SAFC®
Pharma/Biopharma Raw Materials

Whitepaper

Small Molecule Drug Synthesis: Consideration for a Seamless Transition from Preclinical to Commercial Supply of Raw Materials

Introduction

Drug manufacturers continue to face a challenging market and regulatory environment, with evolving and tightening regulations, increasing patient demand and more competition in the form of new therapeutic technologies and generics. To stay ahead, pharmaceutical manufacturers need to accelerate time to market, optimize productivity and mitigate risk. Working at a faster pace across a global manufacturing footprint creates an extended and increasingly complex supply chain. The result is an increased exposure to risk in terms of potential quality failures of materials and supply disruptions and the need for fit-for-purpose raw materials.

Invariably, a robust supply chain has two essential attributes at its core: quality and supply transparency. To have confidence in their supply chains and suppliers, drug manufacturers expect more transparency and greater access to detailed information, where and when they need it, and require assurance that vendors' processes remain in control.

Defining the quality parameters for raw materials used to synthesize active pharmaceutical ingredients (APIs) and ensuring tightly controlled supply chains over the long term are imperatives for manufacturers of small molecule drugs – a segment of the industry that continues to be strong.

Despite an impressive breadth of new innovative therapeutic approaches such as T cell therapy for cancer, RNAi and gene therapy, small molecule drugs continue to be a mainstay in development pipelines and on the market. Reflecting the success of this approach is the fact that 64% of the 59 new drugs approved in 2018 by the US Food and Drug Administration were small molecules. The global small molecule API market is expected to grow to an estimated value of $254 billion by 2026, representing a compound annual growth rate of 6.71% between 2019 and 2026.

In this whitepaper, we explore best practices for ensuring a seamless transition of API raw material supply at critical junctions on the path from preclinical development to commercial manufacturing of small molecule drugs. Among the most significant challenges during the transition are understanding and navigating the different requirements pertaining to the quality and supply chain of raw materials used to synthesize APIs. Ultimately, a network of manufacturers and supply chains that ensures reliable delivery and quality raw materials along with supporting documentation will earn the trust of the drug manufacturer.

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Evolving Standards and Requirements

The quality standards and regulatory requirements for API raw materials increase during the progression from discovery, to early and late phase clinical trials, and finally to commercial manufacturing (Figure 1).

During preclinical discovery, less controlled research reagents are necessary with the appropriate quality standards. At this point, the primary concern of the drug developer is to quickly reach a proof of concept in API development with use of quality raw materials with relatively less concern regarding the supply chain and regulatory documentation. Progressing into Phase 1, the need for controlled raw materials emerges in which change control, traceability, consistency and characterization are critical and guided by ISO 9001 and ICH Q7 standards. ICH Q7, developed jointly by industry and regulators, established one global GMP guideline for APIs. Subsequent ICH guidance (Q8–Q11) also covers risk assessment of whole manufacturing processes, quality by design and sets general approaches for qualification of raw materials.

Continuing towards Phase III, cGMP raw materials may now be required depending on the synthesis step; along with cGMP requirements comes the need for validation, stability and audits. When the commercial phase is reached, security of supply becomes paramount.

