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Challenges Facing Pharmaceutical Excipients

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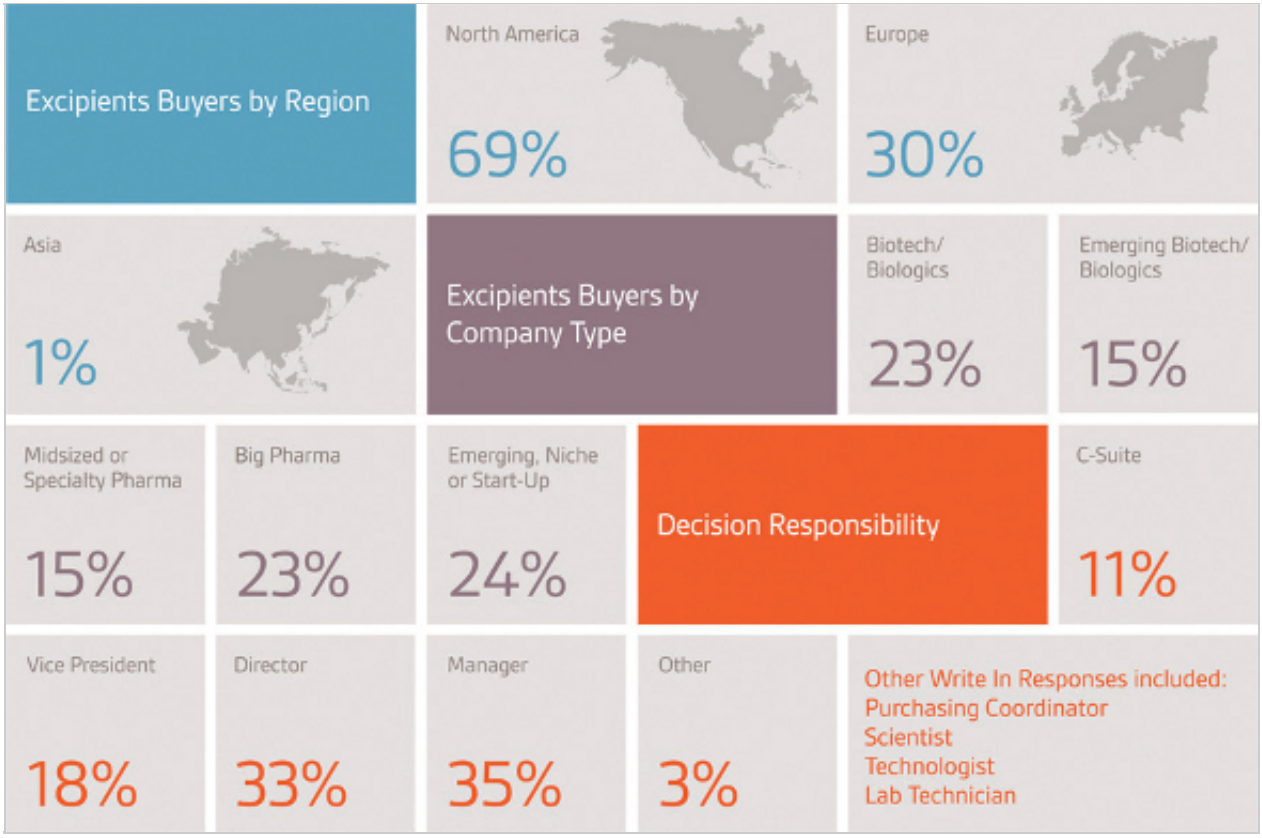
The global pharmaceutical excipients market, a multibillion market, is projected to expand at a healthy pace of 6.7 percent annually in the next five years and reach $8.4 billion by 2019 (Markets and Markets, 2015). This continued growth is largely driven by the increasing demand for pharmaceutical products to serve an aging population and improve healthcare worldwide. Despite the positive outlook, the industry itself faces a variety of challenges to meet the expectations of the regulators, end users/drug makers and ultimately the patients.

