Innovations in API Manufacturing of Small Molecule Drugs

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Throughout the years, innovation has been the driving factor of many industries, allowing them to stay viable. This is also the case for the pharmaceutical industry, including API manufacturing. With the cost of new pharmaceuticals steadily rising, innovation is the only way to reduce it and ensure the future availability of new pharmaceutical treatments. Predicting which fine chemicals or APIs will be significant in the following decades is also challenging. Only through innovation is the industry capable of reacting in time to fulfil the market's needs. This article discusses recent and future innovations in the API manufacturing industry with the potential of reducing manufacturing costs and addressing market demand accurately.

Introduction

Innovation is the practical implementation of ideas that results in introducing new goods or services or improving the offerings of existing goods or services.[1] ISO TC 279 in the standard ISO 56000:2020 defines innovation as "a new or changed entity, realising or redistributing value".[2] Others have different definitions, but a common element is the focus on newness, improvement, and the spread of ideas or technologies.

The pharmaceutical industry, and therefore also the manufacturing of APIs, faces many hurdles, including the availability of a skilled workforce, supply chain disruptions, the rising cost of new therapies, and increasing environmental regulations. Innovation is the only way to decrease costs and secure the future availability of new pharmaceutical treatments. Predicting which f ine chemicals or APIs will be significant in the following decades is also challenging. Only through innovation is the industry capable of reacting in time to fulfil the market's needs.Within the pharmaceutical industry, the 6M methodology has proven a powerful tool for performing root cause analysis or risk assessment. The six factors it is built upon are manpower, method, machine, material, measurement, and mother nature (the environment).[3] Applying the 6M methodology lowers the chance of missing essential root cause analysis or risk assessment items. It helps ensure product quality, safety, and efficacy. This article will use these six factors as a guiding principle when discussing the innovations within API manufacturing of small molecule drugs.

Manpower

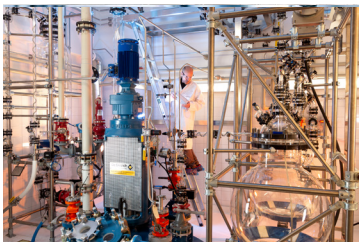
The first factor focuses on the human interfaces involved in API manufacturing. Especially in the industrialised part of the world, a highly skilled, trained, and experienced workforce is becoming increasingly costly. Improving welfare and living standards have increased salaries throughout the past decades. Due to the cost, the workforce must be used most efficiently and competently. Employees' repetitive work and administrative tasks should be minimised as much as possible. One example of such repetitive work is finding the optimum in a chemical conversion regarding selectivity, quality yield, and reaction time, with many process parameters involved and scrutinised. Increasingly, automation is helping with these types of tasks. The group of prof T. Noel recently published an excellent example of such automation, presenting a versatile, allin-one robotic platform for the autonomous optimisation, intensification, and scaling up of photocatalytic reactions in flow.[4]

Method

The second factor focuses on the methods involved in API manufacturing. When discussing methods, we want to focus on the chemical conversions and different types of chemistry involved in API manufacturing. Catalysis involving rare metals like Pd, Ru, and Pt has been part of the standard toolkit of chemists for many years, helping them develop synthetic routes toward new chemical entities (NCEs). The Suzuki-Miyaura coupling is one of the most versatile ways to create carbon-carbon bonds to produce conjugated systems of alkenes, styrenes, or biaryl compounds.[5] During the development of NCEs, the route of synthesis changes over time, typically starting with a "medicinal chemistry" route, which process chemists change into a scalable, safe, and robust route. The resulting synthesis route is often shorter and, therefore, more cost-efficient. Innovations in chemistry that have been used more frequently by process chemists over the past decade involve photochemistry, electrochemistry, and the application of enzymes. A typical example of photochemistry is the production of Vitamin D3, where 7-dehydrocholesterol is exposed to UVB and UVC light, followed by purification.[6] Vitamin D2 (ergocalciferol) is produced similarly using yeast ergosterol as a starting material.[6,7] When we look at nature, enzymes are widely used. The human body is an excellent example of enzymes that perform many conversions to produce hormones.[23] Of course, in the laboratory and chemical plants, enzymes can also be used to manufacture small molecules. An interesting example is the manufacturing of Sitagliptin[24] or Testosterone[25].

