Controlled Release Roundtable

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An interview with:

- *William Wei Lim Chin, PhD - Global Scientific Affairs - Catalent*
- *Robert Dream - Managing Director - HDR Company LLC*
- *Adam Lambert, PhD - Vice President, Product & Process Development - Pharmatech Associates*
- *Andriy Kuzmov, PharmD, PhD - Drug Delivery Innovation Fellow - Catalent*

Looking back at the past year, what are some general industry trends that have resulted in more emphasis being placed on developing controlled release products?

William Wei Lim Chin, Ph.D. Manager, Global Scientific Affairs, Catalent: Historically, the development of controlled release products has been predominantly driven by brand owners' strategies to extend a product life cycle by developing controlled release variations of first-marketed, immediate release products. However, more recently motivations have turned more to addressing unmet clinical needs, such as reducing frequent dosing regimens to increase patient adherence; improving the pharmacokinetic (PK) profile of a drug to sustain the desired therapeutic concentration of drug in blood; and to attenuate adverse drug effects by avoiding high peak blood concentration. The demand for more convenient dosing intervals has steered development towards once daily administration of oral controlled release dosage forms, but to decrease oral dosing further, several companies have begun the development of gastro-retentive dosage forms that extend the oral dosing interval to once weekly. There has also been interest in the development of long-acting parenteral formulations, which could allow for monthly, and sometimes longer, dosing intervals.

We have also seen demand grow for rapid onset with innovation in orally disintegrating tablets (ODTs) for pain management and oral delivery of allergy immunotherapies. Ultimately, the interest in the development of controlled release dosage forms is driven by the desire to improve patient outcomes in disease states where consistent and predictable exposure is critical.

Robert Dream, Managing Director, HDR Company LLC: The global controlled release drug market has observed a graph that represents substantial growth over a short time. The growth in the market revenue and size is primarily due to an increase in the number of human disease cases over the years. The market is adjoined by world-class therapeutics for fighting diseases such as diabetes and dementia conditions but the unwanted results from the drugs

The global controlled release drug delivery technology systems market size will reach US$70B by 2026. According to market research reports;

- Global controlled release drug delivery market will reach US$70B by 2026
- US and Europe market share more than 65% (2019)
- US and Europe to double in market sales by 2026
- Number of controlled release drugs available is more than 140.
- There are more than 250 clinical trials taking place for controlled release products.

Adam Lambert, Ph.D., Vice President, Product & Process Development, Pharmatech Associates: By far, it is the repurposing of existing approved drugs for the treatment of COVID-19 symptoms. And the effort has been monumental, with over 500 clinical trials initiated evaluating drugs. Remdesivir, corticosteroids, and heparins are examples of drugs successfully repurposed with demonstrated efficacy in treating COVID-19. Along with repurposing drugs, significant effort has been put into delivery strategies as well. A lot of drug candidates have associated side effects and administration difficulties that either limit their ability to reach patients with severe disease or prevent them from being administered easily outside a clinical setting. Several controlled release and long-acting versions of remdesivir in development are being designed for injection or self-administration to eliminate the need for infusion, thereby allowing greater patient access. These trends and developments - taking place over the past year - underscore the importance of controlled release dosage as an important delivery strategy for the treatment of disease.

Specifically looking at the COVID 19 pandemic, has this public health crisis changed the way [that] controlled release products are developed?

Chin: In principle, the technical considerations underpinning the development of controlled release products from the perspective of development, manufacturing, and the technology selection have remained constant. But the COVID-19 pandemic could perhaps be a launching point for a wider increase of interest in developing universal antivirals against influenza viruses and coronaviruses to prepare for further outbreaks. As more research efforts are put into discovering new molecules to target a wide range of viral pathogens, it is expected that the physiochemical properties of such molecules may result in unfavorable bioavailability, or a short half-life. The global outlook for the development of controlled release dosage forms of existing antiviral drugs to shorten the duration of infectiousness of the disease seems promising, as this is currently an unmet need for this viral disease. Improving bioavailability, as well as sustaining the effectiveness of antivirals and decreasing any adverse effects, would be the major goal in developing such drugs.

