American Pharmaceutical Review™

Raw Materials/ Functional Excipients Roundtable

Sunday, April 30, 2017

Print

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How have advances in raw materials functionality, supply and quality affected the pharm/biopharma industry?

Jason M. LePree, PhD, Gattefossé USA, Pharmaceutical Division, Application Lab Manager: In the not too distant past, excipients were viewed as inert substances, judged mainly by their conformity to compendia.

This view is not realistic. Increasingly known to the users is that excipients are actually referenced by compendia under general definitions, i.e. chemical descriptions that refer to a major component in the raw material. As a result, smaller constituents that may well contribute to the functionality of the excipient could be overlooked by the user. It is well

understood that two raw materials complying with a single monograph, could have very different functionalities due to these very minor, concomitant components which are inherent to raw material source and manufacturing process.

It is also now clear that excipients are not inert; that excipient performance is relative to the quantity used or the drug system it is in. Meanwhile, the Implementation of Quality by Design principles in the formulation development process has forced drug makers and the suppliers of excipients alike to examine and better understand the non-compendial attributes of the raw materials.

With respect to quality, manufactures of raw materials can assist pharmaceutical scientist in the identification of critical quality attributes of their formulations that are impacted by excipients. Advances in the functionality of raw materials have expanded the available design space for formulators. The increase in functionality has provided formulators with more options to develop APIs with high formulation barriers into quality products that meet targeted product profiles for processability, performance, quality and stability.

David Elder, Consultant: Efforts to define functionality of key excipients in pharmacopoeias have had limited success, as excipient performance tests are application specific, linked to each different formulation and process, and it is difficult, if not impossible for these tests to cover all potential eventualities.

In parallel, there is a greater focus on CMAs (critical material attributes) by both suppliers and customers. It is widely recognized that excipient grade and excipient supplier(s) are important factors in controlling excipient variability and thereby product quality. However, purity and functionality of the excipient are sometimes quite different. It is often other “concomitant components”, in the excipient (not to be confused with impurities), that facilitate enhanced functionality and control of “concomitant components” in the excipient should not be taken to mean either reduction or removal. The presence of these “concomitant components” within the excipient will often have beneficial effects on the excipient’s performance and the product’s subsequent processability. Control is therefore required to ensure consistent levels of “concomitant components” and where possible, that impurities are minimized.

Nigel Sloane, VP Business Development, Excipients, Kerry: Pharma-ceutical customers now have many more choices when it comes to excipient selection and supply. For example, there are several well known and reputable suppliers now of pharmaceutical film coatings, which would not have been the case even just a decade ago. Additionally many excipient suppliers have evolved their product offering to include new advances the development of co-processed excipients to perform in a superior way to a simple blend of those same excipients.

Quite often, pharmaceutical companies adopt their own products specifications, that are in addition to the relevant monograph, but perhaps quite different that the suppliers own ‘standard’ specifications for a given pharmaceutical excipient. It is important therefore that the vendor is able to assess those types of requests quickly, and determine if unique specifications are within their process capabilities, and can be agreed to – and then supplied on a routine basis.

Another key consideration is that many pharmaceutical companies have operations in several countries with many manufacturing plants. This requires the excipient supplier to be able to seamlessly deliver a very consistent, high-quality product. to exacting specifications to pharmaceutical manufacturing plants throughout the world. Customers expect this, and it becomes critical then that and excipient supplier is able to provide a level of world-class service, while at the same time adhering to all of the regulatory requirements associated within the customers market.

Joseph Zeleznik, Technical Manager, Meggle USA: Advances in material performance have had several positive impacts on the pharmaceutical industry. In addition to overcoming the challenges imposed by BCS classes II, III, and IV APIs, improvements in carrying capacity and have allowed pharmaceutical companies to formulated smaller tablet and without traditional complex processes. This had led to greater patient compliance and greater efficacy. Additionally, improvements in material science, and specifically, better performing materials, has simplified Quality by Design approaches to formulation development and manufacture. This, in turn, has provided pharmaceutical manufacturers with greater flexibility in ensuring quality medicines.

