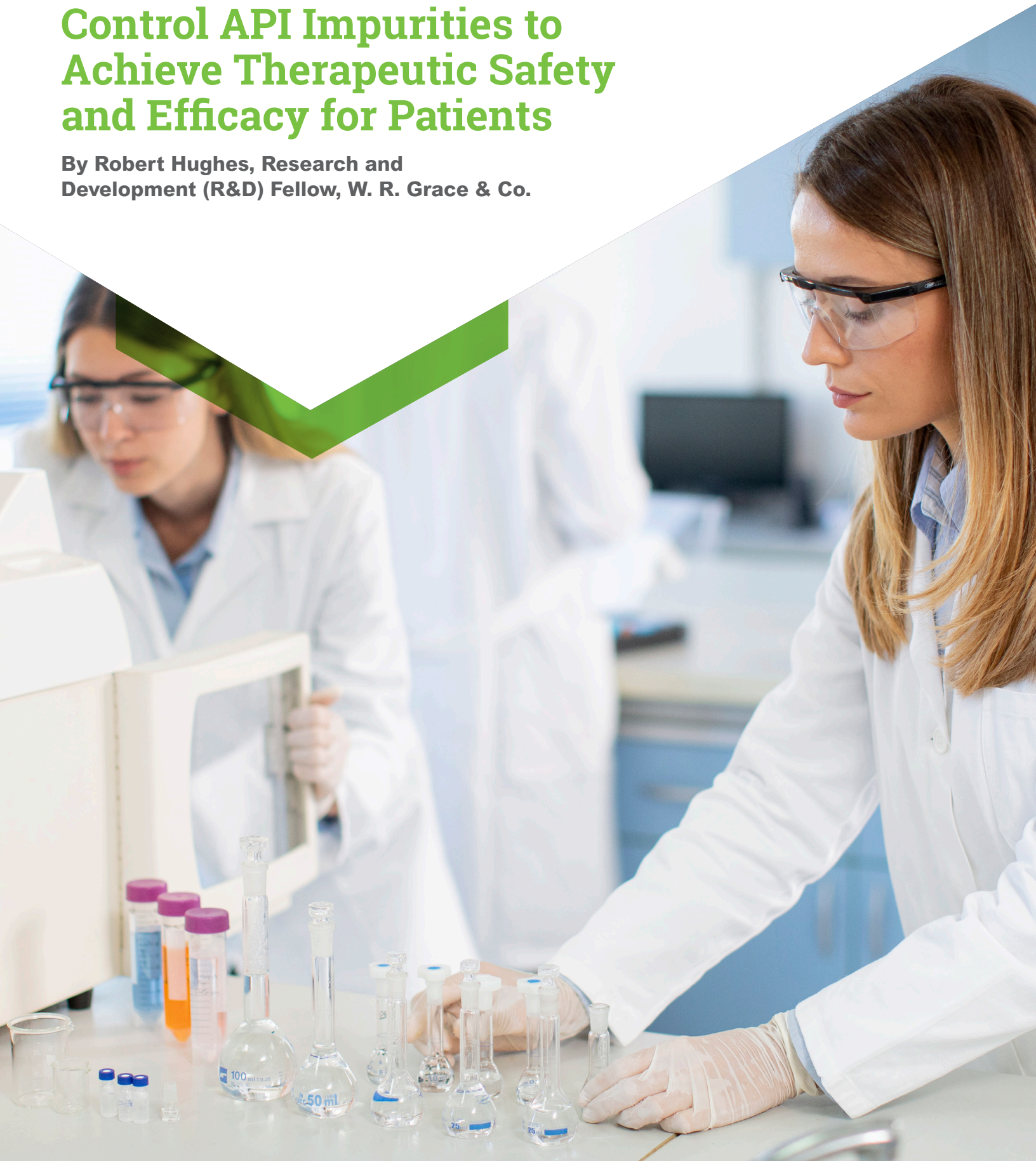

For drug sponsors, the task of delivering safe, high-quality, and efficacious therapeutics to patients is paramount, and it takes a village. To achieve this goal, sponsors and their manufacturing partners must continually prioritize impurity control across all stages of development and manufacturing. Impurities are categorized as the presence of any substance other than the active pharmaceutical ingredient (API).[1] They can arise from a number of sources, including regulatory starting materials (RSMs), production processes, and manufacturing equipment. Left unchecked, impurities can wreak havoc, potentially impacting the quality, safety, and efficacy of an API. These effects could lead to adverse reactions, toxicity, or long-term health risks in patients, and damage the stability and shelf life of an API.[2]

To guarantee safety and efficacy for your therapeutic, it is vital to leverage a thorough approach to impurity management for APIs and RSMs, which includes holistic oversight from a team of R&D, analytical, engineering, and quality experts. Experienced manufacturing partners are adept at navigating regulatory guidelines, leveraging cutting-edge analytical technology to detect and characterize impurities, and implementing quality by design (QbD) principles to minimize process impurities from the start. When considering contract development and manufacturing organization (CDMO) partners, assess whether a manufacturer has the skillset to control impurities throughout manufacture to ensure that a safe, high-quality therapeutic reaches patients.