Dream: The COVID-19 pandemic, caused by the SARS-CoV-2 coronavirus, has highlighted the importance of cross-disciplinary collaboration to rapidly develop (within months) effective treatments and vaccines as well as delivery technologies. Many vaccine candidates for COVID-19 entered clinical trials at an unprecedented pace, in part enabled by the repurposing of delivery systems developed for other therapeutics (oncological drugs, in particular). Vaccine delivery systems have used controlled-release strategies to prevent the need for multiple rounds of injections as well as non-invasive delivery to facilitate patient acceptance and widespread availability. In particular, mRNA vaccines and DNA vaccines can be effective tools for responding to emergent infectious diseases because these vaccines can be rapidly synthesized in vitro and can rely on modular delivery systems with plug-and-play designs. This is the case of the first two COVID-19 vaccines approved for emergency use in the United States (mRNA-1273, developed by Moderna, and BNT162b2, by Pfizer in collaboration with BioNTech), which uses a nucleoside-modified mRNA encoding for the prefusion-stabilized SARS-CoV-2 spike protein. The delivery system for these vaccines is a lipid nanoparticle with ionizable cationic lipids, and was developed on the back of decades of work in technologies for the delivery of siRNA and mRNA. The need for the rapid development of vaccines and for improved global access to vaccines has also motivated the development of other delivery technologies. COVID-19 has heightened the need for universal vaccines and treatments that can raise immune responses to classes of pathogen rather than to a single pathogen.

Lambert: How products are developed has not substantially changed in terms of scope and context, but what has been impacted is the planning and execution of development experiments. Many companies have been operating on split schedules to give opportunities for remote work, in combination with on-site experimental work. This means more emphasis is being placed on studies planning and write-up than has been typically allowed. While the impact of increased time for planning and evaluation on development timelines remains to be seen, one can speculate that fewer mistakes at the bench and increased analysis time will improve the overall product quality as products move through development.

As COVID 19 has demonstrated, the need for the rapid development of vaccines is essential to public health. Considering this, have you changed your business at

all to focus on vaccine development? Or, is that something that is out of the realm of controlled release technologies?

Andriy Kuzmov, Pharm.D., Ph.D. Drug Delivery Innovation Fellow, Catalent: Like all essential businesses, and others that are coming to terms with operating with some altered ways of working, Catalent has adapted to protect its employees, and continue the supply of essential medicines.

Most vaccines are out of the realm of controlled release technologies and applications. Catalent's efforts have largely been focused on repurposing capacity and expediting expansion plans that were in place before the pandemic. These plans have focused on the unprecedented demand for vaccines, and Catalent's output will likely exceed one billion doses in 2021.

The company's core capabilities, in providing integrated development, manufacturing and supply solutions, have remained unchanged, but almost every aspect of our business has changed in some way: from remote work; accelerated speed-to-contract; and new channels of communication between innovators and development and manufacturing partners. Many of these practices will likely survive long after this pandemic.

Dream: In conjunction with development of vaccines to treat COVID-19, the industry employs existing technologies and drug products at hand. For instance, the HIV drug combination lopinavir and ritonavir, which is under evaluation as a COVID-19 treatment, has side effects that include diarrhea, nausea, and liver damage. These drugs have a half-life of about four to six hours and systemic concentrations can vary by a factor of eight between peak and trough. Developing a controlled-release formulation that maintains the minimum effective drug concentration could mitigate side effects by reducing the steady-state drug concentration by as much as eight-fold and reducing the burden on the liver by 81%.

Targeted drug delivery may offer a similar or better ability to reducetoxicity in some cases, particularly for respiratory infections. Because the lungs comprise only about 2% of the total body weight, targeted delivery could reduce the amount of drug required by a factor of 50 or more compared to oral administration. A promising approach is the hitchhiking of drug-loaded nanocarriers on red blood cells - intravenous administration of these constructs improved delivery to the lungs by about 40-fold - which could be used to achieve an effective local concentration without requiring a high systemic drug concentration. The preparation of inhalable particles for local delivery is a simpler approach.

When a pharma company needs the services of a controlled release technologies provider what are some questions that should be asked, and what are some key expertise the provider should have?

Kuzmov: The first step in the development of a controlled release dosage form should include developability assessment of the molecule. Key questions include: what is the total daily dose? What is the dose/solubility ratio? What is the stability profile of the active pharmaceutical ingredient (API)? Is the API absorbed across the length of the gastrointestinal (GI) tract (small intestine, large intestine, and colon)? What is the elimination half-life and metabolism profile of the API? These answers will help determine whether the molecule is a suitable candidate for a controlled release dosage form.

During dose form development, the focus should be on the analysis of available PK data, dissolution and analytical method development, and on the expertise that will be needed in onward development and manufacturing. The development partner should be able to provide a critical analysis of available PK data (often from initial human trials using immediate release formulations). A physiologically based pharmacokinetic (PBPK) analysis of available PK and molecule physicochemical data (stability data, solubility, etc.) can help predict in vitro release profiles for the candidate formulations, which are most likely to deliver the target human PK profile.

