RECENT TRENDS AND DEVELOPMENTS IN INJECTABLE DRUG FORMULATION AND DELIVERY

Here, Martin Gonzalez, PhD, Senior Manager, Formulation and Process Development at Pfizer CentreOne, details current trends in sterile injectable formulations and their delivery devices, and the challenges pharma and its contract development and manufacturing company partners face in bringing emerging breakthroughs to market.

An extremely broad range of increasingly advanced therapeutics are being administered via parenteral administration. Recent stars of the show are the billions of messenger RNA (mRNA) inoculations that continue to be delivered globally. Now a blockbuster technology, mRNA-based pharmaceuticals are poised to take off in the near term and are set to provide a sizeable section of the foundations for a huge growth in parenterally administered drug products.

> "Now a blockbuster technology, mRNA-based pharmaceuticals are poised to take off in the near term and are set to provide a sizeable section of the foundations for a huge growth in parenterally administered drug products."

BIOPHARMACEUTICALS TAKING CENTRE STAGE

The market for all sterile injectable (SI) drugs and their delivery devices is expanding fast. Although the number of SI therapeutics consumed globally is dwarfed by solid oral forms, more and more pharmaceuticals are being delivered to patients parenterally. The uptake of biopharmaceuticals in global healthcare for the treatment of chronic conditions, such as arthritis and diabetes, has become a significant driver of global growth. According to Precedence Research, the global biopharmaceutical market is projected to reach US$856 billion (£655 billion) by 2030 and expand at a compound annual growth rate (CAGR) of 12.5% from 2021 to 2030.[1]

THE PATIENT-FRIENDLY GORILLA IN THE ROOM

Prior to the pandemic, mRNA-based drug products were focused primarily on treating oncology indications as opposed to infectious diseases, such as covid-19. However, technical and scientific advancements have allowed researchers and drug developers to expand the use of mRNA to new therapeutic areas. During this period of R&D, carriers for mRNA were also further developed, increasing the potential of mRNA technology by prolonging antigen expression *in vivo*.[2] What is exciting is that the advances in the science proved instrumental in facilitating the success of covid-19 vaccines as well as showcasing the enormous possibilities of mRNA technology.

With mRNA-based drugs experiencing a surge in development and demand, companies supporting the technology's commercial manufacturing have had to adapt quickly to overcome the challenges involved. Virtually overnight, mRNA became the gorilla in the room for much of global pharma. The impact has been significant. Investment in mRNA's therapeutic potential has been tremendous. At the end of 2019, the combined market capitalisation of the five publicly listed companies focusing on mRNA platforms was $15 billion.[3] As of August 2021, market capitalisation was more than $300 billion.[4]

COMING ATTRACTION: ADVANCED MEDICINAL THERAPEUTIC PRODUCTS

Cell and gene therapies (C&GTs) are also transforming pharmaceutical-based healthcare and continue to demonstrate dramatic therapeutic results for patients.

Dr Martin Gonzalez
Senior Manager, Formulation & Process Development
E: pfizercentreone@pfizer.com

Pfizer CentreOne
235 East 42nd Street
New York
NY 10017
United States

www.pfizercentreone.com

Copyright © 2022 Frederick Furness Publishing Ltd

"Today's SI drugs carry a more complex profile and incorporate new thinking about ways of preserving the value of the drug while also providing additional benefits, including precise, easy-to-administer delivery systems for better dose compliance."

Now grouped as advanced therapy medicinal products (ATMPs), these modalities exhibit the potential to cure disease by addressing the root cause of the condition rather than treating it symptomatically. The science behind these therapies, as well as the means to deliver them, is advancing fast. Valued at $12.3 billion in 2021, the ATMP market is projected to reach a market value of $59.9 billion by 2031.[5]

Recent breakthroughs and approvals in the space have spurred the flow of investment, and this cash infusion is expected to accelerate the pace of development further, as life sciences developers work towards increasing patient access to these exciting modalities. The American Society of Gene and Cell Therapy noted in its *Gene, Cell, and RNA Therapy Landscape Quarterly Data Report* (Q4 2021) that, of the 3,483 C&GTs currently in development globally, 32 are in Phase III, up 10% from the previous quarter.[6]

STERILE INJECTABLES MOVING INTO THE MAINSTREAM OF PATIENT CARE

Because a third or more of all pharmaceuticals are manufactured by external partners, the pressure is on the contract development and manufacturing organisation (CDMO) community to find the capacity and new, efficient ways to speed up production and provide a shorter, surer path to market for these extremely important therapeutics. For many, it is going to be challenging to balance manufacturing capacity with demand in existing facilities, which will likely to prompt renewed capital spending on facilities. Although new ways of delivering SI formulations are being introduced, subcutaneous (SC) and intravenous (IV) delivery via needle will likely remain the dominant administration route for SI drugs.