Machine

The third factor involves the machinery or equipment used in API manufacturing. One of the most challenging aspects of API manufacturing is scalability. Bringing a synthesis route from the lab to the pilot plant on a commercial scale is sometimes hampered by all kinds of physical challenges like dosing times, filtration times, heat transfer, cooling capacity, and the ability to agitate effectively. Also, from a safety point of view, several hurdles must be taken while scaling a process to full-blown commercial manufacturing. Process intensification as continuous manufacturing is being applied increasingly throughout the industry. A recent article on HiGee reactors is a good example of such an application and firm innovation. HiGee are mini reactors that use high gravitational forces, usually by spinning or moving parts, thereby creating high levels of shear. This high shear increases both mass- and heat transfer on a micro level. In this way, process intensification offers a high potential to improve the efficiency of several industrial processes and, thus, reduce the



environmental footprint of the chemical industry.[8,9,10]

Material

The fourth factor focuses on the materials used in API manufacturing or the new types of molecules, concepts, or platforms applied in new therapies. Here, we can mention many recent innovations and trends. A stronger focus on niche products and orphan drugs is observed within the API industry, with new treatments increasingly discovered and developed for smaller populations. Another trend is the increased potency of APIs. Advancements in drug research, especially in oncology, inflammatory diseases, and antiviral compounds, have driven the development of new therapies with highly potent compounds. The lack of data, particularly concerning the novel pharmacological actions of compounds potentially designated as highly potent active pharmaceutical ingredients (HPAPIs), and the transformation of process intermediates to conform with acceptable occupational exposure levels, poses a significant obstacle. A risk-based approach is considered to overcome this issue in early drug discovery.[11,12]

Another innovation in the materials focus area is the development of antibody-drug conjugates (ADCs).[13] Sometimes, generic APIs like Doxorubicin can be rediscovered by applying them to an ADC.[14]

The latest innovation areas we want to highlight are so-called PROTACs (proteolysistargeting chimeras) and molecular glues. The earliest-known published description of the concept of chimeric degraders is in a patent filed in 1999 by a biotechnology company, Proteinix, proposing taking over the cellular protein degradation system.[15,16]

The establishment of the PROTAC strategy was further augmented by the finding of degrader compounds that became known as molecular glues.[17,18] Molecular glues are monovalent small molecules (<500 Da) that reshape the surface of an E3 ligase receptor, promoting novel protein–protein interactions (PPIs) and offering many opportunities to engage currently undruggable targets.

Measurement

The fifth factor concerns measurements used in API manufacturing. Analysis is an essential aspect of API manufacturing. Whether during the release of (regulatory) starting materials, in-process analysis, or the release of the final API, the ability to analyse and characterise the materials or conversions is critical. Therefore, strong analytical capabilities are essential in setting up a proper and successful control strategy for filing your investigational new drug (IND) application or investigational medicinal product dossier (IMPD).

Throughout the years, the field of analytics has developed many innovations, and it will continue to do so in the near future, for example, by creating the ability to analyse impurities like nitrosamines or poly- and perfluoroalkyl substances (PFAS) at levels that were impossible before. A unique innovation we want to mention here is the application of artificial intelligence (AI) within the analytical area. Of course, nowadays, no article on innovation can or should be written without mentioning AI. A milestone in AI application in analytical chemistry is its ability to handle heterogeneous and complex data. Traditionally, analysing such data would require extensive expertise and time. However, with AI algorithms, it is possible to extract relevant information quickly and efficiently.[19,20]

Minise global warming, decrease of biodiversity, and other critical aspects. We want to tackle two examples in this article: solvent use in solid-phase peptide

synthesis (SPPS) and a modular flow platform that streamlines the synthesis of heteroatomCF_3 motifs.

SPPS is the preferred technique for synthesising bioactive peptides. However, traditional SPPS generates significant waste and employs hazardous solvents like DMF and DCM. To overcome this challenge, Giovanni Vivenzio et al. developed a novel green solvent mixture by combining anisole with NOP.21 This mixture can swell different resins, and its capability to solubilise all Fmoc-protected amino acids has been investigated. The exact mix was also assessed with a green coupling agent, TBEC, in combination with ETT as an additive. Model peptides Aib-enkephalin and Aib-ACP were synthesised, resulting in favourable outcomes in peptide synthesis efficiency, 97.81% and 98.86%, respectively.

The last innovation we want to discuss is preventing the use of PFAS chemicals to introduce the trifluoromethyl group (CF_3) on a molecule. The CF_3 group is a key functionality in pharmaceutical and agrochemical development, greatly enhancing the efficacy and properties of resulting compounds. However, attaching the CF_3 group to heteroatoms such as sulphur, oxygen, and nitrogen poses challenges because of the lack of general synthetic methods and reliance on PFAS chemicals. The method developed uses readily available organic precursors in combination with cesium fluoride as the primary fluorine source, facilitating the rapid generation of N-trifluoromethyl(R) [NCF_3 (R)], SCF3 (trifluoromethylthio), and OCF_3 (trifluoromethoxy) anions on demand without using PFAS chemicals, turning it into a strategy that is far more environmentally friendly.[22]

Conclusions

Innovation is essential for any industry, and the pharmaceutical industry is no exception. In this article, a few examples have been given to show recent innovations within API manufacturing. We did not intend to create a complete overview, as it is possible to list many more examples of innovation in this field. Nevertheless, the innovations presented here show that the industry keeps evolving and adapting to be ready for future challenges. Applying these innovations can reduce costs, help develop new therapeutic areas, and meet global sustainability targets. Thanks to some of the innovations mentioned in this article, the API manufacturing industry faces a bright future.

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