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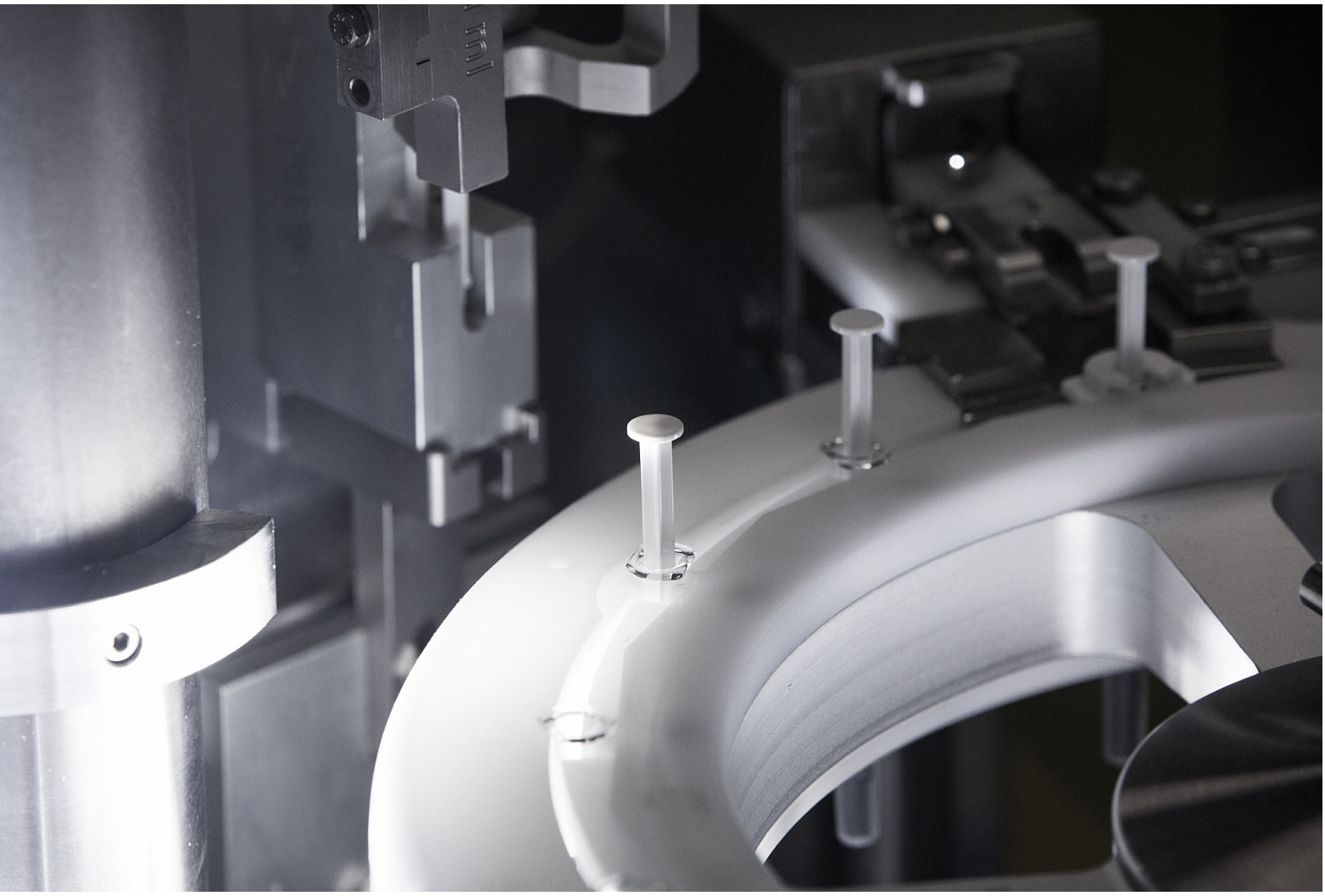

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WHITEPAPER

Focus on drug delivery: What clinical teams should know about the benefits of auto-injectors

