WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 6.041
Volume 5, Issue 6, 2075-2095 Review Article ISSN 2278 – 4357

PREFILLED SYRINGES: A REVIEW ON REGULATORY REQUIREMENTS

Aparna Peri*, Pravalika Methuku and V. Srivani

Gaeethanjali College of Pharmacy, Cheerayala, Hyderabad, Telangana.

Article Received on
19 April 2016,
Revised on 09 May 2016,
Accepted on 29 May 2016
DOI: 10.20959/wjpps20166-6950

***Corresponding Author**
Aparna Peri
Gaeethanjali College of Pharmacy, Cheerayala, Hyderabad, Telangana.

ABSTRACT

Prefilled syringes are pharmaceutical product which is used to deliver parenteral medications. A prefilled syringe is a single dose packet of parental drug to which a needle has been fixed by a manufacturer. Pre filled syringes are ready to use disposable syringes contains premeasured dosage, reduce dosing errors and increase patient compliance ,dosing accuracy, convenience, and safety; enhance patient quality of life; and reduce patient time in the clinic.A prefilled syringe helps to increase dosing accuracy, convenience, and safety; enhance patient quality of life; and reduce patient time in the clinic. It acts as primary container for the drug product like the ampoule. The advantages for drug developers using prefilled syringes are numerous; improved patient compliance and better cost efficiency, as well as mitigating the risks of drug wastage and product contamination. And mainly used for treatment of chronic conditions requiring patients to self-administer medication. The intent of this review article is to provide concise information about latest regulatory aspects of prefilled syringes, its manufacturing, advantages, disadvantages, challenges.

KEYWORDS: prefilled syringes, disposable syringes, medication.

INTRODUCTION

As one of the oldest forms of drug delivery, the first medical application of syringes can be traced back to the 9th century where early embodiments were used as surgical instruments by Egyptian surgeons. For hundreds of years following their advent, syringes were largely viewed as surgical instruments until the nineteenth century and the discovery of early injectable compounds, including morphine and other analgesics. During the 20th century the commercial use and application of syringes as drug delivery devices grew exponentially.

Today, more than 50 biologic medications and vaccines are marketed and supplied in prefilled syringes. Globally, more than 3.5 billion prefilled syringes are produced annually and used by patients and healthcare providers to treat a broad spectrum of conditions. Prefilled syringes are one of the "single entity combination product because it involves combination of two or more different medical products combined and produced as a single entity. An ideal choice for single-dose drugs, prefillable syringes offer easy-to-use fixed dose options that not only help pharmaceutical companies control costs by minimizing drug overfill, but also help to minimize microbial contamination and reduce medication dosing errors As name indicates they are filled by the manufacturer at the time of manufacturing which are ready to use. The usage of these prefilled got increased know a days due to increase in the number of patients who are suffering from chronic diseases for self administration of drug. These are used to administer the appropriate amount of medicament to the patient. They became a preferred device for parenteral administration of medicament, and mainly used for treating chronic diseases. Healthcare workers and patients using prefilled syringes for treatment in hospitals and as well as at home, as it is an efficient, reliable and convenient method for injecting medicament. Medicament which is available in prefilled syringes is potential.

Types of prefilled syringes system (PFS)

There are two types which include glass nased system and plastic based syeste

Glass based system : (**shantanu kale et al. world J pharma sci 2015)**

Traditionally barrel has been made from glass tubing. These glass tubes are transformed by heat in to barrel which is used to hold the medicament. But it has main disadvantages that glass is easily breakable in nature and requires added care while handling. Other drawbacks with glass are glass contains small amount of alkali which may cause a P^H shift in some products.

