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Review Article

Drug prefilled non-reusable syringes as drug-device

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ABSTRACT

Due to a staggering increase in the number of patients who self-administer drugs to treat chronic diseases, and growing use of biologics drugs, manufacturers started showing shift from vial-and-syringe format, prone to dosing errors and low patient-compliance rates to single use, disposable syringes filled with a prescribed unit dose of medication called prefilled syringes to deliver protein-based drugs, sustained release formulations, and other parenteral medications. Being the fastest growing segment of the injectable drug delivery devices market, it has the potential to unlock significant value by providing the next level of safe and highly effective treatments for patients. However, getting these products to the market in a timely, compliant, and sustainable manner is not easy. New and challenging technical problems will persist. Interacting with key regulatory authorities, such as FDA, requires a dedicated and collaborative effort as their approaches continue to evolve. The intent of this review article is to provide concise information on the latest regulatory aspects of prefilled syringe, methods of their manufacture, methods of filling syringes as a drug product. This type of knowledge can familiarize the reader with the prefilled syringes as a combination product & its possible challenges.

Key words: Prefilled syringes, syringes, Prefilled medical devices, parenteral devices, Medical device

INTRODUCTION

First official injection morphine appeared in the *British Pharmacopoeia* in the (1867) and monographs of seven sterile glass sealed ampules appeared in the US *National formulary* in 1926. Since then, list of injectable products has grown. **[1]** Current USP contain monographs for over 500 injectable products. Parenteral administration of drugs by intravenous (IV), intramuscular (IM) or subcutaneous (SC) routs is now an established and essential part of medical practice. Advantages of parenterally administered drugs include the rapid onset, predictable effect, predictable and nearly complete bioavailabilty, and avoidance of the gastrointestinal (GI) tract and hence, the problems of variable absorption, drug inactivation and GI distress gets minimized. In addition, the parenteral route provides reliable drug administration in very ill or comatose patients.**[2]** Many important drugs are now available only in parenteral dosage forms. Notable among them are numerous biotechnology drugs, insulin, several cephalosporin antibiotic products, glucagone, heparin, and protamine. In addition, other drugs such as lidocaine hydrochloride and many anticancer products are available as parenterals. Main problem occurs with the parenteral drug delivery is lack of convenience, associated with pain & discomfort and fear factor of 'needle insertion' affordability, accuracy, sterility, safety etc., which makes it less preferable. Many of the disadvantages can be easily overcome by use of injectable drug delivery which is aimed to maximize patient compliance and reduce the frequency of dosage administration without compromising the effectiveness of the treatment especially for the delivery of drugs that are ineffective when administered orally.

Injectable is very broad segment, **Fig 1** which can be categorized into two sub segments - device technologies and formulation technologies. That can be further subdivided into conventional injection devices, self-injection devices and others (micro-needles, nano-needles and blunt needle injections) that make up the former category.**[3]** The ***thefreedictionary.com*** defines syringe as a medical instrument used to inject fluids into the body or draw them from it. **[4]** A medical equipment database made by MediLexicon International Ltd defines syringe as a device consisting of a barrel, a piston or plunger, and has

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provisions for attaching a needle for use in administering hypodermic injections.**[5]** The item may be glass, glass and metal, plastic, or plastic and metal. It may be designed for single injection (disposable), or multiple use.

Prefilled medical devices, as the term is known in the art, are medical devices that are filled by the manufacturer at the time of assembly and are shipped in a ready-to-use condition to the healthcare provider. **[6]**

SEGMENTATION OF INJECTABLE DRUG DELIVERY MARKET:

Injectable drug delivery market is segmented on the basis of therapeutic application, usage pattern, mode of administration, end user & on the basis of region. Details of this segmentation is given in **Table 1,2,3.** Key players in the injectable drug delivery market include Becton, Dickinson and Company (U.S.), Baxter International, Inc. (U.S.), Gerresheimer AG (Germany), Pfizer, Inc. (U.S.), Schott AG (Germany), Sandoz (Germany), Teva Pharmaceutical Industries Ltd. (Israel), and Eli Lilly and Company (U.S.).**[7]**

The current injectable drug delivery market in 2015 is $326.1 billion. It is expected to grow at a CAGR of 12.0% to reach $574.8 billion by 2020. On one hand factors such as rising prevalence of chronic diseases, growth of the biologics market, technological advancements driving the demand of self-injection devices, are responsible for the growth of this market. On the other hand, alternative delivery methods such as oral and transdermal, safety concerns, and blood-borne infections are hindering the growth of this market **[7].** Conventional injection devices accounts for the largest share of the overall market. Europe is the leader in the self-injection market. Hormonal disorders accounted for the largest share of 50 percent of the global injectable drug delivery market in 2012 and is expected to grow at a CAGR of 13.9% to reach $21.6 billion by 2017.**[8]**

To manufacture & commercialize combination product like prefilled syringe, manufacturers require to integrate novel and fundamentally entirely different technologies therefore it poses a range of very unique sets of unprecedented development, regulatory, commercial, and organizational challenges not faced by "device-only" and "pharmaceuticals only" manufacturers. Being technologically more complex, combination product development requires more discipline and cross-functional coordination like the integration of therapeutic drug, biologic, and device development along with the merging of the engineering, chemical, and biological fields ensuring adequate sterility and shelf life of the drug on a device. This merger introduces entirely new sets of technical and organizational and regulatory challenges in product development. Though the prefilled syringe is combination product, it contains biologic and device components and both components have different marketing applications, regulations, and postmarket reporting requirements. **[9]**

The objective of this review article is to provide information regarding prefilled syringes; to provide concise information on the latest regulatory aspects of prefilled syringe, methods of their manufacture, methods of filling syringes as a drug product, it's advantages, and its future scope

Submission of prefilled syringes application: Regulatory challenges

Combination products are a distinct category of medical products along with drugs, biologics and medical devices. **[10]** Combination products are formed when two or more medical product constituents are combined in a way that fits the legal-regulatory definition of a combination product. FDA's product jurisdiction regulations describe *four* types of combination products. A combination product is a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device and a biological product" The potentially large number of combination products that can result from combining different medical technologies, what constitutes a combination product is not completely clear and it is difficult to develop broad principles on how regulate them.