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Abstract

More drugs are being delivered by injection than ever before, fueled by a steady stream of biological products emerging from research pipelines. In 2017, nearly 38% of pipeline drugs were biologicals, reflecting the accelerating trend toward large-molecule products that cannot be delivered orally. For the first time, the industry's small-to-large molecule seismic shift nudged the proportion of drugs in the development pipeline delivered by injection to 52%, narrowly establishing injection as the leading means of drug delivery in 2017.[1] Other factors contributing to the increase of drug delivery by injection include the global rise in chronic diseases, the need for frequent dosing to control many such diseases, and a growing trend toward self-administration of medical treatments by patients.[2, 3]

A prime example is Type 2 diabetes, which has been deemed an epidemic by global public health bodies. A patient living with diabetes could need to self- administer insulin as many as 90 to 100 times per month in order to control the disease. Neither doctors nor patients could accommodate that volume of clinic visits, which is why diabetes patients have long self-administered their treatments at home. In addition to diabetes, other chronic illnesses requiring frequent self- administration of biological drugs include multiple sclerosis, rheumatoid arthritis and migraine. [3, 4, 5]

It stands to reason that making self-injection as easy and safe as possible serves the interests of all stakeholders, from patients and biopharma companies to healthcare providers and payers. Efforts to do so are driving the selection and importance of auto-injectors—sophisticated single—and multi-use devices that enable patients to self-administer drugs safely, accurately, reliably and conveniently.[3, 6, 7]

Auto-injectors are becoming biopharma companies' delivery method of choice for commercial use and late-stage clinical trials. In addition, auto-injectors ensure that the prescribed dose of medication is delivered fully and completely, making it easier to track compliance in clinical trials. Read this whitepaper to learn about the benefits of auto-injectors.

Introduction

For a host of reasons, auto-injectors are becoming biopharma companies' delivery method of choice for commercial use and late-stage clinical trials. Auto-injectors ensure that the prescribed dose of medication is delivered fully and completely, making it easier to track compliance in clinical trials. Multi-dose auto-injectors such as pens take the guesswork out of dosing by enabling patients to dial up the right dose every time. An added advantage for manufacturers is the combination of drug and delivery device can be branded and patent-protected.

Finally, patients' preference for auto-injectors, thanks to their ease of use, means that patients using these devices are more likely to remain treatment-compliant.[5, 6, 7] That's good news. In the end, regardless of the means, drug delivery is about ensuring that patients receive the right dose of the right drug at the right time.

Self-injection option

While most large-molecule drugs must be delivered via injection, biopharma companies have choices about which form of injection to use. Today, they can choose from a variety of options—ampoules, vials, prefilled syringes and auto-injectors—each of which offers distinct advantages and disadvantages.

Ampoules

Widely used, ampoules or ampules are a traditional type of primary packaging for injectable drugs. Ampoules are small, hermetically sealed capsules containing a single dose of a pharmaceutical product that must be protected from air and contaminants. A user opens an ampoule by snapping off its neck.

Pros

- Although they are commonly made of glass, ampules may also be plastic, thus increasing their durability.
- A major benefit of ampoules is their imperviousness to gases and liquids.[8]

Cons

- The use of ampoules has been associated with safety issues. Glass micro- particles may be generated by snap-opening ampoules, contaminating the pharmaceutical product within. Opening ampoules can also expose users to the risk of percutaneous injuries.Today, they can choose from a variety of self-injection options—ampoules, vials, prefilled syringes and auto-injectors.
- Glass ampoules are more expensive than bottles and other simple containers, but less expensive than other options. Most of the growth in the use of ampoules is taking place in the cost-sensitive markets of emerging nations.
- Ampoules are inconvenient choices for patients who must self-administer a drug frequently.[8, 9]

Products supplied in ampoules

- Epinephrine, xylocaine, metoprolol and others

Vials

Injectable drugs have been supplied in glass vials for more than a century, making vials the most conventional and familiar choice available today.

Pros

- Vials are now available in plastic as well as glass, with plastic somewhat less fragile than glass. Vials are the least expensive option for packaging products delivered by injection.

