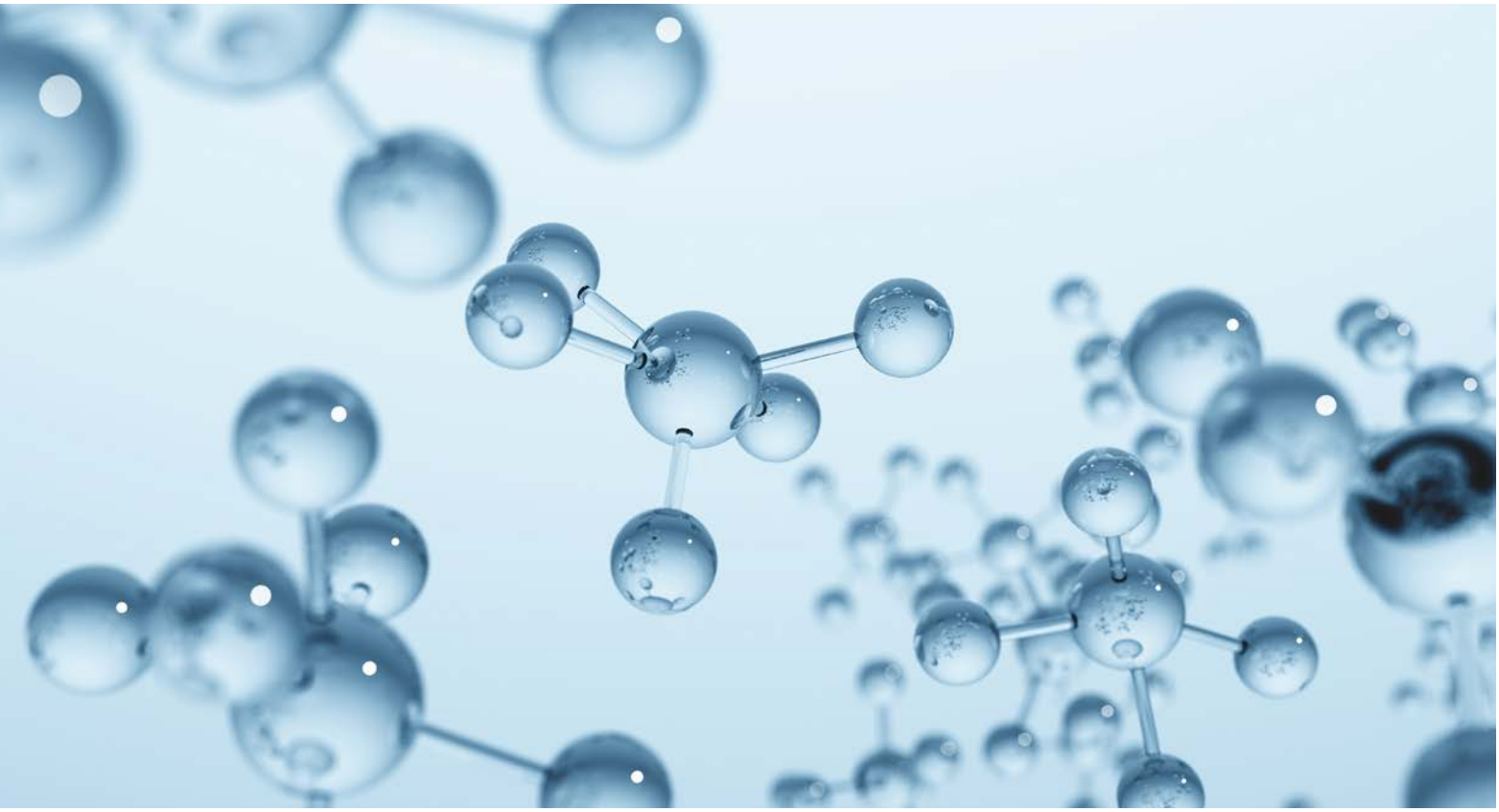

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WHITEPAPER

Anticipating the formulation challenges of complex molecules

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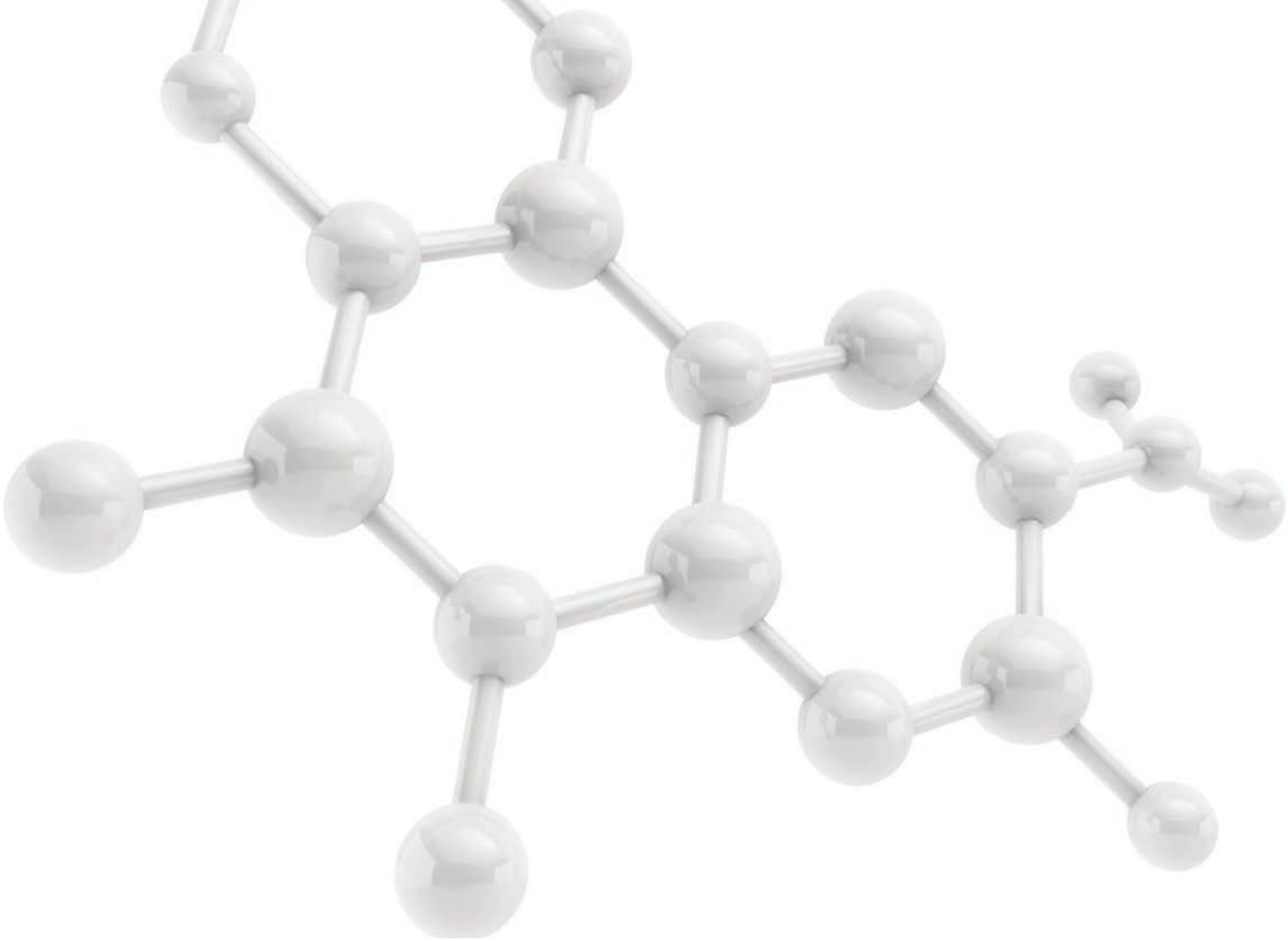


Abstract

If formulation problems surface late in the process of turning active pharmaceutical ingredients (APIs) into beneficial drug products, developers may have to go back and change their API production processes. In the worst cases, Phase I and Phase II trials may have to be redone. And due to the increasing complexity of today's API molecules, formulation problems are arising with greater frequency, delaying development, and burdening developers with unanticipated and heavy costs.

For example, one drug product scaling up to a Phase III trial began exhibiting severe processing challenges. This drug contained a small-molecule API with a low melting point, and difficult physico-chemical characteristics such as low density, static, poor flowability, and compressibility. For the volumes required for Phase I and Phase II trials, these characteristics could be managed. But with the greater volumes of material required for Phase III trials, and with the material adhering to the surfaces of the processing equipment, flowability became an insuperable barrier.