Much of the emphasis in contemporary drug design has shifted from just preserving basic quality attributes, such as safety, efficacy and potency, in a simple container. Today's SI drugs carry a more complex profile and incorporate new thinking about ways of preserving the value of the drug while also providing additional benefits, including precise, easy-to-administer delivery systems for better dose compliance. The patient experience has influenced the development of new and creative ways to deliver sterile formulations, including patches that subcutaneously penetrate the skin, degradable implants and other innovative modalities.

IMPROVING THE PATIENT EXPERIENCE FOR BETTER COMPLIANCE AND LESS STING

According to Fortune Business Insights data, the global injectable drug delivery market was valued at $483 billion in 2019 and is projected to reach $1,251 billion in size by 2027, rising at a CAGR of 12.9%.[7] The SI market is a rapidly evolving industry. A clear example of this is the explosive creation of pharma companies devoted to developing therapies and treatments for covid-19.

For millions of patients who dose themselves daily, there is a growing preference for "smarter" and "friendlier" ways to self-administer injections. The focus on the patient has prompted broad medical device innovation over the past two decades and introduced innovations that include prefilled syringes (PFSs), prefilled pens and automated electronic injection and infusion devices. Needles have also been subject to long and continuous development and are now engineered to support less painful SC and IV delivery, as well as manage the flow of drug substance from device to patient.

Small bore, "low pain" needles (27–31G) are preferred as a way to mitigate pain and discomfort at the injection site, but usually carry the unwanted risk of clogging, rendering the administration process riskier and less predictable. Also, additional challenges exist for high concentration formulations, such as product shear or high infusion pressures, which their devices need to be able to handle. There are many pumps designs that can cope with most of these issues but there is not a one-size-fits-all answer. As mentioned prior, concurrent development of a delivery device and the drug product formulation is usually needed to address some of these challenges.

PFSs, unit-dose autoinjectors and similar delivery modalities have dominated the market for years due to their simplicity and ease of use. Among those technologies, analysts note that PFSs represent the fastest-growing segment. In 2021, the global PFS market was valued at $5.8 billion; the overall market exhibited strong growth and is expected to grow to $11.9 billion by 2028 at a CAGR of 10.7%.[8]

Although connected autoinjectors, such as infusion pumps for insulin delivery, have been on the market for a shorter time, increasingly, innovators are taking advantage of these proven technologies to increase patient-friendliness and promote better therapeutic outcomes.

OUT THERE: LONG-ACTING FORMULATIONS, MULTI-ACTIVE COMBINATIONS AND VISCOUS BIOLOGICS

Developing suitable formulations and matching them to existing and new device platforms is going to keep the industry busy in the near term. Advanced API chemistries and formulation techniques are being developed to protect these drug products from degradation, shear and other forces, including stability and storage temperature, during processing and administration. Formulators are also looking to avoid enzymatic damage upon release, and to provide a more precise delivery of the API and control attributes related to their pharmacokinetic profile (biocompatibility and bioavailability).

Reducing dosing frequency and the overall number of injections is another patient-facing challenge being addressed by the industry in formulation. Although long-acting injectables and multi-API combined formulation concepts offer workable solutions to reduce dose frequency, they can, and will, introduce additional complexity into formulation and device development.

For example, many drug substances, particularly biologics, can be highly viscous in their final commercial formulation due to their concentration and dosing requirements mandating they be kept to minimum volume. SC injections are limited to small volumes, usually 1–3 mL – even when wearable delivery devices are employed, slightly larger volumes can be delivered over time but, even then, there are limits to what patients can tolerate. Furthermore, converting a formerly IV drug formulation to one that can be delivered subcutaneously requires an increase in concentration, and likely some reformulation, to improve flow and injection pressures to reduce pain/stinging/oedema at the injection site.[9]

Copyright © 2022 Frederick Furness Publishing Ltd

This can make dispensing and administration problematic because patients generally prefer SC injections of parenteral drugs instead of IV infusion in a clinical setting. This is especially true for therapeutics that require frequent dosing and is a major driver of the development of higher-concentration biologic formulations, as well as increasingly sophisticated ways to deliver doses accurately and with less pain. The adoption of SC self-administration also relieves patients from spending hours in a clinical setting to receive the drug and makes treatment less expensive for both payer and patient. Here, again, patient compliance is paramount to delivering therapeutic performance effectively and better outcomes.