Cons

- Whether of glass or plastic, single- and multi-dose vials of glass or plastic can crack or break, potentially contaminating and wasting costly biological drugs.
- Lack of convenience, particularly for patients who must self-administer medications frequently. Doing so requires a user to manually pierce the stopper of the vial with a hollow needle and draw the prescribed dose of drug from the vial into a standard hypodermic syringe for administration. This requires training and some skill; it can be difficult to accomplish for sight-impaired patients or those disabled by arthritis or other medical problems.
- Dosage errors, needle-stick injuries, and contamination can occur.
- Since it is impossible to draw all of the drug from the vial into a syringe, some
- drug is inevitably wasted.[10, 11]
- Multi-dose vials have also been linked to outbreaks of infectious diseases such as hepatitis C as a result of administration errors or unsafe injection practices.[12]

Products supplied in vials

- Insulin, opioid painkillers, immunosuppressive drugs for treating diseases such as rheumatoid arthritis, psoriasis and multiple sclerosis, and others

Prefilled syringes

Available for more than two decades, these single-use, disposable devices consist of prefilled cartridges of glass or plastic that contain a measured dose of drug and are designed to fit into specialized syringes.

Prefilled syringes are used in place of standard hypodermic syringes, which patients must fill manually before self-administering a drug dose.

The market for prefilled syringes has been expanding as the number of biological drugs proliferates.

The market for prefilled syringes has been expanding as the number of biological drugs proliferates. Growth of prefilled syringes has averaged 8 to 12% annually for the last few years.

Pros

- Prefilled syringes are easier to use than vials, helping increase dosing accuracy, convenience and safety. This generally makes them a good option for patients who must self-inject frequently, saving time and boosting quality of life.[11, 13]

Cons

- Patients can experience some difficulty in self-administering viscous products using prefilled syringes.
- Prefilled syringes cost more than vials.

Products supplied in prefilled syringes

- Insulin, anticoagulants, drugs to prevent neutropenia in patients receiving chemotherapy, treatments for rheumatoid arthritis and multiple sclerosis, and others.

Auto-injectors

First used by the military to protect troops from chemical warfare agents, auto- injectors have been available for more than a quarter century. Another early use of auto-injectors was the delivery of epinephrine to individuals at risk of anaphylaxis due to severe allergies.

First used by the military to protect troops from chemical warfare agents, auto- injectors have been available for more than a quarter century.

In both cases, the intent was less about convenience and more about ensuring that injections were delivered posthaste. Later auto-injectors—such as the first insulin pen injector, which debuted in 1985—were designed with the purpose of overcoming patient hesitation and anxiety about self-injection.[6, 7]

Pros

- Self-administering an injection using a vial or even a prefilled syringe demands some skill, while an auto-injector levels the playing field by making it possible for virtually every patient to do so successfully, with virtually no training or preparation. As their name implies, auto-injectors automatically insert the needle and perform the injection, making them highly user-friendly.
- In addition to their user-friendliness, these devices offer sterility assurance, a low chance of contamination and increased product yield. This is because auto-injectors prevent drug waste by allowing users to access all of the drug in the device every time.
- Auto-injectors are also a good choice for the delivery of highly viscous biological products, given the devices' even, controlled pressure. Viscous products can be difficult for patients to administer using other delivery systems.[6, 7, 9]
- Often used in late-stage clinical trials, these devices can provide key data about ease of use vs. safety and efficacy. Auto-injectors are also used as a product differentiator.
- All auto-injectors are equipped with safety features. Needle tips are shielded prior to injection to prevent needle-stick injuries and passive safety mechanisms prevent unintentional firing or injection.[6, 7]

Cons

- Auto-injector drug delivery systems carry a higher price tag than vials or prefilled syringes.

Products supplied in auto-injectors

- Epinephrine, insulin, human growth hormone, fertility treatments, drugs for the management of multiple sclerosis, rheumatoid arthritis and anemia, and others.

A trio of flexible options: Auto-injector basics

Since their introduction more than 25 years ago, auto-injectors have evolved to become the most sophisticated and convenient members of the self-injection arsenal.

Their use and importance continue to grow, thanks to many factors: their high level of functionality, the availability of many different designs, the ability to customize them to suit the product, and efforts by drug manufacturers to make self-administration as simple and safe as possible.