To make the API amenable to formulation, Thermo Fisher Scientific had to go back to the manufacturer to have it modify elements of its process (such as crystallization to change the API's morphology, to improve particle size distribution, density, and flowability), adding six long months to the development time of our client's drug. Fortunately, with better preparation, many of these problems—which inevitably will become increasingly common as drugs become more sophisticated and complex—can be anticipated, and thereby avoided.

The costs of complexity

The drive to design APIs that are more efficient and selective in their biological targeting has led to the creation of more complex molecules. For example, among small-molecule antihypertensive drugs, Valsartan, launched in 1991, has one chiral center and a molecular weight (MW) of 436. Aliskiren, launched in 2007, has four chiral centers, and an MW of 552.

This greater complexity makes the physical properties of these molecules more challenging to manage, affecting their stability—and therefore their sensitivity to temperature and pressure—flow characteristics, polymorphism (scaling up production may produce different polymorphs), solubility and bioavailability, and particle size distribution.

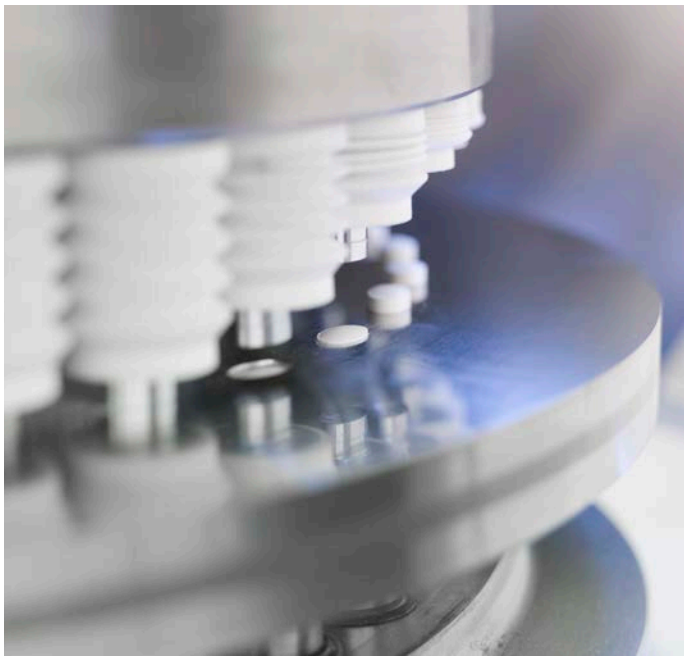
Formulation problems are arising with greater frequency, delaying development, and burdening developers with unanticipated and heavy costs.

In the past, if Thermo Fisher encountered difficulties when scaling up the formulation, we could address problems as they arose. In most cases, solubility, and therefore the bioavailability of products such as penicillins, was generally good, allowing many problems to be resolved easily. When problems arise in small-scale production for early phase trials, workarounds are available. For example, if a blend flows poorly, we can transfer small quantities of blend into the hopper of a tablet press, or encapsulator, by hand. But when production is scaled up for Phase III trials, some API characteristics that are not important at smaller volumes, or do not manifest themselves at all, suddenly become significant. For instance, some variability in particle size distribution might not matter for Phase I or Phase II and might not even be noticed unless one looks closely.

But when processing the larger batch sizes required for Phase III trials, particle size distribution may become problematic. And some segregation mechanisms that don't show up on pilot scale equipment are exacerbated by scale and equipment design, manifesting when the batch size increases.

For example, one product that presented no problems in Phase I and Phase II trials did not work at all for Phase III as the particle size distribution varied between batches. In this case, Thermo Fisher had to look at and characterize all the batches produced, and go back to the API, first to define the physical characteristics that would allow it to be manufactured at scale, and then to refine the API process. All this rework added several months to the trial timeline.

Problems like this can be solved, but revisiting the API process to solve them clearly is inefficient, especially if Phase I and Phase II trials already have been conducted. Along with the time and cost related to modifying the API process, if the changes to the API cause other changes—say, to solubility—they may have a clinical impact that will require repeating the trials. No one wants that.