Kaat Bracquiné, Senior Manager, Quality & Regulatory Affairs, Capsugel: While excipients have no pharmacological effect, suggesting they are inactive or inert is an out of date perspective. QbD principles and the ICH Quality Guideline Q9 on Pharmaceutical Development requires robust formulations where excipients are selected with an understanding of their characteristics that can influence the drug product manufacturing and performance. Today, excipient manufacturers are expected to understand the intended use of their products and have systems in place to capture these application-dependent quality requirements -- exceeding mere compendial compliance. Continuous improvements and technological advances should be processed under change management procedures integrating considerations for customer notification, enabling downstream risk assessments for potential impact on drug product quality, safety and efficacy.

Additionally, operating in today's global environment requires access to materials manufactured in distant location. Procedures to mitigate supply chain challenges to safeguard product integrity and quality from manufacturer to user are essential.

Shaukat Ali, Technical Support Manager, BASF Corporation: As the pharma industry increasingly focuses on biologics and other novel drug delivery forms, raw material suppliers, such as BASF, are partnering more closely with drug manufacturers in the early stages of development to agree upon quality and supply specifications. This allows the supplier to refine their raw material production and packaging processes to meet the availability and quality requirements of the drug manufacturer. Collaborating early in the partnership on these issues mitigates risk as impurities in the raw materials impact the manufacture and quality of all dosage forms (tablets, capsules, or liquids) and shortages in supply (APIs or excipients) can have a direct impact on a drug manufacturer's business and the patients they serve.

When evaluating suppliers of raw materials/ excipient suppliers what processes or steps should a company take? What are some important questions to ask?

LePree: The drug manufacturer must first understand and identify critical factors that influence a product's stability, in-vitro and in-vivo performance, and processability. Once these factors are understood, the company should identify those that are impacted by excipient properties (for example, particle size, and presence of known impurities in the excipient). The company will then work with the vendor to understand the lot-to-lot variability of that property and the controls that are in place to reduce the variability in the product. Companies should ask about the availability of the product and what steps manufacturers have taken to ensure adequate supply, even after unforeseen events such as natural disasters or lack of availability of materials to produce the excipient etc.

Elder: It is important to understand the business model of the excipient supplier to better understand shared concepts of quality. For example, excipients are often chemical commodities manufactured on very large scales using continuous or semi-continuous processes. Such excipients may not necessarily be manufactured according to current good manufacturing practice (cGMP). It is also important to understand that excipient suppliers typically sell their materials to a wide variety of different customers spanning a wide variety of different industries, e.g. food and cosmetic; so there is limited ability of the pharmaceutical end user to influence the requisite quality.

Sloane: First, it is important that a supplier has a history of and supplying products to the pharmaceutical industry. Supplying raw materials to a pharmaceutical customer that are able to meet the customers' expectations regarding their specifications for whatever product it is that they're using is perhaps an obvious criteria, but mutually agreeing to a set of specifications should also be a key first step.

Security of supply should also very high on the list of questions to ask a potential vendor of high-quality excipients. Having a product that is able to meet a required specification is only useful if the vendor can also get them to the customers' door, when and where ever they need it.

It is also very important that vendors of excipient have strong technical and regulatory support. These are vital elements since whenever customers' run into technical, or regulatory hurdles, they must be overcome quickly and the vendor must play a very key role here.

Lastly, the price of the vendors product must be agreed upfront, since a vendor will not be able to provide an excipient for very long if it is not profitable. Likewise, the buyer of the excipient, must be convinced that the value the excipient brings to his or her formulation, at the agreed price.

Zeleznik: Because the pharmaceutical industry is now working within a QbD world, consistency is one of the key factors for which drug product manufacturers should be looking. While lot-to-lot variation is normal, particularly for naturally derived ingredients, the level of variation should be assessed. Understanding ingredient variation can help prevent defects in finished dosages.

Bracquiné: The current regulatory framework on medicinal products requires excipient suppliers to be carefully selected – from start-up throughout the product's lifecycle.

