Six API Challenges That Could be Slowing Your Development

AND HOW TO AVOID THEM

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"The minute you outsource API manufacturing, your whole supply chain depends on your partner."

- JAN RAMAKERS, DIRECTOR, JAN RAMAKERS FINE CHEMICAL CONSULTING GROUP

The challenges for new drugs looking to enter the market are numerous and varied. But many are self-inflicted – especially in small molecule development. A dangerous perception persists that aside from highly potent APIs, small molecule medications have simple process requirements. The reality, however, is that most APIs will require numerous steps or significant work upfront to avoid development delays, rework or outright failure.

One of the best ways to stay on-schedule is to start with a solid understanding of the most common API challenges. Awareness will help you choose a development partner with the ability to solve issues before they affect your timeline.

Issue #1: More complex molecules

Historically, small molecule medications have been relatively simple from a chemistry and manufacturing perspective, but that changed within the last 10 years, and not just for high potency drugs.[1] New therapeutic classes have arisen based on novel chemistries, such as antivirals and oncology medications, that bring a host of new challenges for development. Size, bioavailability and stability issues are all by-products of these more complex NCEs, which sometimes require the delivery method to be figured out in preclinical, rather than Phase I or II. For a Project Manager or CMC Director with a pharma background, the sheer number of synthesis steps can come as a great surprise – examples exist with up to 19 chemical transformations in a row.

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Issue #2: Supply chain issues

Not only are many of today's drug candidates more complex to develop, they have more complex supply chains. A greater number of ingredients – and more steps to create them – are required, calling for more suppliers. Sometimes spreading supply across multiple vendors reduces risk, but more often it increases it, as more links in the chain increase the likelihood of problems.

Another issue is the availability of raw materials, which account for nine percent of drug shortages for approved therapies.[2] Because drug shortages can have a profound effect on patients, the time to ensure an uninterruptible supply is at formulation – when abundant raw materials can be selected to guard against future problems. One good way for sponsors to manage raw material risk is to partner with a CDMO that can take on sourcing and guarantee the supply. Finally, while it's expected that new regulations would impact how drugs are manufactured, their effect doesn't stop there. Now the transportation and border crossing of materials

[1] A. Shanley, "Pharma APIs: It's Still a Small World," Pharmaceutical Technology 39 (5) 2015.
[2] Biopharminternational. Ensuring Robust Raw Materials Supply Chain, web.

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is also subject to regulatory control – a growing problem, given the globalization of drug development. At a minimum, costs may increase due to taxes from multiple countries. However, without expert project manager oversight, it is also easy for the timeline to be broken by paperwork, inspections or other regulatory hurdles.

Issue #3: "Next milestone blinders"

Many pharmaceutical companies or drug programs receive funding only as they reach pre-stated milestones. While it makes sense to investors, it can have significant repercussions for the drug program because companies are forced to make short-sighted decisions based on lack of funds and near-term goals. By Phase II, changing the specification of the API can be very costly, and can doom a project. A route change, for example, can change the impurity profile, and relying on formulation to solve for poor pharmacokinetics can add as much as two years to the development timeline.[3] Pharma project managers who don't think to look beyond toxicology may be blindsided by the time and cost implications of reformulation due to low bioavailability.

Issue #4: Scalability – or lack thereof

The more complex the molecule, the harder it is to scale. It's not uncommon to use non-cGMP materials during research, but this is obviously not an option as the time to go to market approaches. Another factor to consider is that early in development, when APIs are measured in grams or kilograms, the cost of materials is negligible. But at commercial scale, the cost of raw materials can kill marketability, so it is essential to think through this reality early in development, as well.

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Even if there aren't issues with scale, it may be that an API requires multiple vendors or steps that will create a bottleneck at larger quantities, or that no suitable manufacturing facilities exist nearby, introducing logistic and possibly regulatory hurdles.

Issue #5: Surprise Regulations

Regulations have the noble goal of protecting patients – but can also have negative effects on development timelines. This is especially true around toxicology issues with intermediates, as toxicology research focuses primarily on the API. Without careful planning, your synthesis process itself could become a source of delay when new methods using different solvents need to be explored.

Other regulatory issues can also crop up around thermal safety of the drug, transportation, and even registration of chemicals with bodies such as REACH in the EU. While pharmaceuticals are exempt from certain REACH filings, substances that are used in the production of the drug, but do not appear in the final form, are not.[4]

[3] Pharmtech. Starting Early is Key to De-Risking Drug Development, web.
[4] Tammler, U. "REACh – How does it affect the pharmaceutical industry? " 2008