Why it makes sense to look at your API earlier and more deeply

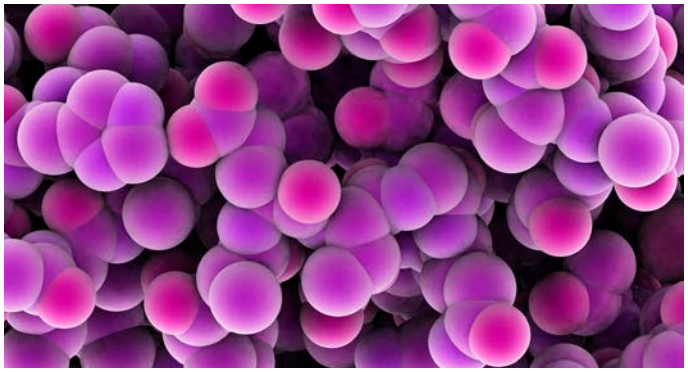
Synthesis teams need to consider not only the chemical but the physical properties of the API, perhaps more deeply than many have been accustomed to previously, to create an API that will work with a specific formulation and dosage form.

This requires the API development and drug product development teams to work together during Phase I and Phase II trials to:

- Characterize the physical properties that are critical to formulation and the intended drug product process in early API batches
- Determine the characteristics of the target API for large-scale production
- Adapt the API production process to achieve these characteristics
- Establish the characteristics of the target API as the formal specification for future production

To do this, it is important to conduct a systematic risk and critical attribute assessment. Inline optical analytics, such as Focused Beam Reflectance Measurement (FBRM), where a laser beam is sent into the mix, can measure the dimensions of the particles. This can provide insights into the effects of crystallization conditions on particle size distribution, and conditions that favor or suppress the formation of a given polymorph. For instance, a typical laboratory process to purify an intermediate substance can involve a solvent switch, the removal of a byproduct by flash chromatography, and product crystallization, but several things can go wrong when the process is scaled up for commercial manufacture.

In one case, the saturation concentration of a product was exceeded during a solvent switch. The product precipitated, interrupting production. The selective removal of the byproduct proved to be kinetically controlled and, on plant scale, with longer residence time, the system behaved differently, requiring a redesign of the purification sequence.

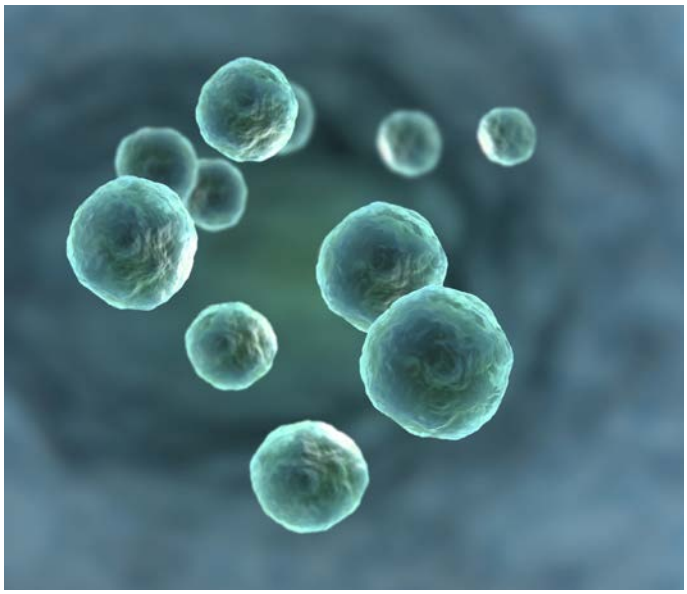


Problems such as this can be avoided prior to scale-up if product solubility in both solvents and their mixtures are examined in the presence of varying amounts of the by-product, as well as in light of the details of the by-product removal, including kinetics and residual content, and, the crystallization of the product and its determining factors. Ideally, these investigations would be assisted by online analytical tools that permit the crystallization process to be followed in real time.

As molecules become more complex, they tend to exhibit more sensitivity to variations in conditions, and because they have more functional groups, they can have a greater variety of side reactions.

It's also important to understand the technical process parameters in as much detail as possible. Heterogeneous reaction systems tend to become more complex as they scale up, affected by plant features—such as shear forces and stirrer tip speed—that may be relevant to the progress of a chemical reaction. Therefore, teams need to understand where a reaction system may be sensitive to plant-scale operations. As molecules become more complex, they tend to exhibit more sensitivity to variations in conditions, and because they have more functional groups, they can have a greater variety of side reactions.

