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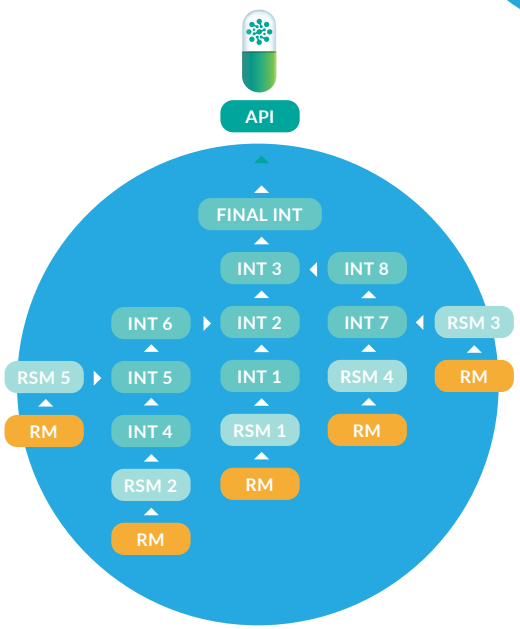
EUROPEAN FINE CHEMICALS GROUP

THE ROLE OF INTERMEDIATES IN THE MANUFACTURING OF APIS

In the manufacturing of active pharmaceutical ingredients (APIs), intermediates play a crucial role as the building blocks or transitional compounds that are formed and consumed during the multi-step chemical synthesis of the final drug compound. Their role is both technical and strategic, influencing everything from process chemistry to regulatory compliance and cost-effectiveness.

ROLE OF INTERMEDIATES

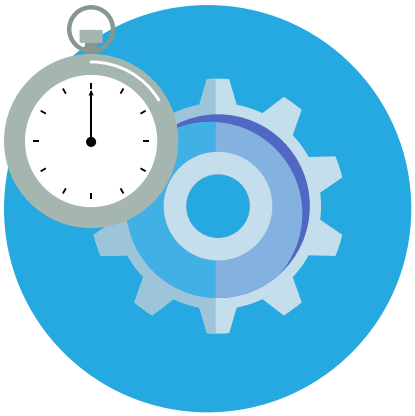
Intermediates are produced during the various stages of the synthesis process and are necessary precursors in the chemical pathway leading to the API. They have a profound impact on the quality, compliance and efficiency of the API. Each phase of the synthesis is efficient, reproducible, and meets stringent quality standards.



1. STEPWISE SYNTHESIS

API synthesis often involves multiple reaction steps, each of them yielding an intermediate, which is then used in the subsequent step. These intermediates help control the complexity of synthesis by breaking it into manageable, predictable stages.

INT Intermediate
RM Raw Material
RSM Regulatory Starting Material



2. PURITY AND QUALITY CONTROL

Intermediates are typically isolated materials that are thoroughly controlled being used in the next step of the synthesis. The purpose of this control is to ensure that no undesirable or unknown impurities were formed during the synthesis that will negatively impact the quality of the API. These impurities can have different origins (e.g. degradation products) and may affect the final API safety and efficacy. Monitoring the purity of intermediates is essential for regulatory compliance and process validation. ICH Q7 emphasises the needs to control and document specifically the critical and/or late-stage intermediates.

3. PROCESS OPTIMISATION

Understanding the reactivity of intermediates helps in minimising unwanted side reactions and improving overall efficiency, as well as optimising reaction conditions, yields and scalability, mitigating the need for additional steps, such as reprocessing that are submitted to the same rigorous Good Manufacturing Practices (GMP) rules.

REGULATORY AND DOCUMENTATION IMPORTANCE

Pharmaceutical intermediates are strategic assets in the pharmaceutical value chain. They are regulated through a combination of GMP guidelines, rigorous quality control measures and specific regulatory frameworks such as REACH in the EU. Manufacturers must ensure intermediates meet strict standards for purity, quality, and consistency, with comprehensive documentation and process validation to maintain quality, compliance and patient safety, as required by regulatory agencies such as the EDQM in the EU or the FDA in the US.

Intermediates usually have to be registered under REACH. To achieve this, specific handling conditions must be met (in most cases) or additional studies must be performed.

The current manufacturing trend is for more steps to be manufactured under GMP conditions, leading to optimum quality control during the production of these strategic intermediates.

HOW DO INTERMEDIATES INFLUENCE THE COST STRUCTURE OF API MANUFACTURING?

API manufacturing is a complex process with multiple cost components. Intermediates have a significant impact on the cost structure of API manufacturing, both directly and indirectly. These can be broken down into:

1. RAW MATERIAL COSTS

The cost of the intermediates is directly linked to the raw materials used in the manufacturing process. Materials with high purity or specialty reagents increase costs. The availability and market volatility can also lead to price fluctuations and supply risks.