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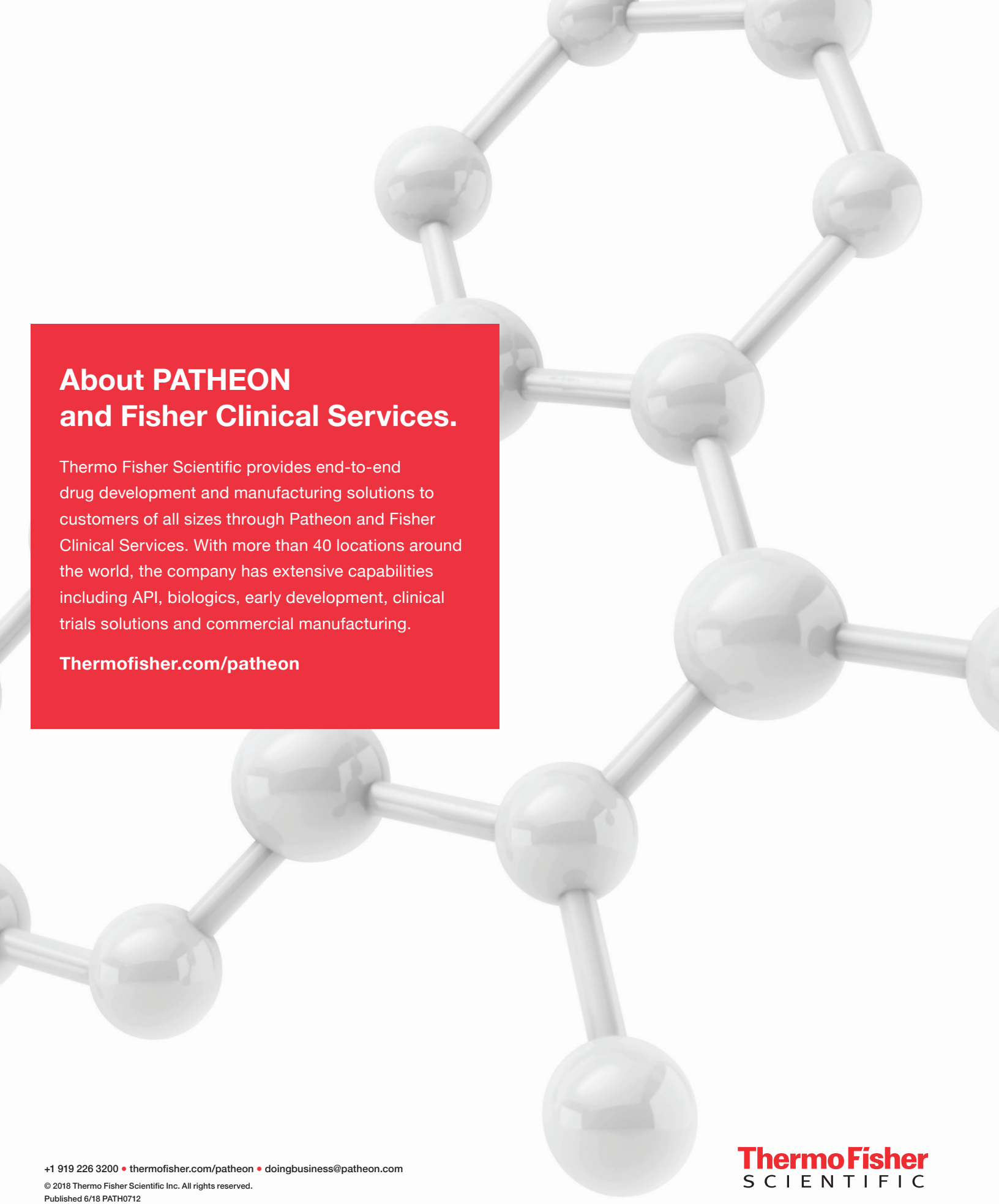
Issue #6: Specialty providers

While it may be tempting to look to specialists – a "best of breed" approach for development – it can backfire, because specialists only do what they're contracted for. In a perfect scenario, each specialist performs his or her task and seamlessly hands off to the next specialist in line. However, perfect scenarios are rare, and this method doesn't support added value through insights that will simplify steps down the line. Nor does it protect against upstream delays cascading throughout the process that may cause an API to miss its window with one of the many specialists under contract.

A simple solution for any API challenge

If you are unsure whether you bring the proper expertise or most updated regulatory knowledge to guide your API through its critical development issues, consider Patheon, part of Thermo Fisher Scientific. We are experienced in all API types and have mastered the complexities inherent in their development. We have the largest API development team in the Western world, can manufacture APIs with commercial demand from one to 800+ tons per year, and have considerable expertise in high-complexity and high-potency APIs. We also have the unique ability for our drug substance and drug product teams to work together, which has been shown to save an average of 14 weeks and $44.7 million.[5] Over the last decade, Patheon, part of Thermo Fisher Scientific, has supported the delivery of as many NDA-approved drugs as the next six leading CMOs combined – and 2.5x the nearest competitor.

[5] Assessing the Financial Benefits of Faster Development Times: The Case of Single-Source vs. Multi-Vendor Outsourced Manufacturing, Tufts Center for Drug Development, 2017



About PATHEON and Fisher Clinical Services.

Thermo Fisher Scientific provides end-to-end drug development and manufacturing solutions to customers of all sizes through Patheon and Fisher Clinical Services. With more than 40 locations around the world, the company has extensive capabilities including API, biologics, early development, clinical trials solutions and commercial manufacturing.

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