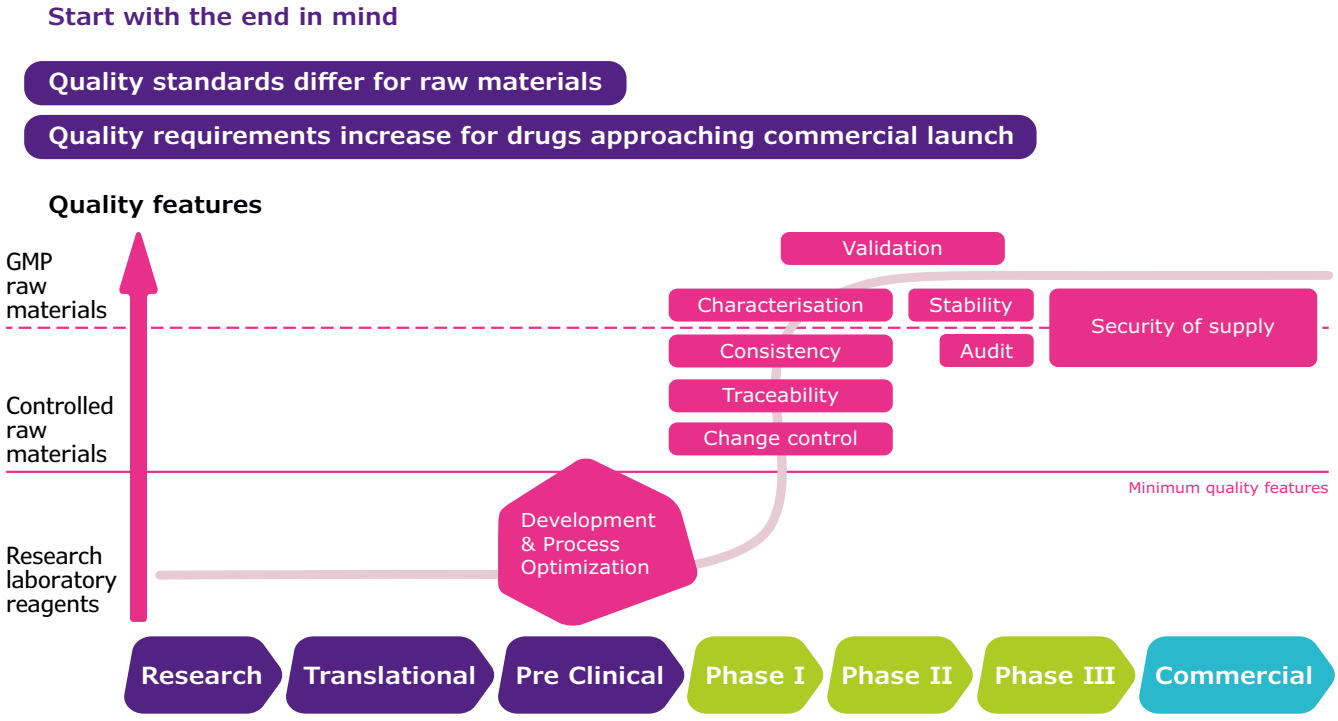

Figure 1. Quality and supply requirements evolve significantly from preclinical to discovery through commercial manufacturing.

Among the risks related to API raw materials are:

- Presence of impurities or adventitious agents with can negatively impact process quality and patient safety such as transmissible spongiform encephalopathies (TSE) such as bovine spongiform encephalopathy (BSE)
- Lack of consistent quality
- Requirement for appropriate documentation
- Counterfeit materials
- Fraudulent supply
- Supply chain disruption, lack of qualification or lack of supply chain control

When something goes wrong in the supply chain, comprehensive investigations are needed to identify the root cause, and depending on the severity, may have significant consequences.

Similarly, when an inspection or audit reveals issues with a vendors' quality management system and corresponding lack of supply chain knowledge or control, a cascade of urgent and costly activities ensues. The process of identifying an alternative supply is likely to lead to unexpected delays. If an immediate, suitable alternative does not exist, a new raw material supplier needs to be identified, otherwise a customized adaption of existing material could be necessary.

Strategies for Risk Mitigation

Figure 2 provides a schematic of API development along with activities taking place in parallel, from the preclinical phase through late phase II, or at the point of time when R&D hands the synthesis process over for establishment of the commercial process.

This workflow reveals a number of opportunities to mitigate risk. There are several critical junctures, during which the choices made regarding raw material quality and manufacturers may impact the efficiency, success and cost of later phases.

- During late preclinical stages, when the drug candidate shows enough promise for filing of an investigational new drug, R&D teams often develop new routes of synthesis for the API. We estimate that 60% of GMP batches handed over to commercial teams are manufactured via a different route of synthesis than the one first used in research.
- At the same time, the sourcing team identifies suppliers with technical and volume capabilities to support commercial-scale production.
- The third critical juncture is the last step prior to establishing the commercial process.

