Panel Discussion on Parenteral Drug Manufacturing

Dear Readers, we are pleased to present you the second Pharma Horizion Panel Discussion for 2018.
This time the topic we asked companies to express their opinion on is the Parenteral Drug Manufacturing Process.
Eight enterprises accepted to join this project: Bormioli Pharma, Corden, Grifols, Lyophilization Technology, Pia Group, Piramal, Shl Group and West Pharmaceutical Services.

All of them were offered the opportunity to think about and provide their thoughts on some different aspects related to the discussion topic. Among them, future perspectives on technical and manufacturing process advancements, the relevance of quality by design, opportunities and treats related to the prefilled syringes world, how to address the mandatory aspects of sterility, quality, productivity and safety of the products, packaging and standardization issues.
Here are their opinions. Enjoy the reading.

PANELISTS

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HOW TO FACE THE GLASS VIALS WAVE OF INNOVATION LEVERAGING ON PROCESSES

Improving glass vials performances starting from quality by design approach

Anna Malori - Bormioli Pharma

In the world market for parenteral products, glass vials continue to be the most widely used primary containers, mainly thanks to strong barrier properties and a broad range of applications served. This trend is expected to be confirmed also over the next years, with a global demand for this type of container that will reach $5.7 billion in 2024 (1).

> The packaging innovation drive: improved shatterproof and chemical-resistant properties as well as security features

From the packaging manufacturer standpoint, the increasing demand for parenteral glass vials results in a constant need for innovation and product development. If we look at the product development activities carried on by the biggest packaging manufacturers in the world, we can easily identify the innovation drive: improved shatterproof and chemical-resistant properties as well as security features. In a few words, packaging manufacturers are focusing on improving glass vials performances.

However, innovating in the parenteral packaging sector means necessarily dealing with the strict regulatory framework for this type of products. The regulatory approval procedures can take years and that is why each single change in the glass vial configuration may be seen as an obstacle towards the final drug product approval. The real challenge that packaging manufacturers must face is indeed matching the need for improved glass vials performances with the standardization need expressed by the pharmaceutical companies.

In order to answer this need, we decided to improve glass vials performances leveraging on the processes behind the product, rather than acting directly on the final product features (i.e., glass composition). This way of intending product innovation results from the QbD (Quality by Design) paradigm, an integrated approach to development, manufacturing and quality, increasingly spread across the pharmaceutical market. In our experience, this implied a full commitment at all levels in the technical organization, starting from Engineering, Operations, Quality and Technician. The contribution of each function was essential to develop an advanced manufacturing technology and to set up robust controls along the whole manufacturing process. The result is a glass vial product having excellent mechanical performance and optimal chemical, dimensional and thermal stability.

Such a superior glass vial positively impacts both patients' health and pharmaceutical companies, ensuring drug stability of today's complex parenterals while minimizing regulatory impact and routine packaging challenges – delamination, leaching, thermal shock, and breakage-.

That is why technological advance in manufacturing process can be the key to rethink innovation in parenteral glass vials.

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1. Freedonia (2015), *World Pharmaceutical Packaging Industry Study #3269*, pp. 73-75

HOW THE SHIFT TO COMPLEX, TARGETED CANCER DRUGS IS RESHAPING PARENTERAL DRUG MANUFACTURING

Jason Bertola - CordenPharma International

Over the past 20 years, Oncology Drug Product development has experienced significant change. Mass-market cytotoxic agents have given way to more complex, potent, and targeted therapies that serve smaller patient populations. This shift, although good for the patient, has put strains on parenteral drug manufacturing plants. Manufacturers that used to dedicate significant production capacity to products like Paclitaxel, now face the logistical and technical complexity of filling capacity with small volume programs for multiple drugs.

The pace of change is illustrated by data from the industry pipeline. Cytotoxic drugs now account for 8% of the cancer pipeline, down from 15% in 2006 (1). Over the same period, targeted biologics' share of the pipeline rose from 21% to 43%. These pipeline changes have reshaped the activities of the companies that manufacture injectable oncology drug products.