PUTTING IT ALL TOGETHER FOR PATIENTS WITH EXTERNAL PARTNERS

Increasingly, the CDMO industry is being tasked to put all the pieces of this intricate puzzle together – from formulation to finished drug product – and prepare products for commercial markets and patients. In their contemporary form, SI delivery devices present several challenges to successful development. High-potency biologics come with higher viscosities, problematic shelf lives, logistics issues and other impediments to commercial development. When evaluating a drug substance's presentation and appropriateness for a delivery device, the first couple of "default options" (vial, PFS) may, ultimately, prove not to be the best path. Regardless, the chemical make-up of the drug product is prompting programme collaborators to pursue an even deeper analysis – not only of the drug's intrinsic formulation properties but also the device's technical limitations, as well as its intended use and end-user.

Depending on the enterprise, the intellectual property owner may understand what pieces of the puzzle need to come together, but not exactly how they should fit, to create the big picture of the product as early in development as possible. Experience, technical capabilities and expertise are required to commercialise and manufacture these sophisticated products successfully. That is why pharma's small and large molecule developers are increasingly turning to contract partners for help delivering their innovations to patients.

ABOUT THE COMPANY

Pfizer CentreOne is a large global CDMO within Pfizer and a leading supplier of specialty APIs. Its service offering is broad, spanning development and manufacturing services for sterile injectable and oral solid dosage forms. Pfizer CentreOne's manufacturing network includes more than 35 sites across six continents.

Pfizer CentreOne was founded in 2015 when Pfizer CentreSource, a global leader in specialty APIs, and Hospira One2One merged. Backed by Pfizer resources, the company delivers technical expertise, global regulatory support and long-term supply.

REFERENCES

1. *"Biopharmaceutical Market Size to Hit US$ 856.1 Bn by 2030". Industry Report, GlobeNewswire, Dec 22, 2021.*
2. *Pardi N et al, "mRNA vaccines - a new era in vaccinology". Nat Rev Drug Discov, 2018, Vol 17(4), pp 261–279.*
3. *Xie W, Chen B, Wong J, "Evolution of the market for mRNA technology". Nat Rev Drug Discov, 2021, 20, 880.*
4. *Stanton D, "Single-use lead times up to 12 months as COVID takes its toll". BioProcess Int, May 3, 2021.*
5. *"The Global Advanced Therapy Medicinal Products Market is projected to reach at market value of US$ 59.91 billion by 2031". Industry Report, GlobeNewswire, Jun 2, 2021.*
6. *Barrett DM, "Gene, Cell, & RNA Therapy Landscape: Q1 2021". American Society of Gene + Cell Therapy, Apr 15, 2021.*
7. *"Injectable Drug Delivery Market Size, Share and COVID-19 Impact Analysis, By Device Type (Conventional Injectable, Pre-filled Syringes, Auto-Injectors, Pen Injectors, and Wearable), By Product Type (Freeze-Dried Products, Injectable Sterile Products), By End User (Hospitals, Homecare Settings, Clinics, and Others), and Regional Forecast, 2020–2027". Industry Report, Fortune Business Insights, Jul 2020.*
8. *"Prefilled Syringes Market Size By Type (Glass, Plastic), By Design (Single-chamber, Dual-chamber), By Applications (Diabetes, Rheumatoid Arthritis, Anaphylaxis, Antithrombotic/Thrombolytic Therapy), Industry Analysis Report, Regional Outlook, Application Potential, Competitive Market Share & Forecast, 2021–2027". Industry Report, Global Market Insights, Feb 2021.*
9. *Challener CA, "Excipients for High-Concentration Biologics". BioPharm Int, 2022, Vol 35(3), pp17–20.*

ABOUT THE AUTHOR

Martin Gonzalez has a PhD in Biophysical Chemistry and over 25 years of experience in formulation development and manufacturing processes for biologics and synthetic drug products. He joined Pfizer CentreOne Contract Manufacturing Services in June 2013. Having previously worked as a scientist at the US NIH's National Heart, Lung, and Blood Institute, Dr Gonzalez has extensive expertise in plasma-derived proteins, polypeptides, enzymes, vaccines and recombinant proteins and antibodies. This expertise has made him a subject matter expert in protein formulation, product development and lyophilisation, manufacturing troubleshooting, delivery devices and final container selection.

BRINGING YOU EVEN BETTER CONTENT IN 2022!

www.ondrugdelivery.com/subscribe

ON drugDELIVERY

Copyright © 2022 Frederick Furness Publishing Ltd