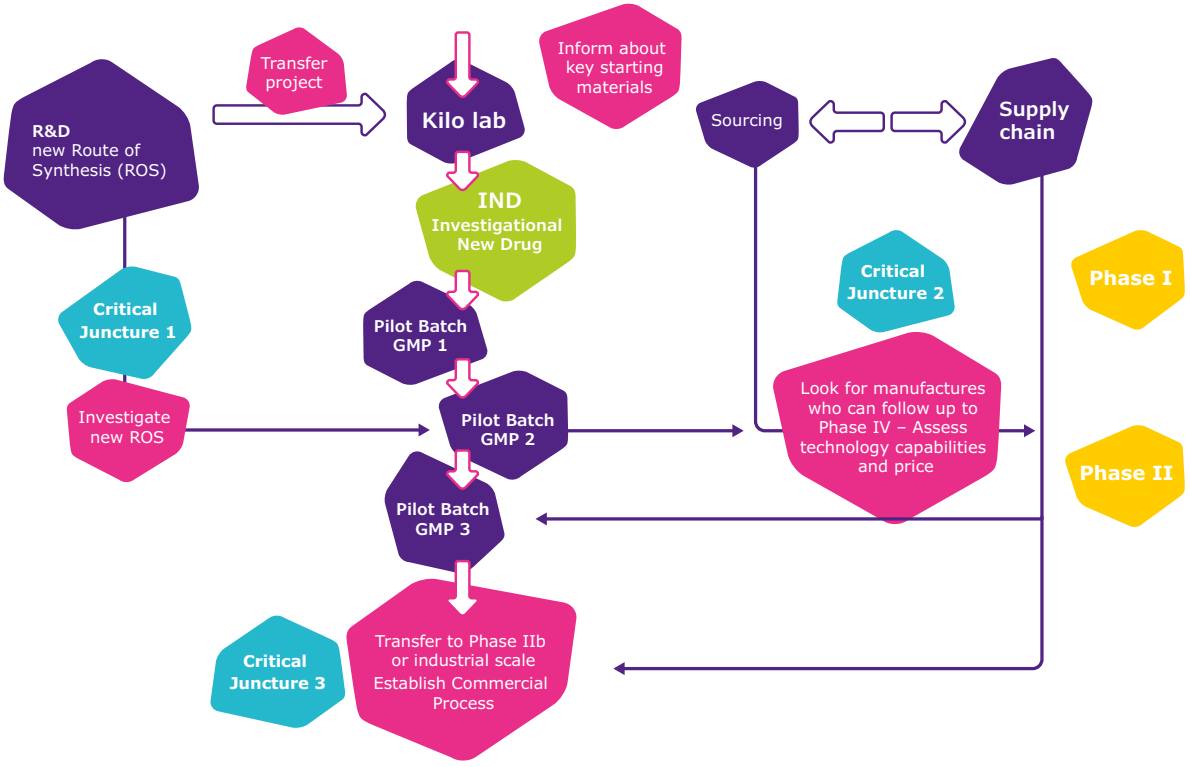

Figure 2. Critical junctures along the pathway to commercial manufacture of small molecule drugs.

Critical Juncture #1: Developing New Routes of Synthesis

Our first critical juncture is when R&D selects raw materials meeting the specifications fitting the synthetic protocol and meeting regulatory requirements. Two important questions should be asked when selecting raw materials for a new route of synthesis:

- Is original manufacturer information readily available?
- Will you be notified of specification changes?

Consider the following scenarios which highlight the need to proactively address these questions.

The Need: Certificate of Origin to Identify BSE/TSE Risk

Scenario: A CRO orders reagents, process aids and building blocks to manufacture an API in Phase II. At the point of release, the certificate of origin is missing from the batch file. A qualified person has put release on hold and the vendor is not able to provide the origin information.

Outcome: Delay in receipt of the origin information causes the CRO to miss their clinical trial start date.

Solution: Assurance of origin information should be built into the raw materials specifications at a very early stage and readily available from the supplier.

The Need: Proactive Notification of Changes

Scenario: The R&D team develops a new route of synthesis with a different building block than used in initial pathway. The vendor changes the specification from 99% to 97%. The R&D team only finds out nine months later upon receipt of an order.

Outcome: Manufacture of a Phase II API batch is delayed

Solution: Check with supplier to determine if change notification is automatic and if not, determine how to access the service. In the case where a critical product is not supported by a change notification service, a risk assessment is recommended.

Critical Juncture #2: Assessing Supplier Capabilities

A second critical juncture occurs when sourcing teams assess supplier technology and cost for support through Phase IV. Unfortunately, hidden costs may result if the supplier does not have a robust quality management system.

Need: Confidence in Supplier Ability to Support Throughout Commercial Phase

Scenario: The sourcing team has identified a supplier with the right technology, capabilities and an attractive price for bulk quantities. The supplier is considered qualified "on paper", having supplied samples and documents including certificates of analysis and completed supplier assessment questionnaire. Several orders are placed.

