DOSAGE FORMS ROUNDTABLE: **JEREMY DRUMMOND**, MEDPHARM; **STEPHEN RODE**, LONZA; AND **TORKEL GREN**, RECIPHARM

Jeremy Drummond joined MedPharm in February 2017. Dr Drummond has spent over 20 years leading the commercial supply of product and services to pharmaceutical companies across the globe. He is responsible for leading revenue growth, key client relationships and marketing MedPharm to its global customer base. He started his career as a technical formulator and has a PhD in organic chemistry from the University of Cambridge, UK.

Stephen Rode is Manager of Business Development for Lonza's Capsules and Health Ingredients group. He received his BS in Agronomy from Pennsylvania State University, US, and a GBA in Executive Management from The Wharton School at the University of Pennsylvania in 1988. With more than 31 years of industry experience, Mr Rode has worked with many top pharmaceutical and consumer healthcare companies. In addition to sales and business development responsibilities, he has actively participated on various internal capsule development teams.

Torkel Gren, Science & Technology Officer, Recipharm, holds degrees in Pharmacy and Business Administration and a PhD in Pharmaceutics (Uppsala University, Sweden). Dr Gren has worked in the pharmaceutical industry since 1988 and has held a number of scientist and manager positions in Europe and the US. He was lead formulator and co-inventor of Detrol OD/Detrusitol SR. Dr Gren is a member of the board of the Swedish Pharmaceutical Society.

In this roundtable discussion, Jeremy Drummond, Stephen Rode and Torkel Gren talk with ONdrugDelivery about trends with different drug dosage forms for different routes of administration, the rise of patient centricity including the shift from the blockbuster model to more tailored products, and how successful industrialisation is dependent on considering factors such as manufacturability early in the development process.

Q In your opinion, what have been the biggest trends that have impacted drug dosage form development and industrialisation over the past 5–10 years and why?

JD The continual rise of biologics has brought with it the creation of new solutions to challenges surrounding these complex entities, in terms of packaging, analysis, delivery and stability. Standing at the forefront of these solutions, MedPharm has demonstrated that some biologics, in this case aptamers, can penetrate skin and still be active despite their large molecular weight (20k Daltons). Through this research our experts have challenged current theories on skin penetration of large-molecular-weight drugs, offering hope for the discovery of new treatments for difficult-to-treat dermatological diseases.

SR Although there have been many development trends in drug delivery recently, one route that is likely to stimulate innovation for years is oral solid dose (OSD) administration. Most of the small-molecule drugs in development right now are being designed for oral routes. Regulators have made a huge impact by creating new, more efficient routes for drug development to help medications reach patients. These drugs are being designed from the beginning to have solid chemistries because oral administration is increasingly recognised as key to supporting patient centricity. Regarding patient preference, dose control and compliance, capsules offer developers proven capabilities with their new formulations. Lonza's Capsugel® business has been out in front of capsule development for decades, and continuous innovation across our product lines is directly serving a wide range of developer and patient needs.

TG Despite the steep increase in new biopharmaceutical products, small-molecule OSD products are still in high demand because of the opportunity they present to extend product lifecycles and leverage growth potential. The ideal dosage form should have broad applicability and that is one reason why tablets and capsules are still on-trend. Using tablets or capsules you can achieve many different release profiles, including immediate, prolonged and delayed release, orally disintegrating tablets and fixed-dose combinations. Consequently, there remains a lot of opportunity for companies across the OSD market.

One of the biggest trends remains developing novel, improved products based

on established APIs. This is not surprising as substantial benefits can be realised, including reduced costs and shortened development timelines, as well as exploring new administration routes to improve compliance.

Another big trend is the increasing demand for drugs that can be locally administered, for instance by inhalation or topical administration. Local administration presents a solution to deliver sufficient levels of drug to a target organ while minimising systemic exposure and side effects. In addition, there is mounting interest in more specialised local administration routes, including ophthalmic and vaginal administration and parenteral formulations for local delivery.

The increasing interest in parenteral products stems from the fact that most new biopharmaceutical products in development require administration by injection. While this is less convenient than oral administration, for many more serious indications, injectable dosage forms are acceptable when looking at the balance between benefit and inconvenience. The ongoing development of convenient and reliable autoinjectors is also contributing to this.