Glass prefilled syringes are of two types

1) Oil siliconised syringes:

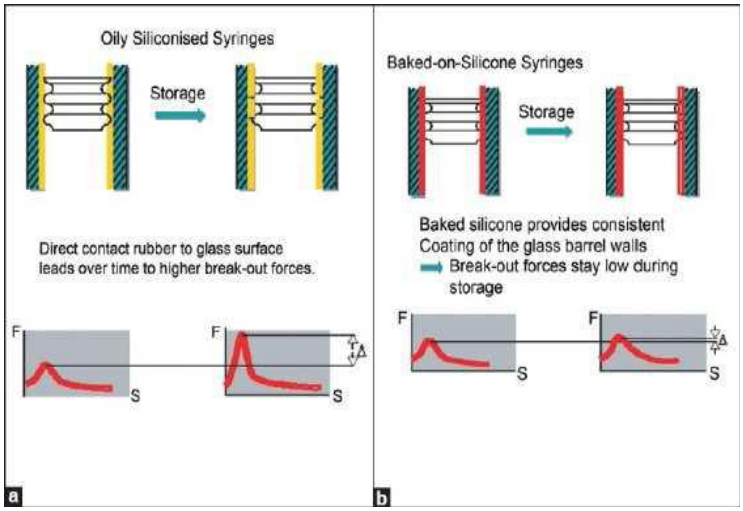
2) Baked on silicone syringes

Plastic syringes

Plastic syringes are gaining high acceptance compare to glass system because they can easily handle. Syringes which are made up of COC and COP (cyclic olefin polymer) have been developed. These cyclic olefin copolymers and polymers have excellent transparency, good

moisture barrier properties, and are chemically clean with very low extractable. They have good dimensional tolerance and high flexibility in design and no tungsten or adhesive is involved in fixing a staked needle to plastic syringes.

At the glass-based system of pre-filled syringe there are also different typesavailable. The manufacturer can choose between **oily siliconised syringes** and**baked-on silicone syringe**



Specification of separate components of pre-filled syringe

Prefilled syringes consist of different components with different materials such as plastic, glass, elastomer and silicone. For these special monographs of Ph. Eur. (1) and USP (2) should be considered following test parameters are described for the **evaluation of glass barrels:**

- Detection of germ content,
- Content of particles,
- Test on inner surface siliconization,
- Detection of glass particles,
- Detection of the influence of cooling on the glass barrel,
- Detection of deviation in the dimension,
- Test of colour adhesion on the glass barrel

Specification for the plastic barrel of pre-filled syringe

For the **plastic barrel** there are a lot of different monographs in the USP (2) and Ph. Eur. (1). For USA and Canada the monograph USP <661> is relevant.

In the **USP monograph**

Parameters and test method and limits for following plastic materials are described:

- Polyethylene high density
- Polyethylene low density
- Polypropylene

Specification for needle (cannula)

The cannula shall be fixed acc. to ISO 7864:193, 13.1. (74) For fixing cannula inside the glass cone an adhesive such as UV hardening adhesive acc. to USP class VI shall be used. The test on retention (steadiness) force shall be made acc. to ISO 7864. (74) The cannula steel shall meet the requirements of ISO 9626. (75)

Specification for lubricants

At the lubricants a distinction between silicone oil emulsion and silicone oil can be made.

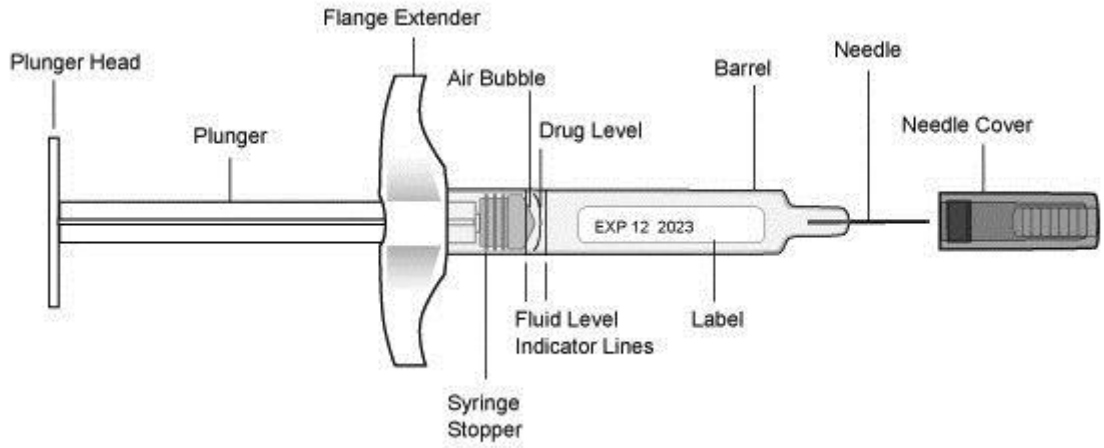
For the different lubricants following monographs of USP-NF (2) and Ph. Eur. (1) could be relevant:

- USP-NF monograph for “Dimethicone”
- Ph. Eur. monograph for “Dimeticone”
- and the Ph. Eur. monograph 3.1.8 “Silicone oil used as a lubricant”

Furthermore physical tests shall be made acc. to the defect evaluation list for “rubber parts” vol. 20, Editio Cantor (73). Based on this defect list following analysis parameter should be evaluated:

- Delivery, labeling of packaging
- The particle test
- Function of sealing lamellas with glass cartridge
- Foreign bodies and spots
- Form or production defects
- Visual examination of other defects

Components	Composition
Barrel	Glass or plastic
Piston	Elastomer
Tip cap	Elastomer
Plunger rod	Plastic
Lubricant	Silicone oil
Needle	Stainless steel
Needle	Elastomer
Needle shield cover	Plastic
Lock adapter	Plastic
Tamper evident	Plastic
Finger grip extender/Back stop	Plastic



Classification of pre-filled syringe in Europe

Acc. to the Council Directive 93/42/EEC of 14 June 1993 (40) concerning medical devices the pre-filled syringe belongs to the combination products (medical device + medicinal product). Furthermore the classification of such combination products is made acc. to the *Primary Mode of Action* as follows:

variant 1:

"Is the ***medicinal product form a single integral product*** *which is intended* ***exclusively for use in the given combination and which is not reusable****, then the single product shall be governed by Directive 65/64/EEC.* " Furthermore the requirements of Annex I to the Directive 93/94/EEC (40) regarding safety and performance related medical device features are concerned. An example for the variant 1 is the pre-filled syringe. Here the Primary Mode of Action **is as a drug**.

variant 2:

Where a device incorporates, as an ***integral part, a substance which, if used separately,*** *may be considered to be a medicinal product within the meaning of Article 1 of Directive 65/65/EEC and* ***which is liable to act upon the body with action ancillary to that of the device****, that* ***device must be assessed and authorized in accordance with this Directive*** An example for variant 2 is a heparin coated catheter. Here the **medicinal drug** is verified **as drug** acc. the Directive 2001/83/EC. (3) But the **catheter** is classified as **medical device of class III**.

EU	**USA**	CANADA
Guideline on Plastic Immediate Packaging Materials (5) CPMP/QWP/4359/03; EMEA/CVMP/205/04 EU-Directive 2002/72/EC Plastic materials and articles intended to come into contact with foodstuffs EMEA/410/01 <Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal> Commission Directive 94/62/EC <Packaging and packaging waste>	Guidance for Industry- Container Closure Systems for Packaging of Human Drugs and Biologics (FDA) (6) Guidance for Industry – Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products (February 2008) (44)	Information Requirements For Food Packaging Submissions - Health Canada Process Validation: Terminal Sterilization Processes for Pharmaceutical Products (GUIDE-0074) Good Manufacturing Practices (GMP) Guidelines - 2009 Edition, Version 2 (GUI-0001) Policy on Drug/Medical Device Combination Products – Decisions (48) DRAFT GUIDANCE FOR INDUSTRY "Quality (Chemistry and Manufacturing) Guidance: New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs) (2001-07-18)

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.(ISO 11040-4:2015 Prefilled syringes -- Part 4: Glass barrels for injectables and sterilized subassembled syringes ready for filling)

Filling process in prefilled syringes

Four principle methods are involved in the process of filling syringes**,** 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 may 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.

Bubble free filling

It is most advantageous method for non-viscous products, since viscous products can be filled without bubbles using online vacuum filling and stoppering alone. The advantages include: Enhanced Dosing accuracy, improved product sterility, decreased waste

STERILIZATION OF PREFILLED SYRINGE

prefilled syringes is considered as combination product therefore challenges posed in sterilization of prefilled syringes are different than challenges faced by medical device manufacturers Sterilization of prefilled syringe is mainly done by autoclaving or by ionizing radiation. Steam sterilization typically involves heating the device in a steam autoclave. Autoclave is not suitable for glass prefilled syringes and normal plastics ,as there occurs a PH shift in glass syringes during autoclave sterilization process. steam sterilization, however, is time and labor consuming, and compromises the aesthetics of the product due to packaging degradation from the steam treatment

Important points which need to be ensured before sterilization are

- Stability of the drug which chosen technique
- Temperature sensitivity and transportation requirement
- Time line between manufacturing and delivery to market

- Should meet Regulatory compliances

Market dynamics

The world wide prefill market is estimated to be one billion units.prefilled syringes in the US market have been growing at a rate of 20% per year many of the professionals are demaning for prefilled use because of its convenience and safety that prefilled syringes provide

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. 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.