Laboratory syntheses of complex molecules frequently involve reactions of multi-functional components. Such reaction systems are especially sensitive to changes in reaction conditions during scale-up. The multi-functional nature of the reagents means that changes in conditions inevitably lead to the formation of by-products. For instance, one synthesis Thermo Fisher worked on comprised the reaction of a diester with a bifunctional amine to produce the diamide. When the process was scaled for production, by-products formed at every stage of the process. It became necessary to modify the product isolation and drying processes, tighten them, and adapt them for the processing speed in the plant—all of which took time.



To avoid these problems, the chemist, formulators and process engineers should model the conditions that can be expected in the plant, asking themselves questions such as whether there will be hot spots; how much time the heating and cooling will take, and whether reaction conditions on the lab scale should be tightened to avoid the formation of by-products during operations. In this case, Thermo Fisher had to develop analytical methods to detect and quantify the by-products quickly. Again, running these analytics before scale-up greatly benefits development.

Another strategy we recommend is to understand the drug substance in greater depth. To determine stability, it is wise to run a forced degradation study, exposing the substance to oxygen, light, heat, humidity, and so on. If it is sensitive to humidity, for instance, that may have little impact on small scale production, but it may have a big one with hundreds of kilos of the drug substance sitting in a humid environment.

Today's more complex APIs need advanced formulation science.

Obviously, one can't do everything. It's smart to focus on those analytical methods that reveal critical attributes according to a hierarchy of what is always important, and what is only sometimes important—depending upon the molecule.

This hierarchy of attributes should include the substance's:

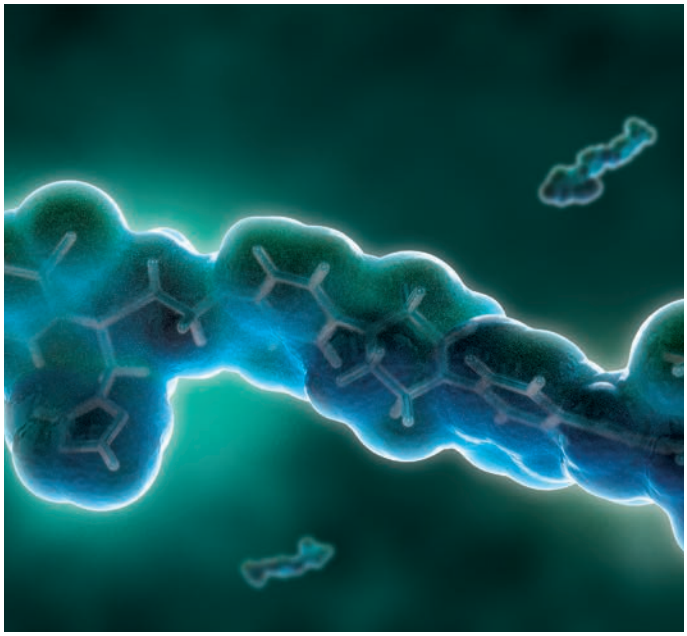
- **Basic characteristics:** chemical purity, by-product pattern (a fingerprint of the molecule that shows the known and unknown by-products, such as salts), and the effects of each
- **Physical characteristics:** particle size, particle size distribution, density and porosity (by untapped bulk, and by tapping until no further volume change is observed)
- **Physics-related characteristics:** solubility, rate of solution, morphology of the crystalline material, and polymorphs and their stabilities
- **Processing-related characteristics:** flowability, cohesiveness, compaction, segregation potential, and static behavior

Many of these attributes can be determined in the crystallization step. If developers don't get them right, they will face the necessity of fixes down the road.

Creating an API for future large-scale production

Determining the characteristics that will make a target API more amenable to large scale production—the right polymorph, the target crystal morphology, whether the drug substance needs to be micronized—requires a more comprehensive specification than is usually relied upon during synthesis process development.

Adapting the API production process to achieve the desired characteristics requires—again—the early collaboration of API and formulation development teams, employing project management familiar with both the API and formulation. This demands the involvement of experienced process chemists with formulation expertise, and analytical methods for API specification and formulation in a structured approach, analogous to the experimental design approach for optimizing chemical parameters, such as yield and purity. This can be done effectively between Phase I and Phase II (as Phase I often focuses on toxicity studies and proof of efficacy, and, therefore likely has neat API fills), and, further refined during the scale-up of the API and drug product processes in Phases II and III.



Unfortunately, there often is little incentive for developers to solve for future production problems in the early stages of development when the prospects of the API are still uncertain. Elaborate crystallization or polymorph studies generally are considered tedious and time-consuming, stealing resources from development. And crystallization still is seen widely as an art as much as a science. However, following the hierarchy of characteristics can be accomplished without inordinate investment if the developer characterizes only those that will be important: purity, and by-product pattern in all cases, and, others only as the situation demands.