Prefilled syringes is one of the "single entity combination product because it involve combination of two or more different medical products combined and produced as a single entity.**[11]** In other words, prefilled syringes is a "single entity combination product consist of two or more regulated medical products that are marketed as a single unit. [**12**] Combination products (e.g., pre-filled syringes, pen injectors, autoinjectors, inhalers, and transdermal patches) are among the most complicated products US FDA reviews, because they involve multiple centers at the US FDA and present regulatory challenges, and because of that they can cause different opinions in the review process. The regulatory landscape for combination product like prefilled syringes continues to evolve as industry and agencies learn more about them. There are still no specific

regulations or regulatory submissions that are 'unique' to combination products. Title 21 is the portion of the Code of Federal Regulations that governs food and drugs within the United States for the Food and Drug Administration (FDA), the Drug Enforcement Administration (DEA), and the Office of National Drug Control Policy (ONDCP).[13,14] Combination products are defined in **21 CFR 3.2(e)**. hence according to **21 CFR 3.2 (e)** the prefilled syringes belong to the combination products. The definition of a combination product is described as follows:

"A combination product is a product composed of any combination of a drug and a device; a biological product and a device; a drug and a biological product; or a drug, device and a biological product"

1. A product comprised of two or more regulated components(i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic) that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;
3. A drug, device, or biological product packaged separately that according to its investigational plan or proposed labelling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where, upon approval of the proposed product, the labelling of the approved product would need to be changed (e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose); or
4. Any investigational drug, device, or biological product packaged separately that according to its proposed labelling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.**[15]**

The Office of Combination Products (OCP), established by US-FDA in 2003, is responsible for the prompt assignment of a new combination product to the lead FDA review center, which may be the Center for Devices and Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER), or the Center for Biologics Evaluation and Research (CBER).**[15]**

According to the guidance document for industry: container closure systems for packaging human drugs and biologics chemistry, manufacturing, and controls documentation." published by the packaging technical committee of the chemistry, manufacturing, and controls coordinating committee (CMC CC) in the Center for Drug Evaluation and research (CDER) in conjunction with the Center for Biologics Evaluation and Research (CBER) at the US FDA prefilled syringes act as the primary container for drug products, and in regulatory terms constitute the immediate packaging in contact with the drug.

Drug and biologic manufacturers generally follow the current Good Manufacturing Practice regulation (CGMP)and medical device manufacturers usually follow the Quality System Regulation (QSR). To ensure full compliance with quality system requirements for a single-entity or kit combination product like prefilled syringes that contains drug and device constituent parts, elements of the CGMP regulation may be added to an existing QSR-based quality system, and vice versa. US FDA refers to this kind of quality system as a "stream-lined" system. OCP has paved the way for companies to establish standardized and compliant development processes by recognizing the overlap between quality system regulation (QSR) and current good manufacturing practices (CGMPs). (**Figure 2**)List of sources from which information of requirements for prefilled syringes as a Container Closure can be gathered is given in Table 4. List of Sources of ISO requirements for prefilled syringes given in Table 5. List of Guidance documents published by US FDA to be referred by prefilled syringes manufacturer is given in Table 6. & Regulatory Assessment of changes Covered in Guidance given by US FDA is shown in **Figure 3 [16]**

The process & need to fill the gaps between the CGMP and QSR is dynamic and will vary depending upon the manufacturing activity being performed and the nature of the combination product being manufactured. **[17]**

In order to function both as a container closure system and as a drug delivery device, prefilled syringes feature many unique design elements.**[13]** The general components of the prefilled syringe given in **Table 7[2]** & comparison between components of prefilled syringes with and without pre-stage needle given in Table **8** [13]

In the European Union, the regulatory process is entirely different. There are EU alternatives of a Decentralized Procedure (DCP) influenced by the Europe-wide Coordination Group (CMD), with national representatives from 27 countries, or by the Centralized Procedure (CP), which is managed by the European Medical Agency (EMA) and assessed by the EMA's Committee for Medicinal Products for Human Use (CHMP).**[18]**

Recently as per US FDA-CDRH (combination products), 'Human Factors' and 'Usability Engineering' to optimize medical device design has attracted an "extraordinary" number of comments. In prefilled syringes, if device component has a potential risk for medication errors or dosing errors then the CDRH (combination products) will look at whether there is human factors information in submission proposal by manufacturer.

REGULATION OF COMBINATION PRODUCTS US AND EU APPROACH

US

- Combination Product defined in statute (21CFR 3)
- Any combination of medical device, biologic, and drug
- Must meet requirements for all constituents
- Approval path determined by "primary mode of action" (i.e., BLA, NDA, 510(k), PMA)

EU

- No formal "combination product" statute
- Drug-Device Combination: Drug is primary and device is only for delivery.
- Medicinal Product Directive (2001/83/EC) drives approval through medicinal competent authority
- Device-Drug Combination: Drug only serves ancillary purpose
- Medical Device Directive (93/42/EEC) drives CE marking through notified body with consultation to medicines
- Competent authority for safety and usefulness of medicinal substance [**19**]

Component materials of prefilled syringes: Prefilled syringes are available in following capacity. Fill 1ml LL, Fill 2.25 ml LL. Fill 5ml LL Prefilled syringes made up of glass & plastic. Prefilled syringes classification based on component materials is given in **Figure 4**

Glass as a component material for prefilled syringes:[20,21,22]

Borosilicate glass has long been the industry standard for parenteral products in prefilled syringes due to following reasons

- its nature and content are better defined and understood
- easy to sterilize
- offers better visibility
- enhanced barrier properties; and
- has low reactivity

Disadvantages of 'Glass' as a component material for prefilled syringes [20,2122]

- Glass is breakable and requires added care when filling and handling.
- Glass contains small amounts of alkali ions which can cause a pH shift in some sensitive products.
- It can have a residual traces of tungsten as a byproduct of the glass-forming process, which can cause protein aggregation .
- Proteins and peptides adsorb to glass which can potentially, lead to a decrease in potency of the drug .