Primary reason behind the growth of prefilled syringes include

- Ease of administration
- More convenient for use for professionals as well as users for home use
- Lower injection costs- less preparation ,fewer materials and easy storage and disposal Product diffentiation
- Reduces risk of dosage errors (https://www.yumpu.com/en/document/view/4550315/prefilled-syringes-ondrugdelivery/3)

Challenges

- The advantages of prefilled syringes seem overwhelming; nevertheless there are also some drawbacks to be taken in to condiseration when assessing prefilled syringes. For one, prefilles syringes are comples medical devices and as such they are more expensive than simpler container forms.it has to be carefully evaluated whether the higher cost of

the container can be compensated by the advantages such as the reduction of waste and product differentiation

- Challenges during manufacturing prefilled syringes include drug stability ,shelf life , leachables, extractables, and rising costs
- The major challenges include the interaction of prefilled syringes with the drug. This causes great concern because it creates stability issues. Manufacturers need to eliminate the interaction between drugs and packaging materials.
- Glass syringes, plunger, needles and some polymeric syringes are coated with silicone oil to reduce the friction when penetrating in to tissue. Biological products that are filled in to the syringes may interact with silicone and may result in the formation of aggregates.
- Regulatory bodies, companies and customers will scrutinize and look carefully at every aspect of needles and syringes especially as they are being used more and more today.
- Processing and quality control issues are therefore important. Manufacturing costs are rising, especially because of the growing concern of needle stick injuries. Safety measures to eliminate needle stick injuries are the major concern in the healthcare industry.
- Syringes with staked needles present another challenge. The needles in pre staked syringes are held with a UV – curved adhesive. this raises the risk for interaction with components of the adhesive that may be extracted
- The safety systems are very costly, and the safety system providers are continuously researching to develop low cost alternatives.
- 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.
- ANOTHER CHALLENGE IS DURING TERMINAL sterilization and shipping .the movement of plunger during shipping may cause plunger to move in to non sterile area of the syringe barrel and compromise the sterility of the content when plunger comes to its intendee position.

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.

Regulatory strategy

For most companies, the process of moving an injectable therapeutic to a prefilled syringe can be fairly complex because of sterility and stability issues associated with small and large molecule in addition to challenges related to the size and structure of biologic molecules. To facilitate a smooth path to regulatory approval, companies must establish a strategy that carefully evaluates proposed changes in manufacturing, packaging, and shipping processes and that ensures the company can validate the effect of these changes on the therapeutic molecule. The US Food and Drug Administration requires that any change in the manufacture of a drug product, whether major or minor, be put into place only after the license holder assesses the effect of the change on the identity, strength, quality, purity, and potency of the molecule, because these factors will influence the safety and effectiveness of the pharmaceutical (7). In addition, FDA has stringent requirements for changes that may affect parenteral drug product. These requirements pertain to moving a therapeutic to a prefilled syringe from another container–closure system; silicone treatments in the closure systems such as in elastomeric closures or the syringe barrels; and changes in the size or shape of a container that holds a sterile drug product (8). Any such change is considered to be "major" by FDA and must be documented in a prior approval supplement. Stability and clinical testing for parenterals depend on a multitude of factors, including the formulation, indication, mode of administration, size and functionality of packaging, and the introduction of new materials. Any potential need for clinical or stability data must be noted and planned for at the outset, and included in the stability protocol.