Q Have there been any significant innovations within the industry that have helped companies take advantage/stay on top of these dosage form trends and what trends do you see in the next decade?

JD Innovations around performance models have positively impacted dosage form development, particularly for products acting locally. Considerable advances have been around the use of *in vitro* models based on fresh human tissue to optimise the activity of drug formulations. Previously only used to measure permeation, these increasingly sophisticated models are now also used to monitor the activity of formulations. In the case of skin, MedPharm has techniques that allow us to keep fresh human skin viable for weeks, not days, in the laboratory – allowing us to conduct experiments over much longer timescales and de-risking any decision to enter clinical trials.

Over the next decade there are general trends which will impact dosage form development, such as more genome-specific products and more biologic-based activities. Undoubtedly the combination of dosage form delivery with technology, whether that be for monitoring the patient or in aiding the delivery, will be an important trend. It is an exciting time in the drug development industry and the COVID-19 pandemic has focused attention on the benefits that innovation can bring to ensuring patient centricity, as well as the value governments and populations place on health and wellbeing.

SR Therapeutic innovation is coming from all corners of OSD development and it seems that each individual capsule or tablet has to do more than ever before. For example, it has to deliver more API accurately, be smaller and easy to swallow, manage bioavailability and be capable of other integrated functions.

Innovation in larger molecules and biotech drugs has also meant increased focus on developing and delivering larger molecules such as proteins, peptides and monoclonal antibodies orally. Functional excipients have been made available to improve the stability and solubility of Class II biopharmaceutic compounds or to allow for targeted delivery – this has removed some potential barriers to oral bioavailability in these formulations.

Over the coming decade, we are sure to see developers packing more patient performance potential in each dose. The 505(B)(2) pathway, for example, provides for coming development of fixed-dose combinations, as well as other formulations to achieve better patient outcomes and dose compliance.

TG Manufacturers are increasingly employing various lifecycle management patent strategies, including the development of new drug formulations such as extended, controlled or rapid release formulations using APIs that are already on the market. Drug delivery innovation is becoming more important for pharmaceutical companies and this increases the need to partner with a CDMO during the early development stages with extensive knowledge of formulation development.

Over the years existing development approaches have been continually improved. This has made it easier to develop valuable dosage forms. Several technologies for modified release, for instance coated pellets, were also developed decades ago but are now easier to use as we have more experience in how to apply them. Another excellent example of innovation and improvement can be seen across the device area. While inhalation and injection devices have been around for decades, new devices are much easier to use.

Looking to the next decade, I think manufacturability will rise higher on the agenda. The cost of manufacturing and packaging could be a considerable part of the total cost of a drug and this is highly dependent on choices made during the development process. This is extremely important as it can impact profits but even more so as it may limit access to valuable new medicines. As such, dosage form development should always be done with large-scale manufacturing in mind.

Another promising development is in the area of precision medicine for smaller patient populations. Adapting conventional manufacturing technology and making it more flexible to allow for smaller batches may be very useful. Pellet technology and minitablets are examples of conventional manufacturing technology that allow a high degree of flexibility as it is easy to combine different pellets and/or minitablets to achieve combinations of multiple drugs in different doses and with different release rates.

Q What are the major challenges to overcome when trying to formulate a user-friendly formulation?

JD Incorporating patient centricity into a finished product must

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begin in the formulation development and design processes, first by looking at the active ingredient. Understanding the key physical and chemical properties of the active are key considerations that cannot be left out as they often point the formulator to a particular dosage form – for example, first-pass metabolism issues which focus the formulator on dosage forms other than OSD.

Additional elements such as packaging of the formulation can play a crucial part in the patient centricity of any dosage form and must be considered in the overall product development. For routes of delivery that stray away from more traditional routes of oral or IV, the use of *in vitro* models, using fresh tissue such as whole eyes, cultured human nasal tissue or fresh skin, have been shown to de-risk the development of the optimal formulation for the patient for that particular API.

SR User friendliness aspects of development now centre on areas such as patient compliance, with manufacturers searching for the most patient-centric form that supports the therapeutic performance and safety of their formulation.

A key consideration when using capsules is the characteristics of the API. The size of a molecule can often make it more challenging to deliver a substance orally, for example with proteins. The solubility required will also require specific formulation approaches and dose, stability, odour and colour during formulation all need to be considered.