> Contract manufacturers can expect to see a continued shift toward more complex formulations and potent compound targeted therapies

Production in the targeted therapy era

The production workflow of modern drugs is more challenging than the dissolve, filter, fill, cap & clamp, and ship process. Now manufacturers deal with complex drugs, and by extension, more challenging formulations. For example, liposomal formulations and antibody drug conjugates are more complex to manufacture than traditional chemotherapeutics.

Targeted therapies act on specific molecular targets associated with cancer. As such, they do not provide benefits to all patients. Ultimately, this also affects contract manufacturers by reducing the volumes their customers require.

Low volumes and complexity affect the economics of manufacturing.

Having flexibility while achieving high utilization rates is the key to success. While older production lines may present a challenge to remain compliant with regulations, justifying an investment/expansion is more complex today. Manufacturers must manage these challenges while meeting customer timeline expectations. With accelerated development pathways removing some constraints on the pace of progress, the onus is on manufacturers not to slow the advance of therapies.

The risk associated with the oncology manufacturing development process can be mitigated by applying a Quality by Design (QbD) philosophy to the development program. This yields better understanding of the process and ultimately increases the robustness and strength of the regulatory package. This is critical in a highly potent environment because there is no direct access to drug product, limited visibility and possibilities of interacting (troubleshooting), along with other restrictions to maintain containment.

The future of parenteral drug manufacturing

Today's oncology drug development pipeline suggests contract manufacturers can expect to see a continued shift toward more complex formulations and potent compound targeted therapies. Although, companies continue to invest in these capabilities, demand remains strong and is expected to grow. There are over 300 companies with compounds in the clinic, and since many of these are virtual or with limited resource, reliance on CDMOs will continue.

For patients, this means safer, more effective therapies. For parenteral drug manufacturers, it means the era of juggling complex, low volume (high cost per unit) projects will continue.

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1. Global Oncology Trends 2017. Available at: https://www.iqvia.com/institute/reports/global-oncology-trends-2017-advances-complexity-and-cost. (Accessed: 27th December 2017)

PARENTERAL DRUG MANUFACTURING CHALLENGES

Marga Viñes - Grifols International

Parenteral manufacturing products are always a challenging process due to the high cost, pressure from competitors and the requirements of the Regulatory Authorities. This type of products are different from all other pharmaceutical dosage forms mainly because they must be sterile, free from pyrogenic contamination and free from visible particles, even after being reconstituted.

It is a complex and costly undertaking to advance a parenteral drug product. To achieve market and therapeutic success, a range of specific requirements is mandatory. This includes category expertise, integrated, aligned resources, advanced and automated aseptic processing systems, operational excellence and a thorough understanding of the market dynamics that effect parenteral drug markets

In addition to being a crucial indicator of quality for injectable products, the presence of particulates in finished pharmaceutical products can have significant consequences for patients. Clinical effects can range from minor problems to serious complications and even death. In the US alone, approximately 190 million liters of intravenous fluids are administered to patients each year, and thus particulate matter contamination is a real concern for the pharmaceutical industry.

> A parenteral product is not just another item; behind each product there is a patient, and we should never forget this

It well established that parenteral drugs and therapeutic fluids require highly controlled, sterile process environments to be manufactured correctly and to current GMP standards. Processing parenteral drugs is extremely challenging and any review of drug recalls over the past 10 years will confirm this. Safety and quality requires a tremendous focus on process and understanding of process technologies as well as an extremely well integrated and aligned quality system backing it up.

The process required for preparing sterile products starts with the procurement of approved raw materials, (drugs, excipients etc.) and primary packaging components (containers, seals, labels…) and ends when the sterile product is properly sealed in the container. Each step in the process is controlled and validated carefully to guarantee the quality required. Process validation is an integral part of cGMP requirements, and is intended to ensure the safety of the product

One aspect of Grifols' commitment to quality has been extensive investment in automation technologies to reduce the risk of error and contamination, and increase both operator and patient safety.