'Plastic' as a component material for prefilled syringes [20 21]

Cyclic olefin copolymers based plastic has been an alternative to glass in prefilled syringes due to following reasons.

- Unbreakable with high heat resistance
- A low level of extractables and leachables, and less permeable to water.
- More transparent, lightweight and shatter-resistant, enhancing visibility and facilitating filling operations as well as ease of use.
- Solvent resistance.
- Wide range of pH, from 2 to 12.
- Excellent low temperature characteristics, including tolerance of freeze drying and liquid nitrogen exposure.
- Prefilled syringes made from cyclic olefin copolymers based plastic has a non wettable surface with low surface energy and a contact angle of 80, compared to 7 for glass. This makes them prefilled syringe with an excellent drain ability

All materials used in medical devices must be screened for biocompatibility so they do not cause adverse local or systemic effects in people. These effects can occur through direct contact or through the release of impurities, extractables, or degradation products. Many tests used to evaluate biocompatibility are defined in the 12-part global

standard known as ISO 10993, "Biological Evaluation of Medical Devices." ISO 10993: Part 1 helps product developers select the tests needed for an application. Other parts of ISO 10993 detail the methods for the tests suggested in Part 1.[**22,23**]

The battery of possible biocompatibility tests includes those for acute, subchronic, and chronic toxicity; irritation to skin, eyes, and mucosal surfaces; sensitization; hemocompatibility; genotoxicity; carcinogenicity; and reproductive effects. Tests that address specific organs or the immune or reproductive systems may also be needed if a device warrants it.

One of the responsibilities of the US FDA's Office of Device Evaluation (ODE), is to develop and interpret regulations and guidelines regarding premarket notification submissions (510(k)s), premarket approval applications (PMAs), product development protocols (PDPs), device classifications, and investigational device exemptions (IDEs). The ODE guidance memoranda, referred to as "Blue Book Memos", clarify these guidelines The USP Class VI standard, which is often used to determine biocompatibility in the United States, involves a series of *in vivo* tests that follow guidelines in FDA's blue book memorandum G95-1.**[24]**

Testing for cytotoxicity is a rapid, sensitive, and inexpensive way to see whether a material has significant amounts of biologically harmful extractables. These tests use extractions drawn from a material to look for acute, adverse biological effects on mammalian cell cultures. They are defined in ISO 10993-5: "Tests for Cytotoxicity—*In Vitro* Methods." **[25]**

In addition, regulatory requirements must be met by those who supply materials in the United States. Especially important requirement mandates that suppliers have FDA drug and device master files for their products. These confidential databases give FDA access to information on materials, facilities, processes, and health and safety studies, so the agency can validate device manufacturers' product approval submissions that include data from molders, converters, and other suppliers. These master files include information on where and how a material is made, polymer composition (including additives), sterilization data, and health and safety information.[**26]**

THE CHALLENGES OF MANUFACTURING PREFILLED SYRINGES

The standard plunger-barrel design of commercially available syringes continues to present many challenges (e.g. drug stability, shelf life, leachables, extractables, and rising costs) for drugmakers. **[27]**

While glass remains the industry standard for prefilled syringes, there have been recent concerns over pharmaceutical glass quality and the possibility of delamination — a process (especially at lower pH) in which microscopic shards of glass can be shed into solution over time. These concerns have led to the development of cyclic olefin polymers and copolymers (e.g. COC, COP, and CZ) that are "glasslike" in appearance; have low extractable, leachable, and protein surface adsorption properties; and are stable over wide pH ranges. **[28]**

SURFACE TREATMENT IN PREFILLED SYRINGES:

Because of the plunger-barrel design of prefilled syringes and the various parts of a glass and plastic prefilled syringes must be free to move in order to facilitate administration of the product. Syringe barrels must be coated with silicone to ensure sufficient glide force for the plunger to easily deliver a drug during injection. Storage of proteins in silicone-coated prefilled syringes can sometimes result in silicone leaching into the product. Also, protein-based drugs (especially those formulated at low or high pH) can leach or extract contaminants from prefilled syringe rubber stoppers. To overcome these challenges, many syringe manufacturers use baking the silicone onto the syringe to lubricate the stopper and plunger, enabling these parts to move free and same time reduce the amount of free silicone that is available, thus decreasing the potential for interaction with the product. **[29]**

Some manufacturers have developed the technique of a silicone-free prefilled syringes for silicone-sensitive products with a fluropolymer barrier film to aid in lubricating the components of prefilled syringe, while protecting the drug product from contaminants that could potentially be leached from the elastomeric stopper which, in a syringe, is in constant contact with the product.