Sustainability is making inroads into delivery innovation. Manufacturers are now prioritising clean-label ingredients for their products. Provenance is vital and the pedigree of ingredients equally so, with the intent to provide vegan and/or all-natural forms where possible. Lonza's Capsugel® business recognised this trend early, introducing a high-quality clean-label HPMC capsules that not only serve cultural/market goals but also answer API compatibility objectives.

TG Different formulations present different user-friendliness challenges. Typically, oral formulations are very user friendly, however size, taste and odour of the product need to be considered. When it comes to inhalation, for most patients this is less natural than oral administration and it's important that the device is used correctly to ensure the right therapeutic effect. Developing a device and product combination which ensures that an unskilled patient receives the intended effect from their medication is the main challenge here.

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There are many different factors at play when it comes to the user-friendliness of parenteral dosage forms. When administered by healthcare professionals the user is very skilled but prefilled syringes can still save valuable time. However, with patients increasingly self-administering parenteral products, devices that are simple to use, store and carry are crucial.

Q Has there been an increasing requirement to develop more user-friendly dosage forms, and if so, why?

JD The continuing rise in expectations of patients for dosage forms that suit their lifestyles as well as positively impacting their health, combined with an acknowledgment that meeting these criteria is directly linked to improved compliance, has driven the development of more user-friendly products. In severe cases patients will accommodate inconvenience, such as the use of injectables for severe psoriasis where topical applications are the convenient dosage form of choice when the same disease presents as mild or even less severe.

At MedPharm, end users' opinions and preferences are crucial from the start. These factors are incorporated into the product profile we establish with our clients from the very beginning. The expertise of the product developer allows them to manage any constraints whilst still delivering a dosage form that patients are happy to use. This knowledge is particularly important for smaller companies where it is not uncommon for some not to have thought about end users' preferences, particularly at the early stage of a project. As patient preferences can be revised and fully understood once a project has started, these new insights can be accounted for within the product and incorporated into any project goals.

SR Patient centricity has become incredibly influential and development pipelines are moving away from blockbuster drugs with one-size-fits-all dose forms to more personalised medicines.

This trend is manifesting itself in different ways, but the idea is essentially to make drugs perform optimally for more individual patients and this is sending pharma development in many new directions.

Market and patient access add to the objectives. For example, in emerging markets where nasal and pulmonary drug delivery is vital in combatting prominent respiratory conditions, capsule-based dry powder inhalants are preferred for their cost effectiveness and ease of use.

The ideal dose form must meet patient needs above all else. Increasingly, this is translating into specifying dose forms that decrease dosing frequency, control side effects and are easier to swallow – all attributes of capsules' continued appeal with consumers.

Pharma manufacturers are more connected to patients now than ever before through internal advocates, representative associations and discussion forums. Pharmaceutical developers are also collaborating with patients more effectively in trials, as well as after with post-market studies becoming a critical element of the process.

TG Compliance is a crucial factor when it comes to medication. If a medicine is not easy to take or tastes or smells unpleasant then patients are less likely to comply with their medication regime. This puts a great deal of importance on the development of more user-friendly dosage forms.

Assessing the user-friendliness of a dosage form is a diverse process as different patient

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groups will have different requirements. Focus groups with patients are vital to this end, using qualitative and quantitative methods to evaluate their preferences.

It is also important to remember that for hospital products the end users are doctors and nurses. When we talk about user-friendly drugs this needs to include how easy they are to administer in a clinical setting too.

Looking to the future, patients will likely demand more control over their own medication. Packages and devices that communicate with smartphones or other devices and make it possible to track dosing are likely to become more prominent.

Q What roles can an outsourcing partner play in optimising a drug dosage form and what benefits can be gained from outsourcing?

JD To ensure a patient-centric approach, pharmaceutical product developers are increasingly looking to expand away from traditional dosage forms. Due to their convenience and affordability, topical formulations for pharmaceutical delivery such as for eye, skin, airways or mucosal membranes have been increasing in popularity over recent years. The requirements for delivery for these specialist topical products mean working with an outsourcing partner has many benefits as the requirements for delivery are quite different from oral and IV routes of administration and require unique knowledge and experience that the majority of development companies do not have in-house.

In particular, the sophistication of *in vitro* models using human tissue, which MedPharm has pioneered, in the development of these products has greatly de-risked these development programmes. What you also get with a specialised contract developer like MedPharm is not only the 20 years of formulation development experience in a specific area but an in-depth understanding of what it takes to get a product to market whether it is a new chemical entity, a re-purposed drug for a new indication, an OTC product or a generic.