We have both "Form-Fill-Seal" technology for the production of polypropylene bags and fully automated glass vial filling lines designed to minimize human interactions with drug products. Artificial vision systems (developed in collaboration with Diagnostic Grifols) also enable the automatic inspection of injectable products for particulates, avoiding the potential for human error in this important unit operation

Everyone involved in the manufacturing process must adopt the right attitude in order to accomplish all the safety requirements.

A parenteral product is not just another item; behind each product there is a patient, and we should never forget this. Our work ethics and responsibility form part of the commitment made by the pharmaceutical industry towards the patient.

IT IS MANDATORY TO DRIVE FUTURE PROGRESS AND REMOVE BARRIERS TO IMPLEMENTING INNOVATIVE TECHNOLOGY, FOCUSING ON A REAL APPLICATION OF QUALITY BY DESIGN

Edward H. Trappler - Lyophilization Technology

There has been a significant expansion in the number of parenteral products. According to Genetic Engineering News (www.genengnews.com), of the 10 best-selling drugs in 2016, with sales totaling $60.9 billion, 7 were parenterals, of which 3 are self-administered. The top seller totaled $16 billion, and is available as a prefilled syringe and an auto-injector. The industry faces new and different challenges in moving from developing products to treat prevalent ailments, to less common conditions having orphan designation, to personalized therapeutics. In addition, the steady increase in parenteral products has led to the investigation and use of alternative drug delivery devices for ease of administration and improved patient compliance. These include a prefilled syringe and an auto-injector, or "pen". For products requiring a greater dose, large volume wearable injectors (LVWI) are under development as a new delivery system. The rapid growth demands an increased focus on better integration of product, quality, and manufacturing method development.

> It is mandatory to drive future progress and remove barriers to implementing innovative technology, focusing on a real application of Quality by Design.

As an industry of scientists, engineers, and regulators we must find ways to drive future progress and remove barriers to implementing innovative technology. At the forefront is a focus on the essential characteristics as a new drug progresses through the development pathway: Not only in product design, but also in product manufacturing. Forward thinking clinical trials and methods for improving processing alternate primary packaging and delivery systems, such as employing the use of robotics and other novel aseptic processing to ensure quality are essential.
To achieve these goals, focus on effectively applying true Quality by Design (QbD) is important. This path to pharmaceutical development begins with pre-established goals in defining the product design with the patient in mind. The foundation for successful product design and development is establishing a Target Product Profile (TPP) very early in development. Use of TPP a guide assists in applying QbD principles and brings focus to desired product attributes. These TPPs are morphed into Critical Quality Attributes (CQAs) and allow for ease of QbD and risk-based decisions, and ultimately greater value to the patient. Among the benefits are increased focuses during development and understanding of the unique lyophilized product quality attributes. The result is a greater level of assurance that a product meets the needs of the ultimate end user, the patient, and that the product is suitable for its intended use.

Challenges in product design have broadened from what was needed to get a product to a pharmacist, to now how to best present a product to the patient. One cannot simply take the product and process in a traditional container closure system, and apply it to the future of drug delivery: a cartridge, syringe, or devices for larger dose products administered over a longer time are required. The ability to successfully apply development concepts to multiple drug delivery formats benefits the pharmaceutical industry and patient by reducing the overall time to market, lowering processing costs, and achieving the highest level of product quality. This new paradigm is realizing these challenges and the total cost of delivering a product to a patient.

MEDICAL DEVICES BECOME INTELLIGENT

Hans-Jürgen Schwarz - PIA Automation Amberg

Due to the medical costs in industrialized countries and the lack of medical care in threshold and developing countries the role of self medication will increase significantly. This has started an upheaval within the pharmaceutical industry. Until now the drug has always been of primary importance. Soon the delivery and monitoring of medication will be included in the range of services pharmaceutical corporations offer. In the future the pharmaceutical industry will not only provide the drug but also the appropriate therapy. More and more mechanical medical devices have been developed during the recent years.