FILLING PROCESS IN PREFILLED SYRINGES

There are *four* principal methods for filling and stoppering syringes, each with its own advantages and challenges. A high-speed equipment filling, Online high-speed filling followed by offline vacuum stoppering & Online vacuum filling followed by online vacuum stoppering. These *three* methods can create bubble in the syringe. This bubble can increase the risk of stopper movement during shipping, and cause loss of product during expulsion activities prior to administration. It can

also cause stability issues for some proteins and oxygen-sensitive compounds. The latest innovation in filling and stoppering syringes using online vacuum filling and stoppering in conjunction with other proprietary patented technology to produce a syringe that is bubble-free is the fourth Method. It is called as 'Bubble free filling'. It is most advantageous for non-viscous products, since viscous products can be filled without bubbles using online vacuum filling and stoppering alone. The advantages of bubble-free filling include:
Enhanced Dosing accuracy, improved product sterility, decreased waste/greater safety and increased product stability. **[30]**

STERILIZATION OF PREFILLED SYRINGE

Medical device manufacturers do not have to face the same challenges as their pharmaceutical counterparts, as devices are normally manufactured using plastics, metals or other materials that are easily adapted to terminal sterilization. But prefilled syringes is considered as combination product therefore challenges posed in sterilization of prefilled syringes are different than challenges faced by medical device manufacturers [**31**]

To ensure that the prefilled syringes can be sterilized using an appropriate technique following detailed considerations are very important:

- Drug stability with chosen sterilization technique.
- Development trials to establish processing parameters and product limitations.
- Packaging configuration – orientation during sterilization.
- Temperature sensitivity and transportation requirements.
- Time lines between manufacturing, sterilization and delivery to market.
- Regulatory compliance: UK MHRA, US FDA and other notified bodies.[**32**]

Sterilization of prefilled syringe is mainly done by autoclaving or by ionizing radiation. Steam sterilization typically involves heating the device in a steam autoclave. Such steam sterilization, however, is time and labor consuming, and compromises the aesthetics of the product due to packaging degradation from the steam treatment. **[33]**

Over the last 20 years, the developments of 10 MeV sterilisation beams (which are commercially viable and used by a large proportion of the medical device industry) have created new options for pharmaceutical manufacturers Solution contained within the syringe may dictate the sterilization method. Goal is not only sterilization but to maintain a safe solution within the syringe which meets pharmacopoeia requirements. **[34]**

Radiation exposure is also commonly employed for sterilizing medical devices, in which the product is subjected to ionizing radiation, such as gamma irradiation. Gamma irradiation of polyolefin syringes can result in weakened container integrity, leakage, increased gas permeability and an undesirable yellowing of the container, and that gamma radiation treatment inherently causes the generation of highly reactive species. The generation of such reactive species can alter the contents of the container being treated, thereby causing the contents of the container to fail the European and/or U.S. Pharmacopoeia requirements, such as pH standards (required to be between 4.5 and 7.0), UV absorbance levels (required to be below 0.2 at 220-340 nm), and the presence of hydrogen peroxide and other oxidizable substances (required to be below 1 x 10"4 mol/L or 3.4 ppm). Syringe made up of radiation stable polyolefin is probably solution to this problem

The version of ISO 11137: 2006, “Sterilisation of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilisation process for medical devices”, defines the requirement to conform to a sterility assurance level (SAL) of 10^{-6} using irradiation as well as the microbiological tests required to achieve this [**31**]

PREFILLED SYRINGES CONTAINER AND CLOSURE SYSTEM INTEGRITY (CCI) TESTING AS A COMPONENT OF STABILITY PROTOCOL

In 2008, U.S FDA further promoted container and closure system integrity (CCI) testing as a component of the stability protocol for sterile products. In response to the increasing regulatory expectations, the pharmaceutical industry manufacturing prefilled syringes has driven and witnessed significant technical advancements in CCI testing. Instrumentation-based technologies employed in container and closure system integrity (CCI) testing, are high voltage leak detection (HVLD), vacuum/ pressure decay, mass extraction, and tracer gas detection (helium, oxygen etc.), These Instrumentation-based technologies employed in container and closure system integrity (CCI) testing, have emerged and demonstrated improved detection capabilities compared to conventional Container and closure system integrity (CCI) testing methods such as dye and

microbial ingress methods. Characteristics of Major CCI Testing Methods given in table 9. Many of the technologies have been used for on-line 100% inspection and/or drug product stability CCI testing.

THE LABEL AND LABELING OF A PREFILLED SYRINGES

Biologic products that are coupled with a device like prefilled syringes are "combination drugs". Prefilled syringes act as the primary container for drug products, and in regulatory terms constitute the immediate packaging in contact with the drug. **[35]** As the prefilled syringe is a fixed product, attention must be paid to the prefilled syringe package label to avoid improper use, (which leads to reduced efficacy), and to minimize adverse drug reactions. The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration), interact with the pharmaceutical product. The carton and container labels communicate critical information including the proprietary and established name, along with the strength, form, container quantity, expiration, and so on. The package insert labeling, (US PI or EU SmPC), communicates all information relevant to the approved uses of the drug, including the correct dosing and administration. **[36]**

ADVANTAGES OF PREFILLED SYRINGES

Prefilled syringes represents changing medical practices creating healthcare reform. Replacing the traditional vial and syringe format, prefilled syringes are gaining strong acceptance as a preferred device for parenteral administration for injectable biologics and biotechnology drugs, protein-based drugs, sustained release formulations, and other parenteral medications like antithrombotic agents, vaccines, blood stimulants, interferons, and other treatment of chronic conditions like rheumatoid arthritis requiring patients to self-administer medication several times a week.

Prefilled syringes have become a preferred device for parenteral administration due to improved convenience, compliance, reduction in the chances of contamination during the injection process and due to cost containment as patients does not have to travel to physicians' offices or infusion centers as patients can self-administer drugs, especially biologics several times a week as and when prescribed. It also and allows home use and saves valuable drug, for instance, the biological used in treating rare disease. Patient compliance with the dose is reliable and the risk of failing on efficacy due to suboptimal doses is preventable.

In terms of clinical supply of high cost of biological drug products where smaller batch sizes are desirable, prefilled syringes as a primary container are very convenient prefilled syringes are also convenient due to accuracy and reproducibility especially in clinical trials where drug is required to be administered at a fixed dose . Risk is lowered when utilizing a prefilled syringe as opposed to withdrawing a product with undefined syringes and needles that differ enormously across investigational sites and countries.