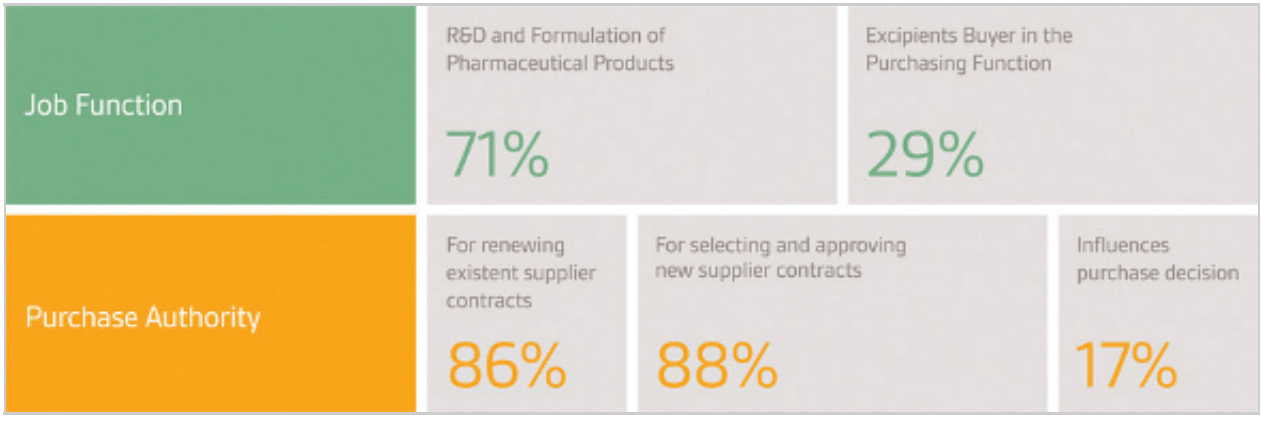
Regulatory Authorities Demand Safety and Quality of Pharmaceutical Excipients

The quality and safety of pharmaceutical products are the top concerns of regulators. In recent years, regulatory agencies have strengthened their position on preventing drug adulteration in both active pharmaceutical ingredients (API) and excipients by enacting new regulations such as the 2012 US Food and Drug Administration Safety and Innovation Act (FDASIA) and the EU Falsified Medicines Directive (FMD or Directive 2011/62/EU). Under these laws, the drug makers are expected to conduct physical audits of all excipient manufacturers and distributors in order to ensure a secure supply chain.

Compliance could be difficult to achieve. Pfizer, a major excipient consumer, reported having over 4,000 suppliers after their 2003 merger with Pharmacia. If these were to be audited annually, that would require more than ten audits per day. The excipient supply side is already feeling the pressure; Ashland's excipient production facility in Texas City,Texas hosts over 300 pharmaceutical audits a year. Further guidelines are needed to help both excipient users and suppliers to implement the regulations at a reasonable economic burden and time frame.



Apart from regulatory legislations, the pharmaceutical excipient industry has long been taking their own steps to ensure the safety and quality of excipients. Back in 1991, the industry formed the International Pharmaceutical Excipients Council (IPEC), an industry group focusing on harmonizing compendia, GMP and GDP standards for pharmaceutical excipients internationally. Its publication of IPEC-PQG (The Pharmaceutical Quality Group) GMP Guide 2006 and IPEC GDP Guide 2006 have been recognized as industry standards and applied in excipient manufacturing and distribution voluntarily. A new revised IPEC-PQG GMP guide is expected to be published by the end of 2015.



In addition, IPEC has been actively engaging with regulatory agencies and advocating for imposing excipients GMP and GDP standards. Their efforts led to the adoption of IPEC-PQG GMP guide into Pharmeuropa 9.2 and USP <1078>. More recently, the European Union Commission issued final guidelines on GMP for excipients of medicinal products for human use (2015) while in the United States, the first American National Standard for GMP of pharmaceutical excipients – NSF/IPEC/ ANSI 363-2014 was released last year (NSF: The NSF International; ANSI: The American National Standards Institute). Both standards are similar to IPEC-PQG GMP standard. Formal guidelines on GDP for pharmaceutical excipients are still lacking.

Drug Manufacturers are Responsible for Supply Chain Safety, Security and Integrity

A pharmaceutical excipient supply chain contains at least two parties: the excipient manufacturer and end user/drug manufacturer. It is possible that the excipient manufacturer and end user are from the same company as demonstrated in Nice Insight's 2014 industry-wide study of pharmaceutical excipients.[6] Among 189 excipients manufacturers, 32 percent of them are from Midsized/Specialty and Big Pharmaceutical companies and 30 percent are from Biotechnology/Biologics companies. Even in this case, the likelihood of the two parties localized in the same facility is quite low. Therefore, components like transportation, warehousing/storage may be added to this chain. In a more common scenario, a supply chain likely contains raw materials supplier (upstream of excipient manufacturer), distributor and/or broker/trader.