Getting started

The choice of a syringe system should be a critical part of the regulatory strategy and must be considered at the outset, perhaps even with product reformulation. The syringe system is

important because a packaging system that is acceptable for one therapeutic will not necessarily work for another because of differences in dosing ranges, patient populations, and in how individual molecules react to surrounding materials and conditions. Evaluation of the proposed syringe system must consider these factors, and regulatory submissions must support the suitability of the proposed packaging and storage conditions. An analysis of proposed syringe systems should take into account their appropriateness, functionality, and materials. First, the dosing device has to be suitable, and its graduations appropriate, for the intended patient population. At a basic level, the syringe must deliver the dose in the amount and rate stipulated in the package insert. In addition, the physical characteristics of the liquid drug formulation must be appropriate for the dosing device to ensure accurate dispersion of the drug through the needle. Second, the proposed system must function correctly throughout its shelf life. The results of coating integrity testing, effect of viscosity, and syringe-ability must be considered. Moreover, scale intervals on the syringe must represent the labeled dosages, and gradations in dose must be easily read. The type should be embossed or printed and legible throughout the shelf life of the product. These markings cannot fade or become dislocated during the use or life of the product. In addition, stopper movement during use, as well as the effect of shipping on stopper movement, must be considered to ensure sterility of the product and to avoid particulate contamination. Third, materials in the proposed syringe must be compared with those of the current vial. The analysis should consider whether:

• The material in the proposed syringe, including in the container, plunger device, and closure system, protects the drug product

• The syringe system introduces a new material

• The system will require any changes to the drug product formulation. Choosing a container and closure system made of the same materials as the vial will eliminate the need for additional extractable and leachable studies. Any new materials, including those in the hub or needle, will need to be evaluated in stability testing. Extractable studies also must include proposed labels, adhesive, and ink if the barrel of the syringe is not made of glass.

Stability protocol. FDA rules governing current good manufacturing practice (GMP) stipulate that companies develop and thoroughly document a testing program to assess the stability characteristics of the drug product (9). Consequently, a company must define stability testing requirements related to the container–closure system. These requirements include how temperature, humidity, and light influence the shelf life of the drug and help to determine appropriate storage conditions and expiration dates for the product. A stability

protocol that is specific to the molecule and the proposed drug-delivery device must be written, implemented, and evaluated to assess the stability characteristics of the molecule in the container–closure system (9). Although some extractable and leachable studies related to the dry or liquid vial presentation may be transferable to the new format, some new stability testing is required when moving an injectable therapeutic to a prefilled syringe (see Table III). The long, narrow dimensions of a syringe increase the molecule-to-surface-area ratio from the previous vial presentation. As a consequence, accelerated and long-term stability studies are necessary to determine whether the change affects the extractable and leachable parameters and to understand the impurity and degradation profile of the molecule in the container–closure system. The stability protocol should detail the sample size, test intervals, storage conditions, validated analytical methods to be performed, the container–closure system, test specifications, and number of batches required. In addition, reconstitution studies will be required for parenteral products offered in a kit with a prefilled diluents syringe or in a dual-chamber prefilled lyophilized syringe. Tests and specifications must be based on knowledge of the degradation pathway for the particular molecule, use validated and Stability-indicating methods, and specify limits appropriately.

Testing

Pre-filled syringes are examined for appearance of the syringe and components and performance as measured by container closure integrity, movement of a plunger within a syringe and retention and delivery of the contents of the syringe. The appearance of a syringe and its components may be affected by simple defects in the materials. These can include spots on plungers that may originate from mixing of the multiple components of the polymeric material or blemishes in the glass. They can also be more severe such as a needle protruding from the inner shield on pre-staked syringes. A protruding needle can be difficult to detect if only the tip of the needle exits the inner portion of the shield. Manual and automated appearance testing should reject syringes with defects by recognizing them as inconsistencies in the materials. The appearance of pre-filled syringes may also be affected by the syringe filling and sealing operations during finished product manufacturing. Plungers inserted into syringes using an insertion rod can occur with black marks or can be damaged during the process. Black marks can occur when the insertion rod is not properly aligned and slides against the insertion tube resulting in stainless steel particles. The plungers can also be damaged during insertion and appear with tears in the ribs (Figure 14). The damage can be prevented by conducting a set-up procedure prior to filling product to ensure that the

equipment is working properly. The damage can also be a combination of equipment setup and a soft or friable plunger formulation. Some plunger formulations may also exhibit creases where the ribs of the plungers make contact with the surface of the syringe. The force required to initiate movement of a plunger and the force required to sustain the movement is often tested during product development.