> Drug will remain important; the simple handling for the patient will influence the choice of the medical device tremendously

The drug will remain important but the look and feel of the device and the simple handling for the patient will influence the choice of the medical device tremendously. The best drug applied by the worst device will not succeed on the market of self medication. This effect will become even stronger with the next logical step of integration of microelectronics and full connectivity of the device. To make the handling simple for the patients, while taking into account different knowledge levels, different education levels and different ages of the patient will be a balancing act.
The processing of microelectronic components holds many more new challenges for the pharmaceutical industry. Starting with storage and operation of the new devices (insulin pens in domestic households have to be refrigerated at 8°C) and continuing with the application of the insulin at ambient temperatures that can range from 8° up to 40°C and at different humidity levels. The medical device has to work properly under all conditions.

Achieving safety and simplicity for medical devices will raise a lot of questions pharmaceutical enterprises will have to face:

- Who will be responsible for the design of electronic components and units?

- How high will the energy consumption of the device be?
- Which energy source will be better? Battery or charger?
- Which battery will be the best one and how long will its life cycle be?
- How do the microelectronic components have to be designed so that they operate satisfactory within a range of ambient temperatures from 8° to 40°C and different humidity levels?
- What about condensation?
- Do the microelectronic components need to be particularly resistant to shock and breakage?
- How can electrostatic discharge and counteraction be handled?
- How will you protect the collected data and patient privacy.

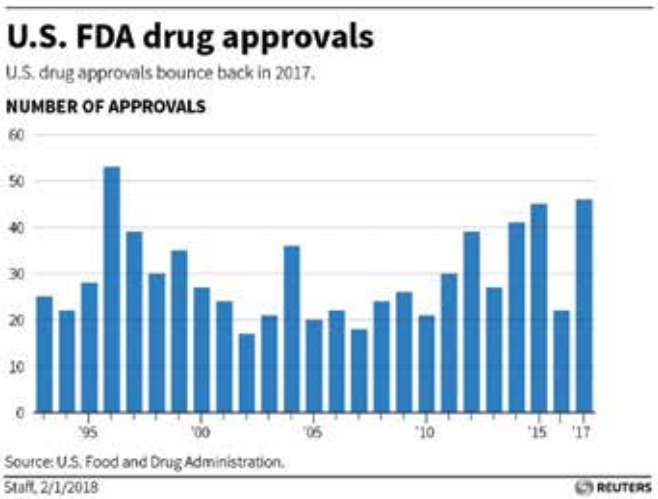
Manufacturers of medical electrical equipment will have to consider the requirements of several standards for the production of their devices. Essential performance, electromagnetic compatibility and the safety of medical electrical devices are covered by the standards EN 60601 and IEC 60601. The medical part of the software within the medical device is regulated by the standard IEC 62304. The manufacturers have to incorporate these guidelines in their everyday production.

The issues stated here only touch on the technical aspects of combining medical and microelectronic equipment. The concerns that come along with data safety and patient privacy will challenge the pharmaceutical industry even more.

A PRICING PRESSURE TO CHALLENGE TROUGH DIFFERENT SOLUTIONS

Adrian Raiche - Piramal Pharma Solutions

FDA approvals for new drugs reached a peak of over 50 in 1996, steadily declining to 18 approvals in 2002. A rise in approvals began in 2007 with 45 new products in 2015 and 2017. Hidden here are two impacts. Firstly, the large number of approvals and patents protecting them resulting in an echo of generic launches. Secondly, the improved standard of care creates a greater challenge for developing the next generation therapies, to once again improve on clinical. As a result, the new molecules push towards more specific disease targets. Both large and small, are complex to manufacture, or cannot achieve the economies of scale associated with the current standard of care. The challenge this creates for parenteral manufacturers is pricing pressure, with a large number of competitors driving lower margins for generic products, and price pressure on finished product production for high-value active ingredients.