The advantages of auto-injectors are their instant readiness and ease of use, permitting patients to self-administer drug doses safely, accurately, reliably and conveniently every time.[3, 6, 7]

Three categories of these customizable devices are on the market today—auto- injectors, injector pens and wearable injectors.

Auto-injectors

While the term 'auto-injector' is a commonly used catch phrase for the entire category of self-injection devices, an auto-injector is actually one such device.

An auto-injector is a single-use, fixed- or variable-dose device containing a prefilled syringe or cartridge containing a drug. These devices can be customized to contain prefilled syringes or cartridges in typical sizes containing up to 3.0 ml of drug.

Injector pens

Since the debut of the first injector pen for insulin in 1985, these devices have been reengineered to become an effective and widely used means of drug self- administration.

The key difference between and auto-injector and an injector pen is that of dose. An auto-injector is a single-dose device, while an injector pen is a multi-dose device capable of delivering a fixed or variable dose of drug. Injector pens feature a cartridge in typical sizes containing up to 3.0 ml of drug.

Decades since their introduction for the delivery of insulin, injector pens continue to be a top choice for the treatment of diabetes. These devices enable diabetes patients to dial up and self-administer the right dose of insulin easily and discreetly.

As the newest member of the auto-injector family, the technology around wearable injectors is expanding rapidly.

Wearable injectors

As the newest member of the auto-injector family, the technology around wearable injectors is expanding rapidly. A wearable device is a single or multi-dose, fixed or variable-dose device containing a prefilled cartridge of drug.

These devices have a greater capacity than other injectors and can accommodate a large volume of drug, 20 ml or more.

Some wearable injectors are fitted with Bluetooth® and can be connected to smart phones or other smart devices for additional functionality. This permits data from the wearable injector to be transmitted to a healthcare practitioner, for example.

These devices can also be designed to help patients determine the optimal dose of drug to self-administer. For instance, a diabetes patient can do a finger-prick to obtain a blood sample, with the wearable injector automatically calculating the correct dose of insulin based upon the glucose level.

Wearable injectors capable of adjusting dose based upon how the patient is feeling or how the clinical trial is progressing are expected to become a reality in the near future.

Benefits of streamlined processing

It stands to reason that a single-source supplier would simplify supply chains while saving time and resources. Independent research now appears to confirm this.

Researchers at the Tufts Center for the Study of Drug Development compared dual-vendor (separate drug substance and drug product vendors) versus single-vendor contract development and manufacturing organization (CDMOs) on cycle times and development costs.

Their findings—that sponsors enjoyed substantial financial benefits and shorter development times from using a single CDMO outsourcing model vs. multiple, fragmented vendors—were recently published in Clinical Therapeutics.[14, 15]

Thermo Fisher Scientific is one of the only CDMOs to offer fully integrated services across drug substance to drug product manufacture for cartridges/pre-filled syringes, auto-injector assembly, clinical trials packaging and labeling, clinical supply optimization and overall trial management.

Auto-injector and pen assembly and packaging

Our service offering—auto-injector and pen assembly and packaging for clinical trial—was launched in 2018. This capability provides simplified logistics and flexibility for sponsors, including:

- Seamless transition from assembly to labeling/packaging, all under one roof
- Improved communication between project managers within a single organization
- Expedited project timelines
- Harmonized quality management system
- Potential to further expand integration to include drug product manufacture and assembly and to provide small-scale commercial services

Deliverables include a finished product ready for the end user, including a cartridge or prefilled syringe containing drug, a cartridge holder, pen or auto-injector with dosing mechanism and pen cap. Both user-friendly and state-of-the-art, this device delivers a precise amount of drug—no more, no less—to the patient every time.

This service is a logical next step in Thermo Fisher Scientific's support for biopharma companies developing and commercializing injectable products. For several years now, we have been meeting the growing demand for filling, assembling and labeling syringes and cartridges at our sites located around the globe.

Capabilities for injectable products

Our auto-injector and pen assembly and packaging activities take place at Thermo Fisher Scientific's Pharma Services facilities in Monza (Italy) and Horsham (United Kingdom).