Additionally, the partner should be able to support the development of discriminatory dissolution and supporting analytical methods. The development of robust dissolution and analytical methods are important during controlled release development, as they can help distinguish between several early prototypes, and aid in the selection of the most favorable options to progress to animal and human studies. Looking ahead, it should be considered whether the partner has the necessary expertise in the development and manufacturing of dosage forms across a variety of controlled release technologies. Each controlled release project will have unique challenges, from the physicochemical properties of the API, to disease-specific patient considerations. A partner with expertise across a variety of

technologies can ensure the optimal release formulation technology is selected to meet the needs of the project throughout development.

Lambert: In the development of a controlled release dosage form, several critical factors need to be considered. It is important to ask at least the following: Has your controlled release technology been successfully administered in a clinical setting? Do you have experience with chemistries similar to what we are developing? What are the limitations of the technology (i.e., Drug loading, Release Profile, Drug Solubility, Stability)?

The range of experience and capabilities within a provider can vary significantly, but at a minimum all companies under consideration should have expertise in applying their technology to your chemistry and desired controlled release characteristics. Providers should have expertise in moving the product from the bench to a clinical setting. Without the ability to evaluate it in a clinical trial, even the best-designed and developed formulation is of no use to patients or the product sponsor.

Many providers are developing novel excipients, and in those cases, they should be able to provide a clear understanding of the regulatory pathway for demonstrating safety and achieving regulatory approval, and have evidence to support it. Providers should provide detailed development plans and be able to identify critical process parameters that define the performance of the controlled release dosage form. Performance characteristics include release profile, drug loading and product stability. If the provider/partner cannot provide clinical or commercial manufacturing, they should be able to identify partners with this capability that they have successfully transferred their technology to.

Dream:

- What is the current business model? Does it play sufficiently to our strengths?
- What kind of collaboration do our companies want to be in?
- Will our current business model enable us to expand into new markets – be these new products, services or countries – and satisfy the expectations of our customers/patients? If not, what sort of business model will we need?
- What is the size of the gap and how can we reduce it as rapidly as possible?
- Do we have a clear picture of the opportunities and risks entailed by each of the alternatives available to us?
- Do we have a plan in place that will enable us to move forward quickly, while maximizing the opportunities and minimizing the risks?

Looking ahead, how do you see the industry reacting to the COVID 19 pandemic, and how do you see this issue changing the industry and how it develops products?

Chin: Transactional relationships limit our industry's potential to develop and commercialize important medicines that benefit patients efficiently. During the pandemic, we have seen the value of strategic partnerships. Through close collaboration throughout supply chains, the pharmaceutical industry is in a position to respond better to dramatic changes, and continue essential operations to maintain supplies of often life-changing medicines, as well as respond to the demand for billions of doses of vaccines.

Perhaps the most enduring lesson from the pandemic will be that our industry can operate safely at pace. Through a strong sense of shared goals and responsibility, we have seen changes from initiating discussions to contracting, through to regulatory review and worldwide distribution. We have seen our teams working tirelessly to meet the urgent demands of fighting COVID-19; but I think the legacy will see us retain the best parts of our changed routines, and timelines will likely be shorter than before the pandemic.

Dream: London Business School Professor Michael G. Jacobides recently argued that successful companies do not compete in a sector; they shape the nature of a sector, they redefine the part of the value chain they occupy, and keep most of the value add through the intelligent design of their collaboration with others in the sector. Thus, collaboration is not just a tool for doing the same things more effectively. At its most powerful, it can reshape an entire market, as Apple has shown. Apple redefined the mobile music sector by outsourcing the production of the devices and accessories, while retaining control of the iTunes software.

The sector as holistically as possible will come together to enhance vaccine-drug delivery as a unit and not as competitors. BioNTech in collaboration with Pfizer is an example. Collaboration speeds-up the delivery of needed vaccines to patients helping to stem the tide of the COVID-19 wide spread pandemic by putting together combined knowledge and know-how into practice.

Lambert: Given the nature of the circumstances, Industry has reacted rapidly and efficiently to the pandemic, with development, manufacturing and supply resources shifting to address the public health crisis. One significant takeaway from the pandemic is a clear understanding of the fragility that exists within our supply chain for pharmaceuticals. Single suppliers for critical excipients and APIs caused significant delays in the manufacture of both marketed products and clinical trial supplies. Even if the drug products are made locally, many critical active pharmaceutical ingredients are manufactured in India and China. Disruptions in shipments from these geographically distant locations caused shortages of critical medicines, expanding the health crisis beyond that of COVID. These issues have increased awareness of supply chain risk mitigation by manufacturers, who will need multiple sources for critical drug product ingredients. Onshoring of the synthesis and manufacture of drugs deemed critical to healthcare will be a factor in drug development going forward.

Formulation Development »

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