Of all the aspects of manufacturing increasing including labor, materials, and regulatory changes, two things are decreasing in cost: data and processing power. This is especially driven by an increase in wireless implementations meaning not only can more data be collected and evaluated, but more conveniently from more places at low cost.

With the publication of ICHQ8 in 2009, the non-regulated development process was no longer viewed as separate from GMP manufacturing, testing, and release. Two elements comprise this approach, quality by design from the development side and process analytical technology on the manufacturing side. Inexpensive, plentiful, and often disposable sensors offer the promise to unite the relevance of QbD studies in the laboratory to batch production in manufacturing.

> Quality by design from the development side and process analytical technology on the manufacturing side

Data and processing power focuses on opportunities created by declining prices. The opposite approach is also being addressed in at least two ways. In the first, the active ingredient cost has a fraction of the whole has increased. As dose filled into traditional vials decreases in volume, the amount of allowable overfill per USP increases from a minimal value of 2% for 50 mL volumes down to 20% for 0.5 mL volumes due to the challenge of aspirating an acceptable dose into syringes from vials. Effectively, placing high value therapeutics in vials creates an inherent waste of approximately 20% of each dose. For every 5 patients treated, a potential 6th is lost. This inherent waste is the motivating factor driving direct filling into prefilled syringes.

The second approach to reducing cost is an outgrowth of the transition to prefilled syringes. Based on nested packaging designs, eight-head filling, and small fill volumes, the inclusion of people slows processing time. This not only decreases processing time, but also makes additional use of data and processing power to directly integrate critical process parameters and critical quality attributes.

Contract pharmaceuticals is confronting new challenges by leveraging decreases in cost for process analytical technology and driving decreases in cost by making sure more patients receive the more doses from the same active ingredient lot. Additionally, transition to different container closures is enabling direct feedback between new measuring technology and finished pharmaceutical product.

SAFE AND EFFICIENT DRUG DELIVERY

Magnus Fastmarken - SHL Group

We all know it: drug development is long, costly and filled with risks. With development timelines often longer than 10 years from discovery to regulatory approval, forward planning is key. What will the healthcare system look like at the time for launch? What will be the willingness to pay and the therapy trends? Adding a drug delivery device to the mix makes the calculations even more complex. Will the device live up to future standards and can we add features like connectivity in the future? Even more important, will the device live up to regulatory requirements throughout the whole life cycle, 20 to 30 years after launch? When developing a device, what's involved is so much more than meeting the functional needs for drug delivery. A suitable device developer is one that profoundly understands the industry and can assess both current and future regulatory requirements to develop a device that goes further.

> A total integration between device and machine development can guarantee faster communications and tighter quality control.

Auto injectors are by nature designed to be handled by patients without the supervision of healthcare professionals. They must be safe and intuitive in order to support patient convenience and compliance. To achieve this, a device provider must work closely with its pharmaceutical partners to develop devices based on human factors studies to understand how the patient understands the device.

Then there is the fact that the delivery of drugs carried in auto injectors relies on the intricate interaction between the primary container and device components. For developers of auto injectors, the leachability of syringes and primary containers needs to be carefully assessed to establish the optimal packaging and delivery solution to ensure product stability. The recent increase of biologics to treat chronic conditions has brought this important factor into focus.

Auto injectors for subcutaneous or intramuscular injections offer patients the opportunity to administer their treatments in the comfort of their own homes. However, the complex structure of biologics poses a technical challenge to traditional injection devices. As large molecules, biologics need to be formulated in high concentrations in order to achieve efficacy as well as to prolong the duration between treatments. This results in an exponential increase in the drug's viscosity. Because biologics have a higher potential for destabilizing or aggregating in the pre-filled syringe, stabilizing the drug or decreasing its viscosity with excipients can also cause the volume to increase.

On a technical level, higher volumes and viscosities pose a challenge to the drug's syringeability, in other words, the ease with which the formulation can be pushed through a needle. For the patient, a long and viscous injection may also result in increased discomfort and user anxiety. As a result, the delivery of these types of biological formulations call for a powerful and stable means of delivery. In order to ensure safety and support patient comfort, the delivery mechanism should also be complemented by a patient-friendly design.