Therefore, pharmaceutical formulators should embark on a dialogue with raw material suppliers to build a genuine understanding of the excipient characteristics and variables based on its starting materials, their origin and manufacturing processes. This ensures a science and risk-based selection for a robust formulation by taking into account the use and function of the excipient in the finished drug product.

Additionally, supplier qualification processes should include an evaluation of the manufacturer's adherence to quality standards and, more specifically, to excipient GMPs. This will ensure – beyond mere product purity and safety – a commitment to change management and notification procedures. This safeguards product performance throughout its lifecycle and ongoing regulatory compliance with product registrations.

Ali: Today, more than ever, the pharma industry is looking to build relationships with solution providers and not just suppliers of raw materials. This is critical in situations involving advanced raw materials that are either single sourced or where alternative options are limited.

Some important questions to ask are i) Is the raw material manufacturer willing to commit to a long-term relationship? ii) Can these suppliers help meet the stringent and increasing regulatory burden required to bring the end product to market? iii) Is the supplier financially stable and will they be in business in the coming years? iv) Does the supplier have the proper supply chain network with full end-to-end visibility and transparency (i.e. for security and special storage requirements)? v) Does the raw material meet the drug manufacturer's specifications? vi) Is there a documented and verifiable quality system in place to provide the essential information, such as, specifications, labeling details, safety data sheet, certificates for quality systems, residual solvents statements, BSE/TSE evaluations, analytical test methods and etc.?

In addition to supplying raw materials/excipients/ ingredients what are some other value-added services suppliers of the products can offer their customers?

LePree: Indispensable are the services of excipient suppliers that work closely with their customers to better understand their needs and who take action to address them with pertinent information on their excipients in the form of application notes, publications and guidelines. As a further step, excipient suppliers could offer laboratory services, free of charge, to assist their customers with formulation development problems.

Elder: A good dialogue with the excipient supplier is a value added activity. Suppliers need to understand their customer's needs, but equally customers need to understand what suppliers can and can't do. For example, asking excipient suppliers for "batches" at the extreme ends of the excipients specification in order to stretch the resultant drug product in a QbD fashion may well be impossible if the supplier is operating a continuous process.

Sloane: In addition to the global availability and supply of the raw material itself, a raw material vendor should be viewed as a key partner not only in the supply of those raw materials, but in the development of the customers' dosage form itself. The vendor should be trusted to provide the right type of information & guidance to recommend the appropriate fit for purpose excipient. This is extremely important in solid dose farms which can be, and are manufactured using several manufacturing techniques; each one requiring a unique grid of excipient selection.

The excipient vendor must also be relied upon and trusted, to provide a regulatory service. This may seem obvious, but it is important not only that the excipient choice is fit for purpose, but will be provide the path of least resistance when it comes to FDA, or other regulatory body scrutiny of the drug product filing itself.

Zeleznik: Many ingredient suppliers offer services beyond simply providing ingredients. Some offer formulation assistance while other imbed personnel at customer locations to guide development and scale-up of manufacturing processes. Still other suppliers assist with analytical method development. While this can be important, it cannot replace suppliers' ability to provide quality ingredients.

Bracquiné: Drug product manufacturers and ingredient suppliers work together today as partners to develop, manufacture and maintain life cycle support. This partnership is focused on achieving quality compliance and resource efficiency.

Beyond valuable knowledge about their products, suppliers with extensive experience in formulation provide the expertise needed to address formulation challenges. As every compound and development program is different, involving suppliers in product design helps Capsugel to provide a tailored approach to optimally meet our customer's specific target product profile and commercial objectives.

Ingredient suppliers offering products under independent excipient GMP certification (such as EXCiPACT™) provide evidence of compliance with expected GMPs and facilitate regulatory compliance. This EXCiPACT™ certification may replace the on-site auditing, saving time and resources.

Further, carefully selected ingredients suppliers using robust qualification procedures may qualify for a lean incoming control process under optimized resources, without jeopardizing a guaranteed release of a high quality and compliant product.

Operating in a highly regulated environment requires suppliers of excipients to invest in ongoing regulatory expertise and to have deep experience and understanding of changing excipient requirements. This expertise should be continuously shared through information about regulatory compliance on evolving or emerging topics and the organization of exchange platforms with experts or dedicated notifications.

