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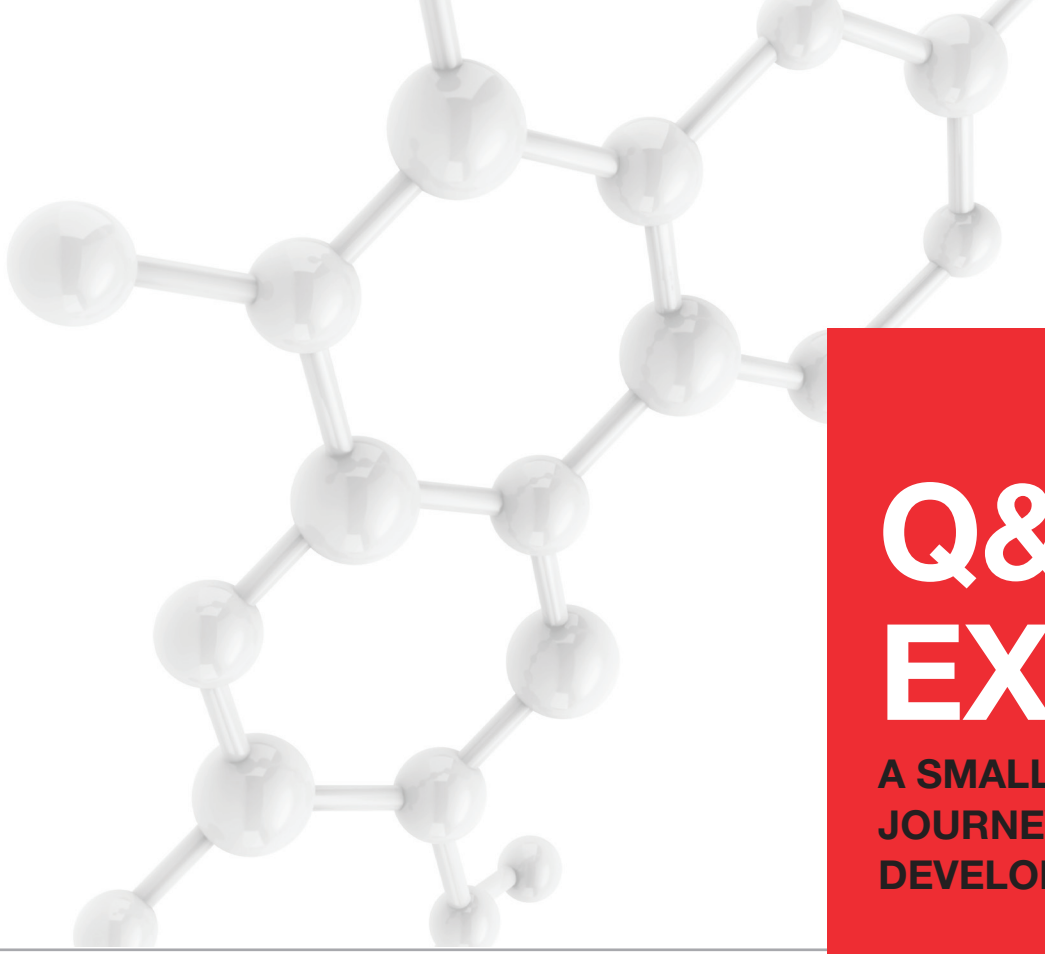

Q&A: API EXPERTS

A SMALL MOLECULE'S JOURNEY THROUGH API DEVELOPMENT

Developing a small molecule API is often a perilous process for new and emerging pharma companies. The primary goal, whether in early- or late-phase development, is to obtain sufficient material to support your clinical requirements. Yet the regulatory requirements for each phase are different, and they require different skill sets. Here, three of our leading API experts discuss these key challenges, what your company needs to succeed, and how partnering with a capable CDMO can make the biggest difference of all.

Featuring:

- **Stephen Boppart,** Director Business Management, API
- **Matt Frizzle,** Senior Business Manager, API
- **Iain McGroarty,** Senior Business Development Executive, API

Why is small molecule API development so challenging?

MCGROARTY: Think of API development like preparing for a journey: you know the final destination (delivery of regulatory-compliant API) and mostly know what you need to bring (the data required for the API) for a successful trip. Yet no matter how well you pack, you risk forgetting an essential item that you only realize upon arrival, which you now must buy at additional cost and time.

FRIZZLE: This is where a reputable, experienced CDMO partner can really help ensure that when you reach your final destination, be it first-in-human studies or process validation, you have all the data and material required for your planned study – with no delays or cost impact.

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The primary goal of API development is to obtain sufficient material to support your clinical requirements.

What is the first step in the small molecule's journey?