Understand Your API's Impurities with Technology and Expertise

When you embark on an API manufacturing journey, impurity identification and understanding must be top of mind. A CDMO's team of experts will need to gain an understanding of any known impurities from your team to guide their strategy for impurity management. As their R&D team begins developing an approach to API manufacture, the impurity profile of your product must be established. An impurity profile accounts for the identity and quantity of any impurities within your product, and regulatory agencies and ICH guidelines dictate limits on allowable levels of impurities in APIs.[1]

Effectively controlling impurities requires determining their sources, identities, and levels within an API. To do so, an R&D team begins by running experiments to determine the origin of an impurity, and once a source is found, they use analytical technologies to identify the impurity. Critical analytical tools for impurity analysis include high-performance liquid chromatography mass spectrometry (HPLC-MS), gas chromatography mass spectrometry (GC-MS), and/or nuclear magnetic resonance spectroscopy (NMR). The application of NMR can provide an analytical team with key structural information, while the use of HPLC-MS provides the molecular weight and molecular formula. This information helps to determine the identity of an impurity.

Prior to commercial launch, a validation campaign should be executed to ensure the process can be run at scale to consistently produce API that meets all critical quality attributes (CQAs). A supporting activity for the validation campaign that is performed in the process R&D lab is an extensive QbD program that includes a spike, purge, and fate study. In such a study, identified impurities that have been synthesized are spiked into reactions at elevated levels to determine how well they purge throughout the processing and isolation of the intermediate or API, if in the final step of the synthesis. This allows the CDMO team to determine a process's effectiveness at removing impurities, assess how much of each individual impurity can be tolerated at intermediate steps, and aids in developing intermediate specifications. Data from spike, purge, and fate studies is used to demonstrate impurity control strategies to global regulatory agencies.

Consider The Potential Impact of RSMs on Purity

An RSM is defined in ICH Q7 as: "a raw material, intermediate, or an API that is used in the production of an API and is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API starting materials are normally of defined chemical properties and structure."[3] Because RSMs are a potential source of impurities, it is critical to have a strong understanding of their impurity profile. However, in many cases, RSMs are procured from third-party vendors, and understanding their impurity profile requires CDMOs to gather information about their route of synthesis and reaction conditions from the vendor.

Thus, it is important for your manufacturing partner to have transparent, communicative relationships across their supply chain.

To minimize impurity formation, a manufacturer should also vet third-party vendors to assess whether they are upholding the highest standards of quality and impurity control during RSM production to guarantee regulatory compliance and safety for patients. When impurities are detected in an RSM, an analytical team will leverage the same strategies and technologies used to assess API impurities.

An RSM vendor must also be able to provide a reliable supply of high-quality, impurity-controlled RSMs at scale to mitigate timeline delays. Some RSM suppliers may not be geographically accessible, which could lead to transportation impediments; others may lack the technical capabilities and sophistication to achieve proper impurity management. Because of these factors, you might consider whether a CDMO offers the option to self-supply RSMs. The capacity to self-supply creates an added layer of security within the supply chain while helping to ensure that RSMs are manufactured to regulatory agency expectations. A self-supply option is an added benefit from manufacturing partners.

Prioritize Experience in CDMO Selection

As you assess whether a CDMO has the capacity to develop and manufacture your API at the necessary scale, keep impurity control strategies top of mind. The success of your project will fall into the hands of your CDMO's expert teams; because of this, it is vital to consider their ability to solve complex impurity puzzles. With previous experience in API process development and manufacturing comes the ability to anticipate regulatory expectations, identify impurities more rapidly, and solve problems with agility. A seasoned CDMO team will understand how to build quality and regulatory considerations into a program from the start, using process optimization, design of experiments (DOE), machine learning (ML), and robust manufacturing processes to bolster impurity control.

To mitigate risk, achieve high product quality, and maintain regulatory compliance, a CDMO should prioritize well-honed QbD workflows. For manufacturing processes, QbD generally encompasses four major steps:

1. Identification of API CQAs, which includes impurity levels in the final API
2. Completion of an ICH Q9 quality risk assessment
3. Completion of a QbD program, which includes implementing a control strategy for impurities
4. Final design of the defined manufacturing process

If you are curious how a CDMO implements QbD in their workflows, ask them to provide greater insight into their approaches.

A partner must also demonstrate cohesion across different functions, including R&D, analytical, engineering, quality, and regulatory teams. Throughout your relationship with a CDMO, your team should engage regularly with representatives from each of these departments, all of whom should be collaborating to create a well-rounded strategy that accounts for all critical stages of your process. Ideally, your CDMO team will guide you through each phase of this process, checking in via frequent touchpoints.

Consider how strong team communication can impact your therapeutic's development. At the outset of a project, the process R&D and analytical services teams work closely to identify impurity structures and implement control strategies. If a critical process parameter (CPP) is identified during this work, engineering and quality assurance ensure this is captured in the batch record so that plant operators are fully aware of any CPPs that may be present in the process.

Though a regulatory team doesn't typically weigh in until a program approaches commercialization, a CDMO can enlist regulatory experts to provide guidance to sponsors that may not have regulatory resources on staff. Said experts will provide guidance on impurity control requirements to meet regulatory standards. If you are curious how a CDMO partner handles communication and collaboration, pay attention to how they handle the earliest stages of engagement with your team.

Build Your Strategy with an Expert Team

Impurity control is critical to the success and efficacy of your therapeutic. An experienced CDMO will have control measures in place to ensure that an out-of-spec product is never released, protecting patients from potentially harmful impurities. In your CDMO search, prioritize finding a partner who recognizes impurity control as a critical component of patient-focused drug development. With the right CDMO on your team, robust impurity control measures will be built into your workflows from day one.

References

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About the Author

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About Grace Fine Chemical Manufacturing Services

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