Oftentimes, biopharmaceuticals are formulated as a lyophilized formulations as they are not sufficiently stable when formulated in aqueous solution. These lyophilzed formulations require aqueous solubilization just before administration. For this purpose, prefilled dual-chamber systems (DCS) can provide safety, convenience and compliance. The main fields of application of DCS are self-administered lyophillized products, emergency-drug, cytotoxic drugs, and administration of biologics such as incompatible liquids and vaccines (antigen + adjuvant).

A change from the a standard vial-and- syringe format to a prefilled syringe offer a second generation, more flexible, ease-of-use product model for biopharmaceutical companies for brand differentiation and life cycle management of their products which differentiates the same medicinal product in the same therapeutic category compared to other competing drugs.

For the marketing authorization holder prefilled syringe can represent optimized product and therefore it can have premium price tag compared to the price tag of the current conventional primary packaging. The increase of attractiveness of this medicinal product for the physicians and patient can lead to an increase of sale.

Prefilled syringes is one of the example of single-use technology (SUT) Packaging medications in a unit-dose. It can be manufactured on single platform called aseptic blow-fill-seal (BFS) which can offer many benefits to a manufacturer, including lower overall cost-per-dosage-unit as compared with syringe and vial formats, reduced cleaning requirements, a smaller footprint, less capital investment, more flexibility, and reduced risk of cross-contamination.

Prefilled syringes are primary packaging which contain an exact amount of drug to be delivered whereas vials are typically overfilled 10% to 25% to account for any drug that may be lost during injection preparation and administration.

Elimination of vial overfills can result in substantial cost savings, especially for biologics manufacturers whose products are very expensive to produce.

From a logistical and supply chain management perspective, prefilled syringes are easier to handle, store, and ship than vials. Prefilled syringes weigh less and take up less space than vials, so they cost less to ship. Prefills occupy less shelf space at distributors and pharmacies, which makes them easier to store than vials, which can also help to reduce costs."

"Retailization of immunization," a growing trend set up by prefilled syringes where people can be vaccinated outside of traditional medical settings such as pharmacies, schools, retail outlets, and even airport, railway stations and state transport centers and kiosks by using prefilled syringes. Vaccination with prefills offered substantial cost savings over conventional vial-and-syringe administration.

Advancement like autoinjectors, spring-loaded glass syringes that keep needle tips shielded or hidden prior to injection in prefilled syringes are becoming increasingly popular for patients who self-administer injectable drugs. These devices offer patients who self-administer a "one-click solution" — pressing a button releases the needle, which is inserted a predefined depth into the skin, and the drug is subsequently delivered.

'Prefilled syringe biosimilars' represent a new opportunities. Due to advantages of prefilled syringe, US-FDA allows a biosimilar, "a pre-filled syringe or in an auto-injector device" (which are considered the same "injectable" dosage form), even if the reference product is licensed in a vial presentation. This is an important provision in the US regulation as it indicates the US FDA's preference, namely a prefilled syringe to a vial. In addition, it addresses the possibility for a biosimilar to have a prefilled syringe presentation in cases where the originator has a biologic/drug plus device with patent or trademark protection.

Recent developments in prefilled syringe treatment has caused a shift from surgery to injection, and brings therapy options to patients who could not be cured previously.

In cataract surgery, the opaque lens is basically removed and replaced by an intra-ocular lens (IOL). In order to protect the delicate cornea cells during surgery, a prefilled syringe is used to administer hyaluronic acid into the cavities of the anterior chamber and lens. The other field of applications comprises treatment of the inner eye by intravitreal injections of monoclonal antibodies to prevent the growth of veins, corticosteroids to fight bacterial infections, and silicone oil to fix the retina to the eye after retinal detachment. **[37]**

ADVANCES:

The rising demand for prefilled syringes is driving the manufacturers to introduce improvements in technology related to the material of prefilled syringes, and lubrication technology to reduce leachables and extractables. These developments are primarily to accommodate the increasing number of biologic drugs reaching the market. Additionally, the companies have developed multi-chamber prefilled syringes for use with lyophilised drugs.

Advances in the industry with respect to syringe design include new types of components, changes to the manufacturing process to reduce the quantity of silicone used to coat the syringe, changes to the process to decrease tungsten and adhesive residuals, dual-chamber devices, and needle-free devices. Advances in types of components include changes in the materials of construction such as the polymeric syringes changes in tip cap and plunger formulations as well as changes in the design of plungers .**[38]**

FUTURE

The numbers of innovative injectable products available are increasing. If a greater number of new drugs are placed in prefilled syringes then uptake of these by end users will increase. Prefilled technology needs to adapt to these new innovations for this pharmaceutical companies will require more sophisticated forms of delivery. This means greater investment is required by the manufacturers in order to maintain competitiveness in the market place. Presently there is not enough supply of prefilled syringes. Manufacturers will need to keep up with demand. The major processing and quality control challenges for the manufacturers of prefilled syringes include the stability issues due to interaction of packaging materials of prefilled syringes with the drug. Manufacturing costs are rising because of adaptation of safety measures to eliminate needle stick injuries. The safety systems are very costly. The percent of prefilled syringes with safety systems is very low and this trend is expected to change in the forthcoming years with more focus of the healthcare industry on needle stick safety aspects.