Manufacturing of cartridges and syringes is conducted in Monza, while assembly, packaging and labeling take place in Horsham. In 2019, we will extend manufacturing capability to a second location, our facility located in Greenville (North Carolina, USA) which will collaborate with our Allentown (Pennsylvania, USA) site.

Located in dedicated and flexible Good Manufacturing Practices-compliant (GMP) cabins, we can accommodate 10 auto-injector and eight pen styles. Output rate is approximately two million units per year under normal operations (running two shifts with all machines operating). We can support a 24/7 operation should greater output be required. We can also accommodate both small and multi-million unit runs with ease.

Assembly and labeling are available in both ambient and cold environments. Our facilities have the capacity to hold and store high volumes of product in a cold environment.

In addition to our plant and processes, Thermo Fisher Scientific maintains strong relationships with equipment and component manufacturers for the benefit of our clients. Our operators and engineering staff were trained by these manufacturers to operate and maintain our equipment. We continually work with manufacturers to increase levels of automation and commercial scalability while maintaining the flexibility for which we are known.

Eye on the future: Examining market trends

Thermo Fisher Scientific continuously monitors and analyzes drug delivery trends to deliver the capabilities our clients need and expect. Our support for late-stage clinical trials using auto-injectors, the delivery devices of choice for an increasing number of commercial products, is accelerating steadily.

In 2017, for example, the auto-injector market for commercialized products alone was $80 billion, based upon sales of almost 1.7 billion units for the delivery of 337 individual products.

The market for branded products was split almost evenly among the five key countries of Europe (collectively 23 percent) and North America and other European countries (each of which represented 21 percent).

Meanwhile, North America dominated the generic auto-injector market with a 60 percent share.[16]

Strong growth potential

The global auto-injector market is on the rise, projected to grow by a robust 18.6 percent CAGR between 2017 and 2023.

Drivers behind the projected double-digit growth in the auto-injector market include emerging biologics, continuing demand for anaphylaxis treatments, efforts to prevent needle-stick injuries and the proliferation of self-administration therapies.

Estimated sales of two billion prefilled unit dose syringes on the global market leaves considerable room for expansion via switches to new auto-injection devices.[16]

- More than two-thirds of intravenous (IV) drug manufacturers indicated that they expect growth in usage of single-dose injectable products through 2022.[17] A comprehensive analysis of several marketed and pipeline products suggests that more than 100 drugs not currently available in auto-injectors are suitable for delivery via auto-injectors.[18]
- In 2017, 15 identified products in auto-injector format were being evaluated in clinical trials, compared to 11 products in 2016. Most of the products in development were new formulations or delivery systems for existing marketed products or biosimilars. A small number of new molecular entities (NMEs) were also being evaluated.[18]
- The top therapeutic targets for auto-injector growth are diabetes and rheumatoid arthritis.[19, 20] Diabetes is estimated to affect more than 500 million people worldwide in 2018.[19] Rheumatoid arthritis, another chronic disease increasing in prevalence, is expected to affect nearly seven million people in the eight major global markets (United States, France, Germany, Italy, Spain, United Kingdom, Australia, Brazil and Japan) by 2025.[20]
- Other leading therapeutic targets for auto-injection devices are multiple sclerosis, psoriatic arthritis and migraine.[17]

Thermo Fisher Scientific will continue to monitor these trends, proactively investing in facilities, equipment and personnel in order to meet the changing needs of our clients.

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About us

Thermo Fisher Scientific provides industry-leading pharma services solutions for drug development, clinical trial logistics and commercial manufacturing to customers through our Patheon brand. With more than 65 locations around the world, we provide integrated, end-to-end capabilities across all phases of development, including API, biologics, viral vectors, cGMP plasmids, formulation, clinical trials solutions, logistics services and commercial manufacturing and packaging. We give pharma and biotech companies of all sizes instant access to a global network of facilities and technical experts across the Americas, Europe, Asia and Australia. Our global leadership is built on a reputation for scientific and technical excellence. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to Care™ program. As a leading pharma services provider, we deliver unrivaled quality, reliability and compliance. Together with our customers, we’re rapidly turning pharmaceutical possibilities into realities.

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