Adapting the API production process to achieve the desired characteristics requires the early collaboration of API and formulation development teams, employing project management familiar with both the API and formulation.

A growing imperative

In the past, medicinal chemists have been asked only to advance new molecular entities to clinical development with acceptable physical properties for formulation. But today's more complex APIs need advanced formulation science. Characterizing physical properties is not business-as-usual for chemists. And because the disciplines of characterizing chemical and physical properties tend to be separated along the development timeline between API chemists and formulators, there is often an imperfect understanding of each other's problems and solutions.

This is why it behooves developers to bring these parties together early on to examine and mitigate risks. In early discussions, a formulator could remind a medicinal chemist that needle-shaped crystals do not flow well, and, ask him or her if anything can be done to modify the crystal's shape. This communication can help avoid process redesigns, and repetitions of entire—or parts of—clinical studies. Getting formulation right at an early stage can accelerate the development timeline while guarding against unnecessary costs.

In the future, molecules will not become simpler. Formulation challenges will not get easier. And the costs of reworking processes or trials will not go down. On the other hand, it does not cost anything to bring drug product scientists into the picture between Phase I and Phase II; it does not cost anything to facilitate conversations among chemists, formulators and process engineers about potential challenges. Doing both can save a lot of time, and money, downstream.

Anil Kane, PhD, MBA

Senior Director, Global Technical Scientific Affairs, Thermo Fisher Scientific

Dr. Kane has more than 25 years of experience in the science and business of taking molecules through the entire drug development process. His extensive knowledge spans early stage development to scale-up and commercial manufacturing, and includes technical transfers between global sites and drug life cycle management. Dr. Kane received his Bachelors, Masters and Ph.D. degrees from the Bombay College of Pharmacy, University of Bombay, India, and served as a post-doctoral fellow at the School of Pharmacy, University of Cincinnati, Ohio. He has also earned an executive MBA from Richard Ivey School of Business, University of Western Ontario, Canada. Dr. Kane is a member of various international pharmaceutical professional organizations, and is often asked to speak about scientific topics on formulation, technology other technical aspects, QbD, etc at major industry events. He has also published many articles in International journals and delivered many talks at meetings and conferences cross the globe. In his current role, Dr. Kane leads a team of "Subject Matter Experts" to support our clients in developing sound formulation and process development strategies and closely works with the scientific teams at Thermo Fisher Scientific's global sites for execution, provides leadership in the complete development of novel lead compounds and line extensions. He is also responsible for evaluating drug delivery technologies to support the business. Dr. Kane has been an invited speaker at many global conferences, workshops, seminars and training programs and has published several articles, interviews and white papers across the world including North American, European, Japanese and Korean publications.

Andreas Stolle

Vice President, API Project Management & Strategic Initiatives, Thermo Fisher Scientific

Dr. Stolle serves as General Manager for Linz site and leads a global team responsible for process development, project management and small-scale manufacturing for clinical supply of small molecule APIs. Dr. Stolle is responsible for the global API research and development strategy as well as innovation in API synthesis and manufacturing with the objective to expand Thermo Fisher's ability to continuously meet the unique technical challenges posed by new drugs and the needs of clients. Dr. Stolle joined Thermo Fisher in 2015 and has more than 20 years of experience in pharmaceutical research and development. Before joining Thermo Fisher, held various leadership roles for companies such as Bayer AG, Saltigo GmbH, and Lanxess Deutschland GmbH. Dr. Stolle received both his BS and his PhD in Organic Chemistry from the University of Hamburg in Germany.

Stephen Closs

Vice President, Technical Operations, Thermo Fisher Scientific

Mr. Closs joined Thermo Fisher Scientific in 2000 and has more than 28 years of experience in engineering and pharmaceutical research and development. He currently oversees the global strategic technical activities related to the technical transfer, commercialization and continued performance of multi-drug product portfolios for clients. He also leads a team of process and quality engineers to facilitate site coordination with client technical groups on development and commercialization efforts. In addition, Mr. Closs has led Thermo Fisher Scientific's Centers of Excellence teams for Design of Experiments (DOE), Process Analytical Technology (PAT) and Quality by Design (QbD). Mr. Closs earned his BA from the University of Toronto in Canada.

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