BOPPART: Let us take the example of a new chemical entity transitioning from discovery to development. The main focus is obtaining sufficient quantities of API at suitable quality to initiate pre-clinical toxicology studies. You want to start the journey quickly without investing too much in the process, knowing that solvents may be less than desirable, the batch may not be very pure, and the final phase may need chromatographic purification. Analytical methods are fit for purpose to provide confidence in identifying the API and determining assay, purity and residual solvents.

What are the key process steps after pre-clinical studies?

FRIZZLE: Once a new candidate has been successfully evaluated in pre-clinical studies, the focus switches to development of a formulation-ready API. You start to establish links between drug substance quality and final drug product, scrutinizing the process and asking what critical quality attributes (CQA) could impact that final product.

BOPPART: At this stage, you need to build a picture of the physical, chemical and microbiological properties that, if altered, could negatively impact quality. For example, drug substance solubility of the final drug product should be assessed. Particle size is paramount if the product is intended for inhalation. For analytical requirements, you must demonstrate that the methods for releasing the substance are sufficiently developed to correctly identify the drug substance and confirm chemical purity prior to formulation.

When is it too soon to start thinking about future process steps and scalability?

MCGROARTY: It is never too soon. As initial formulation work continues, use that time to consider the rest of your route. In fact, each production campaign provides an opportunity to assess your process, determine the impact on impurities and how well your analytical methods detect them, and then make improvements. Consider:

- What does the ideal commercial process look like?
- Is an efficient convergent synthesis possible or are you limited to a longer linear synthesis?
- Should you consolidate steps to speed production or isolate steps for scheduling flexibility?
- Should you look for safer reagents or consider flow chemistry?
- Which catalyst, solvents, temperature and pressure provide the best yield and purity?
- Is chromatography required or can an intermediate be crystallized to purge impurities?
- Can you safely and efficiently scale up the process?

Keep in mind, the more significant the process changes, or the later the changes are made, the more likely new toxicological or bridging studies may be required. Worst case, a clinical study may need to be repeated.

BOPPART: You should also consider your regulatory starting materials (RSM), which can significantly impact cost. If your sourcing strategy is not executed carefully, you could be in for an unwelcome surprise during filing. RSMs should be well characterized, readily available and ideally not too expensive. And make sure you are confident in the reliability and systems quality of your chosen raw material supplier.

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What role does data play in regulatory approvals?

FRIZZLE: The importance of data is the same no matter the development phase, but regulatory expectations of what the data can inform about your molecule change. For example, in the early stages of pre-clinical assessment, the analyst will focus on accurately determining the amount of molecule administered, as well as purity levels, to define the safety and tolerability margins.

Moving into clinical trials, robustness of the data gains importance. Phase-appropriate analytical validation begins at Phase I and continues to product launch. You must

As API development progresses, make sure you can safely and efficiently scale up your process.

build a repository of data that will form the basis of your regulatory submission and support the setting of appropriate specifications while providing a framework to determine molecule quality and acceptable use.

MCGROARTY: As we move through the phases of development, the requirements for data increase, as do the costs. This is why it is important to know what is needed, and when, so you can avoid unnecessary expense on a potential drug substance that may not reach the final destination.

What is the last stop along the small molecule's development journey?

MCGROARTY: The last milestone moves you from development to commercial supply, where your process becomes fixed. The chemical process and analytical methods need to be fully optimized and validated. And you must show control over potential impurities that could impact the final drug product quality. The principle of process validation (PV) is simple: you must have conducted sufficient process assessments that consistently demonstrate – through the execution of an established process parameter – a resulting drug substance of reproducible quality and quantity.

FRIZZLE: Yet the approach to PV depends on several factors, including process complexity, number of processing steps and the technologies employed. That leads us back to the importance of choosing a CDMO partner that can guide you to this final stage of your new drug substance journey.

How can a CDMO ensure a successful journey?

BOPPART: The journey of a new drug substance from early-phase development to commercial supply is complex and challenging. It is important to partner with a CDMO experienced in development of both drug substances *and* drug products. Understanding that correlation will help you avoid many common pitfalls in drug product development, such as poor solubility, poor material flow properties and differing solid state form.

FRIZZLE: In the case of Thermo Fisher Scientific, the strong alignment of our small molecule API and drug product network is critical to providing our clients with a true end-to-end service for lead candidates in pre-clinical, IND, PI-III through commercial supply. In other words, you can start here and stay here.

MCGROARTY: No journey is without its detours. That is why choosing a partner who is committed to guiding you through any obstacle is critical. Our experts have seen it all, and we know how to help ensure a robust, efficient and successful trip so you reach your final destination on time – and on budget.

Contact us today to see how the experts at Patheon pharma services can accelerate your API development journey.

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