Table 1: Injectable Drug Delivery Market Segmentation By Therapeutic Application

Therapeutic Category	Disease
Autoimmune Diseases	Rheumatoid Arthritis
	Multiple Sclerosis
	Crohn's Disease
	Psoriasis
	Other Autoimmune Diseases
Hormonal Disorders	Diabetes
	Anemia
	Reproductive Health Disease
	Antithrombotic/Thrombolytic Therapy
	Osteoporosis
	Growth Hormone Deficiency (GHD)
Orphan Diseases & Oncology	Hemophilia Ribose-5-phosphate isomerase deficiency Cystic Fibrosis, and Wilson's disease
Others	Pain Management
	Allergy Treatment
	Aesthetic Treatments
	Hepatitis C

Table 2: Injectable Drug Delivery Market Segmentation by Uses Pattern, Mode of Administration & End User

Injectable Drug Delivery Market Segmentation By Uses Pattern
Curative Care
Immunization
Other Usage Patterns
Injectable Drug Delivery Market Segmentation By Mode of Administration
Skin
Organs
Central Nervous System
Circulatory/Musculoskeletal
Injectable Drug Delivery Market Segmentation By End User
Hospitals and Clinics
Home Care Settings
Research Laboratories
Pharmaceutical and Biotechnology Companies
Other End Users

Table 3: Injectable Drug Delivery Market Segmentation By Region

Injectable Drug Delivery Market Segmentation By Region	
North America	U.S.
	Canada
Europe	Germany
	France
	U.K.
	Italy
	Spain
	Rest of Europe (RoE)
Asia	China
	India
	Gulf countries
	South Korea
Rest of the World (RoW)	

Table 4: **Container Closure PFS requirement sources**

FDA Guidance –Container Closure Systems for Packaging Human Drugs & Biologics	Device is suitable for intended use (e.g., protects, compatible, safe, performs, etc.)
USP General Chapters	<1> Injections, <381> Elastomeric Closures, <660> Containers, <1031> Biocompatibility, <1207> Pkg Integrity
ICH M4Q – CTD (Quality)	Suitability of container closure device (e.g., materials, protection, compatibility, safety, performance, etc.)
ICH Q1A(R2) -Stability	Functionality tests for dose delivery system
ICH Q6A -Specifications	Test procedures and acceptance criteria related to functionality of delivery system
ICH Q8(R2) –Pharmaceutical Development	Demonstration of reproducible and accurate dose delivery

Table 5: List of Guidance documents

Guidance documents

- Medical Devices with Sharps Injury Prevention Features
- Applying Human Factors and usability engineering to Optimize Medical Device

Design (Draft)

- Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO)
- Standard 11040-4 (Draft)
- Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with

Drugs and Biologics

- Design Considerations for Devices Intended for Home Use

Table 6: **ISO sources**

SOME PFS REQUIREMENT SOURCES ISO

- 10993: Series on Biocompatibility
- 11040-4: Prefilled Syringes –Part 4: Glass barrels
- 11040-5: Prefilled Syringes –Part 5: Plunger stoppers
- 11608: Series on injection systems
- 14971: Medical Devices –Application of risk management to medical devices
- 23908: Sharps Injury Protection –Requirements and test methods

Table 7: **General components:of the pre-filled syringe [2]**

Components	**Material**
Barrel	Glass /Plastic
Piston	Elastomer
Tip cap	Elastomer
Plunger Rod	Plastic
Lubricant	Silicone Oil
Needle	Stainless steel
Needle	Elastomer
Needle shield cover	Plastic
Lock adapter	Plastic
Temper evident	Plastic
Finger Grip extender/Back stop	Plastic

Table 8: **Comparison between components of pre-filled syringes with and without pre-stage needle** [13]

Components of prefilled syringes with prestage needle	**Components of pre-filled syringes without pre-stage needle**	**Material of the component**
plunger rod/piston	plunger rod/piston	plastic
plunger stopper	plunger stopper	elastomer
barrel	barrel	Glass/Plastic
needle	-----	stainless steel or elastomer
needle shield cover	-----	plastic
------	tip cap	elastomer
------	luer lock adapter	plastic
lubricant	lubricant	silicone oil

TABLE 9: Characteristics of Major CCI Testing Methods

CCI Testing Methods	Advantages	Disadvantages
Vacuum Pressure decay/ Mass extraction	Non destructive	Proteneous product may interfere defect detection
	100% Testing feasible	
High Voltage leak detection	Non destructive	Prefilled container should contain liquid which should able to conduct an electricity May cause degradation of drug
	100% Testing feasible	
	Applicable to the high concentration Proteneous product	
	Carried out under normal atmospheric pressure	
Tracer gas (He) leak detection Head space oxygen testing: Frequency modulated spectroscopy	Non destructive	Require He containing head space for He based testing Or Require modified atmospheric packaging for oxygen based head space detection
	100% Testing feasible	
	Quantitative leak size determination is possible	
	May detect past transient CCI failures	
Dye Ingress	Established technology which is familiar to regulators	Destructive & less sensitive Leak size less than 20 μm cant be detected
Microbial Ingress	Established technology which is familiar to regulators	Destructive & less sensitive Leak size less than 20 μm cant be detected Cant be applied to the product filled syringes

Table lists the major CCI testing technologies available for prefilled syringes and their key characteristics. Note all the technologies have major limitations. When selecting appropriate methods, the following key aspects should be considered.