Ali: Storage and the ability to build inventories in warehouses in relative proximity to customers is oftentimes a requirement for raw material suppliers to provide high service levels. BASF maintains safety stock in North America based on customers' forecasts. Our logistics and supply chain group is proactive and works closely with manufacturing sites to ensure raw materials are available with all the required documentation, such as certificates of analysis and material safety data sheets. Additionally, first pass quality and on-time delivery are viewed as some of the most highly value added services.

How has the globalization of the pharmaceutical industry affected the quality/supply/cost of pharmaceutical raw materials?

LePree: Globalization of the industry has improved the quality of the excipients as critical quality attributes must be met for several regional standards, including the US, Asia and Europe. This could increase the excipient cost as several quality standards must be met, and the quality must be built into the manufacturing of excipient, including appropriate materials sourcing for the excipient, appropriate process controls during manufacture and testing for release.

Elder: Globalization has had a positive impact on supply and cost, but unfortunately quality seems to have been adversely affected. There are still far too many examples of failure of basic cGMP at CMOs and CROs. In addition the increased incidences of counterfeiting speak to the intrinsic problems of supply chain integrity.

Sloane: The globalization of the pharmaceutical industry has required many excipient manufacturers to set up manufacturing operations that are geographically close to their customers. This also extends to suppliers having multiple sites that are capable of providing laboratory or technical support, in addition to local sales offices. This certainly adds significant cost to the vendor of the raw materials, but it is necessary as speed to market of the finish drug product is always a primary concern. Thus it is imperative that excipient vendors are able to react and respond in a most efficient and effective manner possible. Having multiple manufacturing plants also provide customers with supply security and assurance that the global pharmaceutical customer requires,

More recently we have seen mergers and acquisitions within the excipient supply landscape, as vendors try to add breadth to their portfolio of offerings to the global pharmaceutical industry.

The globalization of the pharmaceutical industry has also seen increased focus and scrutiny on pharmacoeconomics, within diverse geographic markets. This is turn drives manufacturing and product strategies at most major excipient manufacturers, who participate in the global market.

Zeleznik: Globalization has created two diametrically opposed effects. First is the development of specialized, unique materials to differentiate suppliers. These are the ingredient manufacturers that will provide long-lasting innovations benefiting both drug product manufacturer and patient. The second effect is greater competition and the commodization of ingredients. This, unfortunately, is a race to the bottom. As a result of cheaper (cheaper vs. value) ingredients, quality and consistency might suffer with time. And, because standards are not universal, ingredient safety could also be compromised. It will be important for regulators to monitor the global supply chain if this is to be avoided.

Bracquiné: In recent years, several highly publicized contamination incidents have underscored the challenges associated with the increasing complexity of global supply chains and outsourcing. Good Distribution Practices (GDPs) provide guidance on best practice related to transportation, distribution and warehousing to ensure product integrity and quality. The ultimate aim is to provide door-todoor reliability throughout the value chain around the world.

The globalization of the industry also introduces the challenge of meeting the requirements of all target markets in an environment which is highly regulated but not harmonized. It is critical that excipient producers engage with customers to clarify where the finished product will be marketed or intended to be marketed in the future. This will not only mitigate the risk for regulatory barriers, but also opens the opportunity to design products that maximize the specific future market potential.

Ali: All BASF products are available globally. Having such a vast portfolio of excipients also brings complexities and unique opportunities as more drug products are being manufactured outside the United States in other parts of the world. The regulatory requirements can also be different for raw materials used in different dosage forms (orals, parenterals, topicals and biologics). The qualities of the raw materials and their compliance with the compendia (USP, EP and JP) are crucial as these high functional excipients find their ways into multiple formulation dosages depending upon the allowed daily intake (ADI). With the drug industry moving towards continuous manufacturing and the use of process analytical technologies and quality by design approaches to develop robust manufacturing processes, the quality of raw materials is more critical than ever before. As the industry moves forward and continues to transfer technology and manufacturing across the globe, a quality supply chain will be a key factor when evaluating excipient suppliers.