Depending on the complexity of the intermediate's synthesis, or its commercial availability, it can be either purchased or synthesised in house. In-house synthesis will increase the cost due to:

- Additional synthesis steps
- Specialised reagents
- Labour and equipment needs

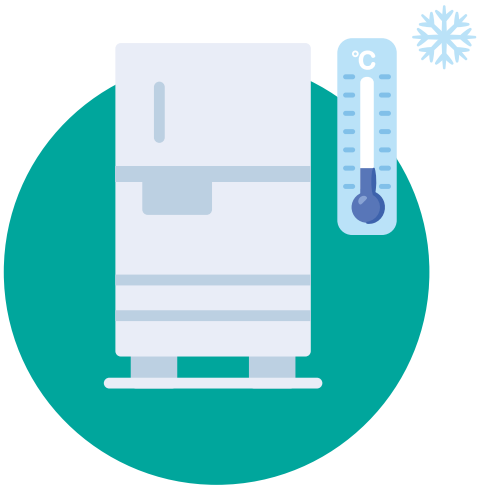
Example: Chiral intermediates. These molecules play an important role in pharmaceuticals as they are not identical to their mirror image. This is important because the two mirror forms can have very different effects—one might work as intended, while the other could be inactive or even harmful. Making a pure chiral intermediate is therefore complex, requiring special techniques to separate and produce only the desired form, and involving expensive catalysts and multiple purification steps.

2. NUMBER OF SYNTHETIC STEPS

- The more intermediates involved, the longer the synthesis route, which means:
  - More solvents and reagents used
  - More energy consumed
  - Greater labour and time costs
  - Additional REACH registrations and notifications
- Each step adds operational overhead, including equipment use, maintenance, and waste management
- The industry trend is to implement innovations that reduce the number of steps in the synthesis route

3. YIELD AND EFFICIENCY

- Poorly optimised intermediates can lead to low yields in subsequent steps
- Loss of material at any intermediate stage means higher input requirements to achieve the same final API output
- High-yielding and stable intermediates reduce waste and cost



4. STORAGE AND HANDLING

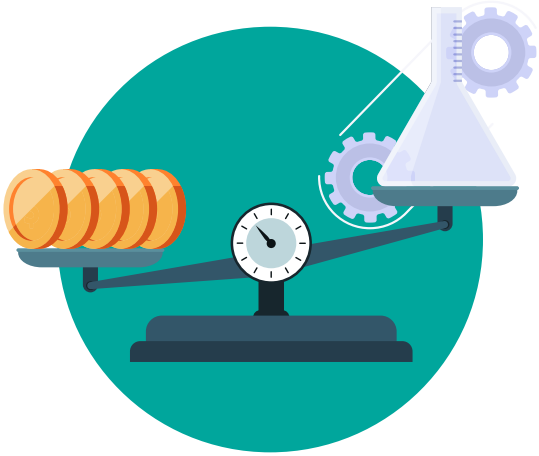
- Some intermediates are unstable or hazardous, requiring special storage (temperature, humidity control) and/or handling procedures, adding to the overall cost in terms of infrastructure and safety compliance
- If intermediates are registered as such under REACH, they must be handled under strictly controlled conditions (closed handling) throughout their life cycle, which requires special equipment and procedures (e.g. weighing, cleaning)

5. OUTSOURCING VS. IN-HOUSE PRODUCTION

- If intermediates are purchased from third parties, the cost depends on:
  - Supplier pricing
  - Global availability
  - Import/export duties
- Outsourcing may reduce capital investment but adds dependency and supply chain risks

6. REGULATORY AND QUALITY ASSURANCE COSTS

- Most intermediates must meet strict quality standards, including:
  - Analytical testing (e.g., purity, residual solvents)
  - Validation of manufacturing procedures
- The more intermediates used in the synthesis, the more QC/QA checkpoints, adding to the overall cost
- Any changes either in the process or sourcing of materials require GMP controls (change control, validation) and regulatory reviews and the costs can be substantial



7. SCALABILITY AND TECHNOLOGY TRANSFER

- Some intermediates behave differently at scale
- Process development for intermediates (e.g., crystallisation, filtration) impacts scale-up costs and tech transfer to commercial manufacturing

ABBREVIATIONS

ICH Q7: International Council for Harmonisation (ICH) guideline Q7
EDQM: European Directorate for the Quality of Medicines & HealthCare
FDA: The US Food and Drug Administration
REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals

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