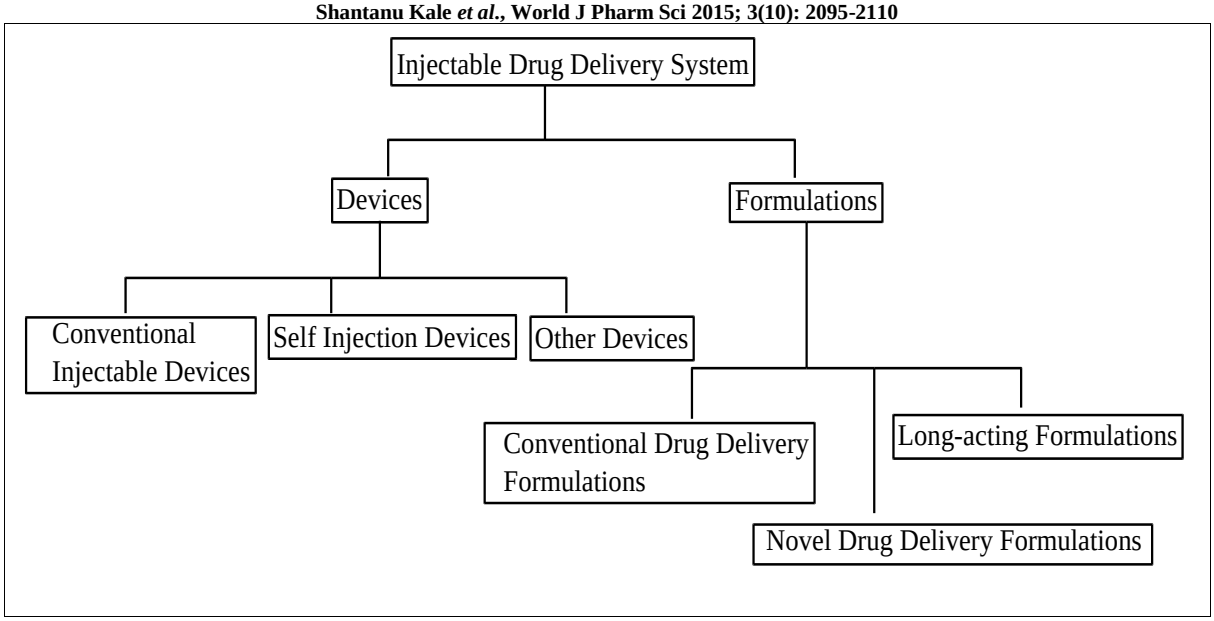


Figure 1: Injectable Drug Delivery System

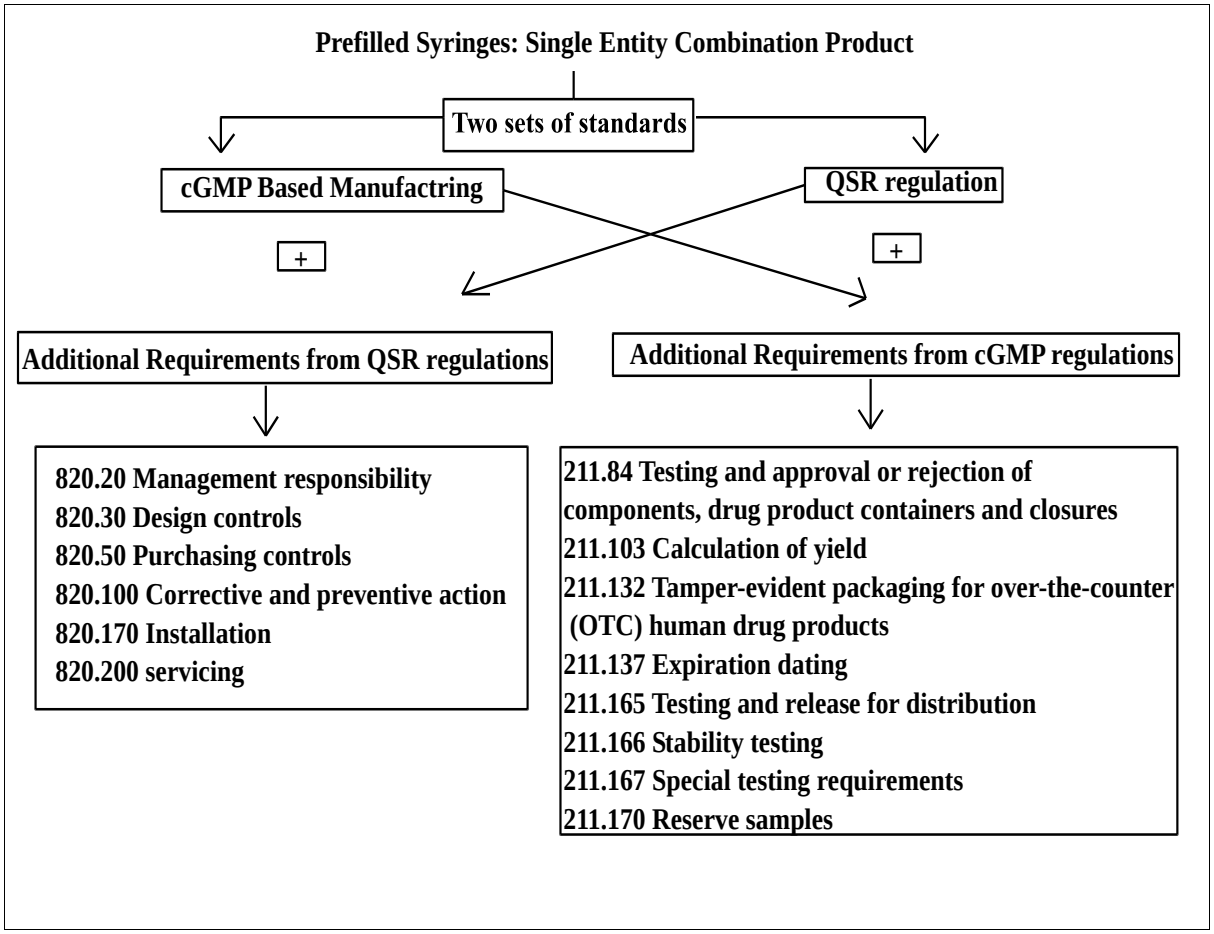


Fig 2: Stream lined system