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SR The dialogue is yielding a great deal of influence in drug development, but also driving the need for expert partners and suppliers to deliver the technologies and capabilities pharma needs to pursue the patient-centric aspects of their drug products.

Nevertheless, emerging development and therapeutic goals are introducing manufacturing complexity in new ways. For example, many new APIs are highly potent and many have complicated chemistries that make controlling and modifying release a critical aspect of therapeutic performance and dose compliance. Increasingly, those goals are being met with external partners.

TG Today, there is growing interest in more specialised products often with relatively low production volumes, as well as a continued interest in new products with improved properties based on existing APIs. Although globally there is a lot of manufacturing capacity for solid dosage forms, much of this capacity was designed to suite the old "blockbuster" paradigm. As a result, many manufacturers are looking to work with CDMOs that can offer more flexible manufacturing capacity.

Pharma sponsors rely on CDMOs to help them get new products on the market. Many customers have very innovative projects and the ability to solve different challenges and manage complexity when developing and scaling up an innovative product is vital. These customers need a partner in innovation. Access to more technology, expertise and competence for dosage form development, locally as well as globally, can be gained through partnering with a CDMO.

> "Developing the dosage form with manufacturability in mind can have many benefits. Working with an end-to-end CDMO can help to reduce complexity, timelines and ensure smoother progress of a drug to market."

CDMOs that offer both development and commercial manufacturing services can help guide their customers' molecules from concept to market. As discussed earlier, developing the dosage form with manufacturability in mind can have many benefits. Working with an end-to-end CDMO can help to reduce complexity, timelines and ensure smoother progress of a drug to market.

ABOUT THE COMPANIES

MedPharm is a contract provider of topical and transdermal product design and formulation development services. MedPharm is expert at reducing risk and accelerating development times for generic and proprietary pharmaceutical customers through its unique, cost-effective and industry-leading performance testing models. Well established as a global leader in dermatology, nail, mucosal membrane and transdermal product development, the company can also offer innovative solutions for ophthalmic and airway preparations recognised for their scientific rigour by regulators and investors. MedPharm has fully established Centres of Excellence in the US and the UK.

Lonza Capsules and Health Ingredients is a global capsule and equipment developer and manufacturer which designs and produces innovative products for a wide range of oral dosage forms across the pharmaceutical and consumer health and nutrition market. By combining science, engineering and expertise with innovation and flexibility, the company provides quality products to more than 4,000 customers in over 100 countries and can offer advice on how to achieve customised solutions that optimise formulations and align with project and consumer requirements.

Recipharm is a CDMO headquartered in Stockholm, Sweden with development and manufacturing facilities in France, Germany,

India, Israel, Italy, Portugal, Spain, Sweden, the UK and the US. The company continues to grow and expand its offering for customers. Employing around 5,000 people, it is focused on supporting pharma companies with its full-service offering, taking products from early development through to commercial production. For more than 20 years, it has provided pharma expertise and managed complexity for its clients throughout the entire product lifecycle.

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EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
Sept 2020	Wearable Injectors	PASSED
Sept/Oct 2020	**NEW TOPIC – INAUGURAL ISSUE!** Drug Delivery & Enviromental Sustainability	Sep 14, 2020
Oct 2020	Prefilled Syringes & Injection Devices	Sep 24, 2020
Nov 2020	Pulmonary & Nasal Drug Delivery	Oct 8, 2020
Dec 2020	Connecting Drug Delivery	Nov 5, 2020
Jan 2021	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 3, 2020
Jan/Feb 2021	Prefilled Syringes & Injection Devices	Dec 17, 2020
Feb 2021	Novel Oral Delivery Systems	Jan 7, 2021
Mar 2021	Ophthalmic Drug Delivery	Feb 4, 2021
Apr 2021	Pulmonary & Nasal Drug Delivery	Mar 4, 2021
May 2021	Delivering Injectables: Devices & Formulations	Apr 1, 2021
Jun 2021	Connecting Drug Delivery	May 6, 2021
Jul 2021	Novel Oral Delivery Systems	Jun 3, 2021
Aug 2021	Industrialising Drug Delivery	Jul 1, 2021