While auto injectors using pre-filled syringes are designed with permanently hidden needles, cartridge-based solutions require the user to manually attach the needle onto the device. This not only makes it less convenient for the patient to handle, it also poses the challenge of avoiding contamination and preventing needlestick injuries.

Cartridges offer a broad range of options for fulfilling various drug characteristics and therapeutic needs, including for both single and dual-chamber therapy solutions. The challenge to support patient convenience and increase sterility and safety can be addressed with a unique solution where the needle is pre-installed in the device and automatically attached with a simple initiation process prior to injection. With the needle permanently hidden throughout the entire process, the risk of metal contamination can be mitigated.

However, an impressive industrial design, effective delivery mechanism and a unique safety solution for cartridge-based auto injectors are only useful when the product and components can be produced for scalable, high-volume manufacturing. As the FDA's Quality by Design promotes continual improvement in quality across the entire lifecycle of the product, a device developer that designs, develops and manufactures devices, and also much of the machinery that produces the devices in-house, can successfully support this objective. A total integration between device and machine development can also guarantee faster communications and tighter quality control, resulting in a smooth transition between each of the development and manufacturing stages, and a fully integrated service from device design to commercialization.

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MORE THAN HAVING AN EFFECTIVE MOLECULE

Graham Reynolds - West Pharmaceutical Services

Effective drug therapy requires more than having an effective molecule. It involves the combination of a safe, effective drug within a suitable container or delivery system designed with the end-user in mind. This is especially important with the increase in both in-home self-administration and new biologic and biosimilar medicines to treat many chronic, autoimmune diseases.

To ensure safe, effective delivery of injectable medications, there are four considerations that drug manufacturers and their packaging delivery system partner should contemplate early in the development process.

Compatibility between the drug and its container
It is critical that the container material is safe to pair with the injectable drug product. This can be especially challenging with sensitive biologics—drug containment and delivery systems must have the ability to prevent drug product alteration and maintain container closure integrity, even in cold storage.

It is important to explore all available options for containment materials. While glass is suitable for many pharmaceutical products, high pH drugs or otherwise sensitive drug products may be incompatible with glass vials or syringes; therefore, it may be beneficial to consider containers made from alternative materials such as cyclic olefin polymers.