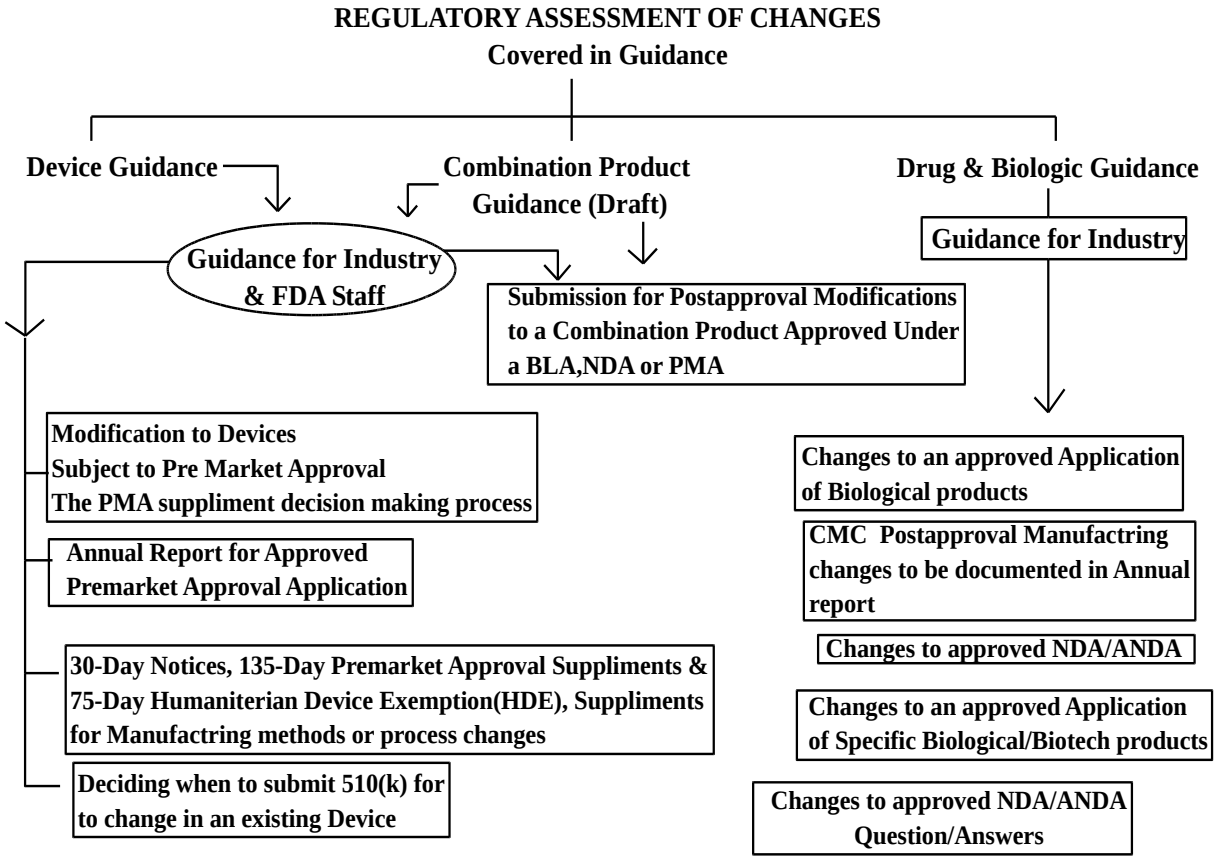
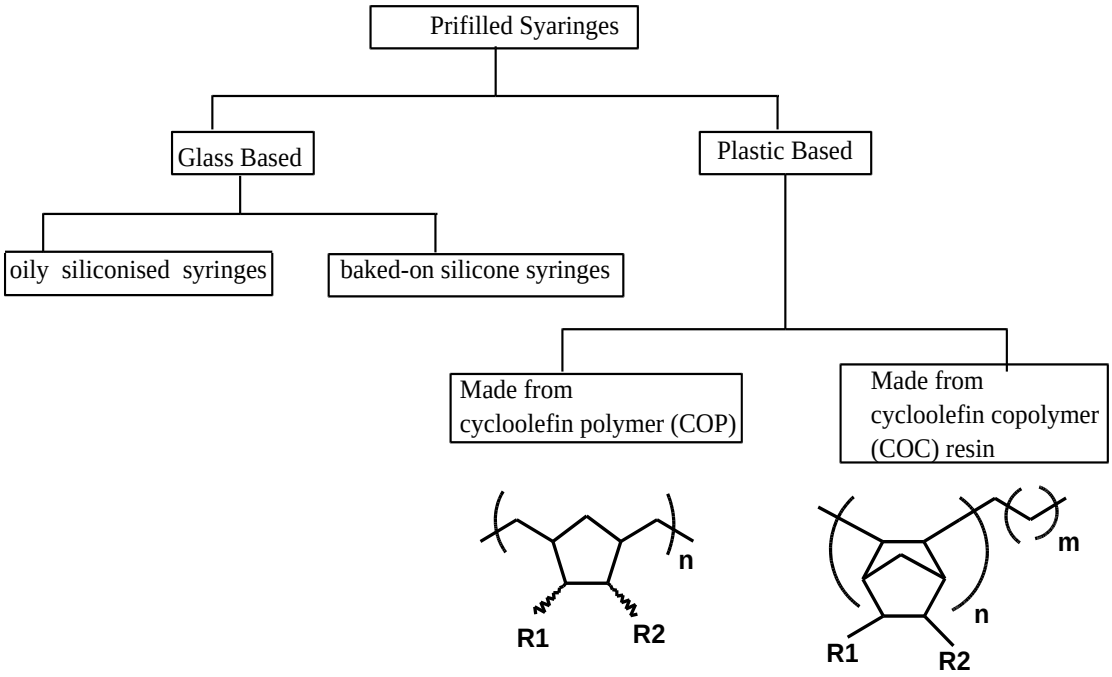


Fig 3:Regulatory Assessments of changes US-FDA



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