What do you see as the future for raw materials/functional excipients/ ingredients? Will suppliers continue to provide more advanced products? Will products have broader applications? Will product applications become more specific?

LePree: Excipient manufacturers could offer more advanced products (new excipients?) to overcome difficult formulation challenges including solubilization of poorly soluble compounds, stabilization of labile compounds and stabilization the physical state of the compound in the drug product (amorphous and polymorphic forms). However, the advances will be tempered by the industrial end users who must decide if the benefits of the advances warrant additional toxicological studies if such data for the excipient are not available.

Elder: Although there is clearly a need for newer and better functional excipients, the economics from a supplier perspective is still very challenging. In particular, the costs for performing long term safety studies can often be prohibitively high. The Innovation and Quality Consortium (IQ) and IPEC-Americas have established a collaboration to assess the intrinsic challenges of novel excipient use, and to identify potential solutions. IQ and IPEC-Americas are currently exploring regulatory pathways to facilitate and enable the use of novel excipients.

Sloane: The future for raw materials will indeed become more specialized. It will require vendors to focus in their specific areas of expertise, or to expand into other areas (via acquisition or merger) to continually develop new products and services that bring value to their pharmaceutical customers. There will continue to develop and evolve synergistic, co-processed excipients that will provide unique manufacturing benefits or efficiencies. Additionally pharmaceutical customers, particularly those in the OTC market, where consumer preference is a key differentiator, will look to excipient providers to develop excipients with consumer appeal, this will enable those customers to further different differentiate themselves from their competitors by offering their drug to consumers that appeal to them in terms of taste, appearance, or efficacy.

Undoubtedly, regulatory and quality expectations of excipients will continue to increase, which will put more pressure on excipient companies to invest in the areas. World class manufacturing operations are the expected norm, for any excipient company involved in the supply to the pharmaceutical industry. Last, but certainly not least, scrutiny of an excipient manufacturers supply chain will continue to be an area of focus from customers. Not only to assure themselves of uninterrupted product supply, but that supply is secure from tampering and any form of adulteration.

Zeleznik: Suppliers, at least those focused on the pharmaceutical industry, will continue to development materials with greater performance. Given the challenges that each new API brings, there will be a continued need for new and better performing formulation ingredients. Some of these new materials will be more broadly applying; however, every indication is that more of these materials will be developed to meet specific needs and challenges.

Bracquiné: As demonstrated in several scientific studies over the past decade, excipients are not inert substances. Infact, they may play a role, for example, in mitigating multidrug resistance (reversibly inhibiting protein receptors such as the P-glycoprotein or Breast Cancer Resistance Protein) and mediating metabolism (sub-enzyme families such as the CYPs). While there has been an initial reluctance to acknowledge and describe such an active role, the scientific community will continue to articulate and expand such evidence and bring it to the regulatory authorities' attention. This will lead to a more open and robust dialogue and the development of comprehensive guidelines on the use of such materials.

Formulators work with compounds that are increasingly complex. Access to powerful tools will only benefit pharmaceutical development as a whole.

Suppliers will continue to investigate, develop and innovate through more advanced products that, for example, target specific applications such as targeted delivery of drug product to the small intestine. This is evidenced by the recent launch of Vcaps® Enteric and enTRinsic®, two unique capsule based platforms that bring a high level of complexity through inherently enteric and gastro-protective functions.

Ali: The industry continues to explore excipients in multiple formulation platforms which include instant and modified, solubilization, skin delivery and biologics. With many of our ingredients having high functional properties, they are suited for multiple dosage formulation applications including binders, solubilizers, and/or coating polymers. Ingredients have been used as a solubilizers for poorly soluble drugs in solid dispersions such as melt extrusion, spray drying, and electrospraying among others, but it also opens doors to opportunities for broader application in topicals, ophthalmic, and novel formulation delivery technologies. Suppliers continue to play an important role in working with the innovators and generic companies alike to enable new drug products as well as generic chemical entities and bring them to market faster and more efficiently.

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