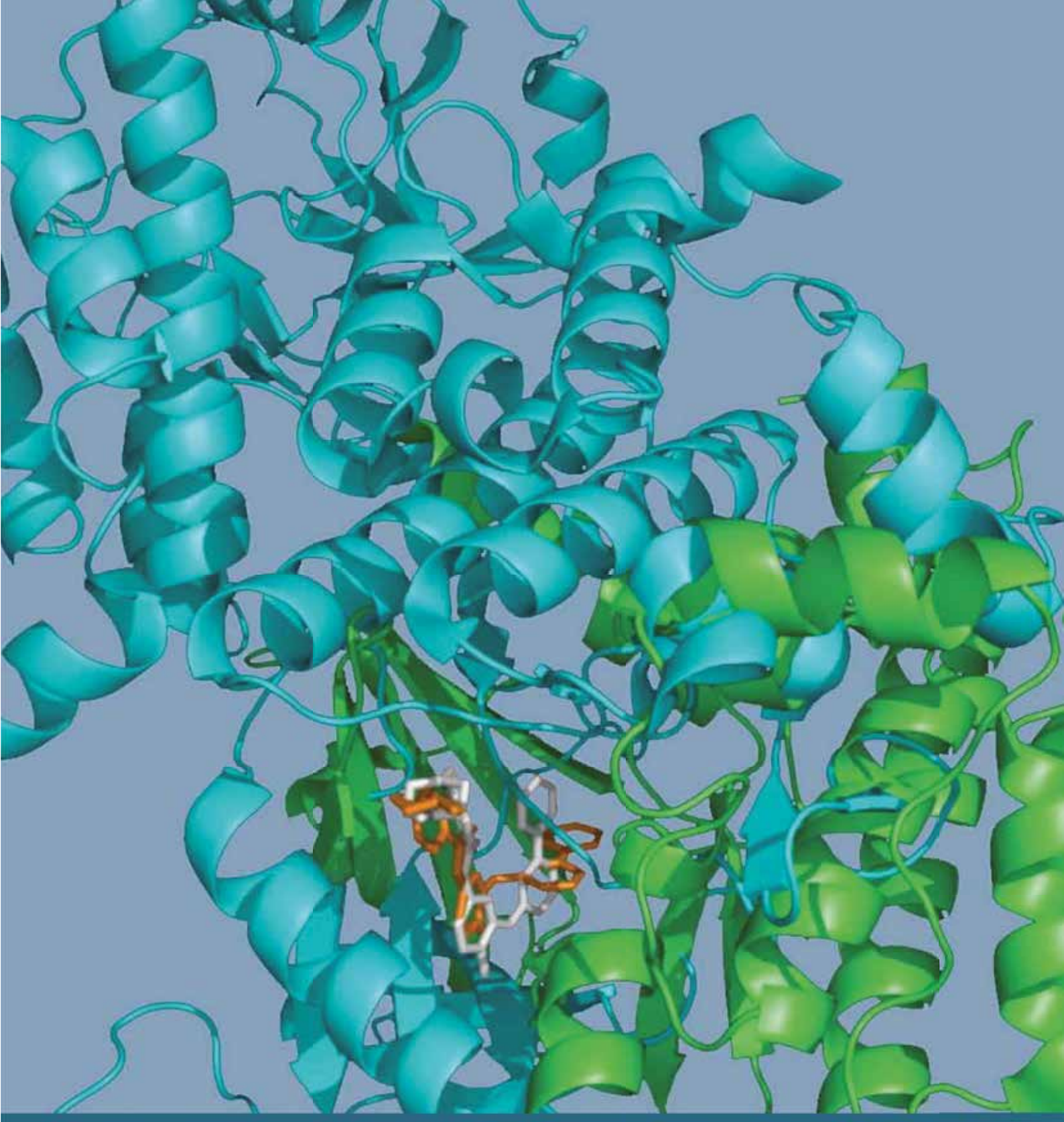
> Working to produce dugs in a safe and effective integrated containment and delivery system that benefits manufacturers and patients alike

Building in quality from the start
Drug packaging components play a vital, but often overlooked, role in drug safety and efficacy. To ensure high levels of reliability, consistency and compatibility with sophisticated drug products and delivery systems over the course of their lifecycle, the adoption of Quality by Design (QbD) concepts in the design and manufacturing of packaging components is paramount. When designing and developing a product using QbD principles, manufacturers must define desired product performance goals and identify Critical Quality Attributes (CQAs). The product and process can then be designed to meet those CQAs, enabling manufacturers to ensure consistent product quality, potentially improving functionality.

The interface between the container and its delivery system
Once the primary container system and components are selected, focus on the interface between the primary container and the delivery system is important. Testing dimensional tolerances and functionality can ensure proper activation and gliding forces in a system. Without this, there is potential for a number of patient safety issues, including breakage (in an auto-injector with a glass prefillable syringe, for example) and incomplete dosing.

Ensuring patient centricity
Perhaps the most essential consideration is how the patient will use the drug delivery system. A drug can only provide therapeutic benefit if it can be delivered effectively and the patient adheres to the treatment regimen. To that end, it is critical to understand the patient journey and—through human factors analysis, for example—build drug delivery systems that are intuitive, non-intimidating and, when possible, less painful for the patients.

By partnering with a packaging and delivery system partner that possesses strong scientific expertise, proprietary technologies and a thorough understanding of the patient journey, drug manufacturers can ensure these key considerations are addressed early in the drug development process. The end result – a drug introduced to the market in a safe and effective integrated containment and delivery system that benefits manufacturers and patients alike. ■



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