Outcome: Quality is not consistent among batches causing delays and additional works. QA team audits the supplier and disqualifies it due to lack of a quality management system. A new supplier must be qualified and a new route of synthesis may be required.

Solution: Consider the total cost of quality, which goes far beyond the price provided on the quote.

Critical Juncture #3: Transfer to Industrial Scale

A third critical juncture takes place at the last step of the development flow, when the process is handed over to the team to move it into commercial. At this point, industrial scale is prepared, raw material specifications are formalized, supply chain risk assessment starts and discussions with suppliers are initiated.

During this transfer, a spectrum of approaches exist to assess the risk for the entire bill of materials; at one extreme is a minimalist approach and at the other, an "over-engineering" approach. A comparison of these approaches is provided below:

Minimalist Approach

- The drug manufacturer concentrates efforts to assess and mitigate risk on the key starting materials. Other critical or important products, such as process aids or reagents are subject to relatively less scrutiny.
- Gaps related to process aids or reagents may be revealed in late phases, usually after a complaint is generated.

Over-Engineering Approach

- GMP requirements are mandatory for most products.
- Suppliers receive full GMP questionnaires or GMP documentation to comply with, even when not applicable.
- ISO 9001 sites are audited according to GMP guidelines. There is a potential for corrective action preventative action (CAPA) to require an upgrade of the supplier's plant or quality management system.

When building the raw material specification and running the supply chain risk management, a balanced approach is likely to be more practical and effective; it considers which products are critical, important, or low-risk and reflects the relevant regulatory guidelines, ICH Q9 and Q11. For each group, requirements to mitigate the risk are defined and manufacturers work with vendor based on meaningful agreements, enabling better control and monitoring the cost of quality well into the future.

Proactive Steps to Mitigate Risk

There are three key takeaways from this exploration of API synthesis and areas in which drug manufacturers can be exposed to risk:

- Evaluate manufacturers with the proper level of scrutiny needed to understand their philosophy and strategies for risk mitigation, their quality systems and the value-add programs they offer to ensure delivery reliability and quality.
- Work in close collaboration with suppliers, early in the process to proactively establish needs and expectations.
- Consider the total cost of ownership when it comes to the bill of materials. Understand that the ultimate cost isn't simply the price quoted for a delivery of raw materials.

MilliporeSigma has developed a number of programs to help mitigate risk associated with critical raw materials. We invite you to learn more about our Chemiflex™ and EMPROVE® programs.

Chemiflex™ Critical Raw Materials Program

The Chemiflex™ Critical Raw Materials program includes fit-for-purpose materials, documentation and contract manufacturing services that save time and prevent possible setbacks by ensuring that critical raw materials chosen for API synthesis will be available in quantities and qualities suitable for cGMP manufacturing.
The program is a solution for the sourcing of high-quality, critical raw materials that meet increasing regulatory documentation and supply chain requirements for small molecule drug development and manufacturing.

Benefits include:

- Accelerate time to market
- Mitigate risk
- Increase supply chain transparency
- Access extensive regulatory support

For more information

sigmaaldrich.com/chemiflex

Custom manufactured

API Starting Material

Qualification (Supplier, Supply chain)

Documentation, e.g.:
- Change control
- Supplier qualification/Supply chain
- Residual Solvents/EI
- BSE/TSE

Intermediate

ICH Q7 GMP Documentation on API level

Emprove® Program

Solvents and Reagents

Qualification (Supplier, Supply chain)

Documentation, e.g.:
- Change control
- Supplier qualification/Supply chain
- Residual Solvents/EI
- BSE/TSE

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EMPROVE® Program

Ensuring the compliance of your pharma and biopharma products involves the compilation of a vast amount of data, which can be time- and resource-intensive. The EMPROVE® Program includes 400 pharma raw and starting materials and a selection of filtration and single-use products. Each product in the portfolio is complemented by three different types of dossiers supporting you throughout qualification, isk assessment and process optimization.

Benefits include:

- Support risk assessment, management and mitigation
- Facilitate qualification processes
- Expedite approval preparation and extending compliance
- Increase supply chain transparency
- Save time and money

For more information

EMDMillipore.com/emprove

The Emprove® Suite provides 24/7 access to all Emprove® dossiers online:

EMDMillipore.com/emprovesuite

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