The IPEC-PQG GMP and IPEC GDP guide provide the basis for managing a quality-based, safe, and traceable pharmaceutical excipients supply chain. IPEC has also recommend implementing an excipient pedigree scheme to aid drug manufacturers' understanding of the complete supply chain history of the excipient. According to the IPEC guidelines, all the parties in the supply chain "must share responsibility for the quality and safety of the materials and products."[1] Ultimately, the drug manufacturer is accountable for assessing the risk in the supply chain, implementing a risk management program, and having risk mitigation strategy in place.

Due to the globalized nature of the pharmaceutical market, most companies have supply chains that extend beyond the domestic level. Similar to APIs, a large portion of excipients could be imported; the FDA estimates that over 80 percent of APIs are imported into the US.[2] Although the exact percentage of excipients imported is unknown, concerns have been raised as the excipient industry has experienced more FDA import holds, as reported by IPEC-Americas. An unexpected hold can delay drug production, negatively impacting its timeline to market or worse, causing a shortage in drug supply. In one case, the hold led to the shutdown of the production line. On the other hand, importation increases risk and difficulty in managing the supply chain; drug manufacturers must respond with greater surveillance and vigilance in supply chain management. Meanwhile, overseeing pharmaceutical excipient manufacturers out-side the homeland can impose a challenge for the regulatory authority.

Novel Pharmaceutical Excipients Lacking

Despite the need for innovative excipients, developing a novel pharmaceutical excipient can be a risky business decision for excipient producers. In general, new excipients can be developed through two pathways: modification of a known excipient as a derivative or successor or by creating a new chemical entity without base structure. The latter is similar to developing an active ingredient, which takes six to seven years from structure screening and optimization to pilot scale-up and toxicological testing/production scale-up for Drug Master File (DMF) submission.[3] This lengthy, costly development process presents a major hurdle for excipient innovation.

Applying for regulatory approval presents another hurdle to the novel excipient development. Currently, a novel excipient can only be approved for a particular function as part of a drug dosage formulation because there is no specific approval process for novel excipients. If the pharmaceutical product failed to gain approval, the excipient would remain unapproved. Compounding the problem of excipient innovation is the slow industry adoption, usually taking seven to ten years for it to become a commonly accepted excipient.[4]

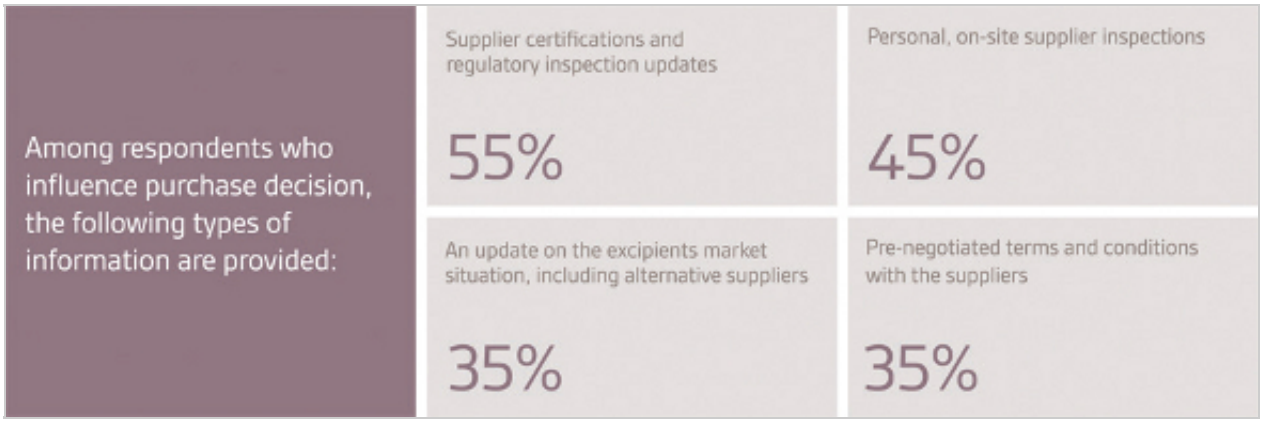
The challenges of innovation in the current regulatory environment may explain the lack of novel excipients in the market. However, the pharmaceutical industry craves novel excipients that are multifunctional and safe to use. The desired functionality for a novel excipient includes improving solubility and absorption, enhancing disintegration, and aiding controlled release for oral formulations or increasing stability for biologics/parenteral formulations. Novel excipients are also in high demand for use in developing novel drug delivery systems, (i.e. nanotechnology-enabled drug delivery systems and liposomal drug delivery systems). Another trend in excipient innovation is developing co-processed

excipients by combining two or more existing excipients into one product. The co-processed excipients are expected to gain market approval faster than those with a completely new chemical entity. The main regulatory concern is whether there is a significant chemical change in the new entity after physical modification. Moreover, this concept can be applied to develop customized co-processed excipients with defined characteristics and functionality for specific applications.

Surprisingly, one regulation, Quality by Design (QbD), may lead to a closer working relationship between drug manufacturers and excipient manufacturers/suppliers, which may form a platform for developing custom designed novel excipients. The implementation of the QbD concept has allowed the drug makers to better understand their products, including every component in the formulation, and manufacturing process. When designing a new formulation, drug makers need to consult with excipient experts to select excipients or to design a new excipient that will help them achieve desired product performance and quality. Dr. John Hogan, a seasoned industry veteran, stated “high-tech excipients with greater functionality {can be} developed in partnership with drug companies and in a manner akin to an active pharmaceutical ingredient”.

Another possible way to foster innovation in pharmaceutical excipients is through strategic partnerships or alliances among excipient manufacturers who possess complementary specialty sets. One example is the Dow-Colorcon Controlled Release Alliance, a marriage between Dow Pharma and Food Solutions’ expertise in controlledrelease and Colorcon’s expertise in coating. In 2013, the Alliance launched its next-generation METHOCEL™ DC2 polymer which can potentially save oral tablet manufacturing costs up to 60 percent while reducing waste and shortening development time.

From a business point of view, the alliance between Dow and Colorcon sets up a perfect win-win strategy for excipient manufacturers to expand their product and service portfolio, penetrate new markets, and fortify their ability to compete globally. Although pharmaceutical excipients constitute the vast majority of a drug product, their market value only accounts for 0.5% of the total pharmaceutical market.[5] Furthermore, the global pharmaceutical excipients space is quite crowded with 10 leading companies taking 60 percent of the market and plenty of smaller companies splitting the rest 40 percent (Markets and Markets, 2012). Since many pharmaceutical excipients come from natural sources (i.e. food, plant, animal, mineral, and petrochemical) and can be widely used in other industries (i.e. food, cosmetic and personal care), they inevitably become a commodity, competing primarily on price. Emerging markets including China, India and Brazil are associated with lower labor and production costs. To stand out amongst this competition, pharmaceutical excipient companies in developed markets have to invest in differentiated products, which will allow them to enjoy a much higher profit margin and maintain a competitive advantage. Other applicable strategies include strategically building partnerships with pharmaceutical or excipient companies and providing clients with supreme technical, regulatory and compliance expertise.



Overall, the pharmaceutical excipient industry is highly driven by the growth and demand of the pharmaceutical industry.

Increased importation of pharmaceutical excipients adds a layer of complexity and uncertainty to the supply chain. Pharmaceutical manufacturers bear the burden to ensure the safety and quality of their excipients. Complying with excipient GMP and GDP standards can help minimize risk in the supply chain. Both excipient and drug manufacturers are required to implement QbD. Conforming with this leads to better control over the product and process resulting in consistent production of quality pharmaceutical excipients and medicinal products.

References

1. WHO, Good trade and distribution practices for pharmaceutical starting materials, 2003
2. Irwin B. Silverstein, Ph.D., How Excipient GMP Certification Enhances Patient Safety
3. Karl Kolter, Novel Excipients, A Rare Species, Pharmaceutical Technology Europe, 2011
4. Sean Milmo, European Union Introduces GMPs for Excipients, BioPharm International, 2013
5. Pharmaceutical Quality Group, International Excipients Certification Project, 2009

Nice Insight, 2014 Excipients Study, November 2014 If you want to learn more about the report or about how to participate, please contact Guy Tiene by sending an email to guy@thatsnice.com

Survey Methodology: The Nice Insight Excipient is deployed to R&D and Formulation personnel and excipient buyers in the purchasing function. The 2015 report includes responses from 412 participants. The survey is comprised of 60+ questions and randomly presents ~25 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions of the top ~45 excipient manufacturers and distributors serving the pharmaceutical industry. Five levels

of awareness, from "I've never heard of them" to "I've worked with them" factor into the overall customer awareness score. The customer perception score is based on six key influencers to purchase: Quality Assurance, Financial Stability, Regulatory Track Record, Affordability, Product Specifications and Reliability of Supply. In addition to measuring customer awareness and perception information on specific companies, the survey collects data on supplier selection criteria and formulation requirements as they relate to excipients.

- **Excipients »**
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