Clinical testing

Clinical studies are required when there is a change in indication or new route of administration for the drug. However, movement from a dry or liquid vial to a prefilled syringe also necessitates clinical testing if the reformulated drug's degradation or impurities profile change.

Submission of application and Regulatory challenges

The FDA has reviewed numerous pre-market notification and pre market approval applications for injection devices. The list is useful for identifying all of the technical and scientific issues that should be considered during the development and registration of an injection device. However, the purpose of a guidance document for industry and FDA staff should be to reduce regulatory uncertainty.

Interested parties should carefully read the draft guidance document and provide their perspectives to the FDA. The following is intended to point the reader to parts of the draft guidance that may have important ramifications for injector marketing applications.

Typically, general use injection devices intended for the delivery of a variety of drugs and biologics, are cleaned for marketing by FDA though the 510 (k) pre market notification process. On the other hand, AN INJECTION device intended to deliver a specific drug or biological product is regulated by the FDA as a combination product is regulated by the FDA as a combination product and these typically gain marketing approval through an NDA or BLA.

US

- Any combination of medical device, biologic and drug which are included under 21 CFR2 must meet the requirements. Approval path determined by **primary mode of the action**
- 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

Finding regulatory sources

FDA (CDRH) website – can use product codes to look up recognized standards, guidance documents, etc. applicable to a given device type

•Standards and guidance documents reference other guidance documents and standards

•Adverse events and Medical Device Reports

•MEDDEV guidance's

Container closures PFS requirement sources includes FDA guidance for closure system for packing human drugs and biologics ,USP general chapters ,ICH M4Q-CTD i.e. stability of container device ,ICH Q6A i.e test procedures and acceptance criteria related to functionality of delivery system, ICH Q8(R2) I.e. demonstration of reproducible and accurate dose delivery

DEVICE RELATED CHANGES – EU Approach to Determining Reporting Category

•Device related changes are assessed according to EC Medicinal Product Variation guidance

•Specific change types defined, along with a reporting category. Conditions for the reporting category must be met in order to submit at IA, IB and documentation required in the submission are defined

•If the change type is not included in the guidance OR the conditions are not satisfied, a Type II variation is needed

•Type 1B unforeseen may be appropriate depending on the circumstances of the change

•Consider whether change has an effect on the Essential Requirements

Submission approach

PFS presented BOTH as a container closure system and as a combination product.

Typical C/C content presented in 3.2.P.2.4. (Pharmaceutical Development: Container Closure System) and 3.2.P.7 (Container Closure System) according to ICH recommendations .Supplement 3.2.P.2.4 with summary of combination product design and development .Supplement 3.2.P.3 or 3.2.P.7 with combination product manufacturing and controls Provide a roadmap of device and combination product related content as part of the Module 1 Information for Reviewers .

General Regulatory Differences

Each Center has a different set of laws and regulations acting as the basis for its authority Food, Drug and Cosmetic Act (drugs and devices)

Public health services act

Biologic

Code of federal regulations (21 CFR)

- 314 drug
- 600 biologics
- 800 devices

Any available laws or regulations may be applied as necessary and appropriate for regulation of specific combination product This will change as new regulations are promulgated

Least Burdensome provisions of the FDA Modernization Act do not apply to the complete combination product only apply to the device component

SPECIFIC REGULATORY DIFFERENCES

- Electronic submissions
- Meetings
- Clinical studies
- Non-clinical studies
- Marketing applications
- Manufacturing and compliance
- Regulatory Meetings

  CDER/CBER
- Type A,B or C
- Formal processes
- 30,60, 75 days

  CDRH

- Pre submission
- Informal
- 60 day clock

  Regular request
- Informal
- First available date

  Agreement
- Formal
- 30 day clock

  Clinical studies: CDER/CBER

  Investigational New Drug (IND)
- Phase 1 Primarily Safety and to determine pharmacologic and metabolic activity and side effects
- Exempt from CGMPs
- Phase 2 Often dose-finding studies
- Study efficacy in a limited group of individuals Phase 3 Used to evaluate overall benefit-risk relationship of the drug
- Provide adequate basis for physician labeling
- Clinical Hold

Clinical studies: CDRH

Investigational Device Exemptions (IDE)

- Feasibility
- pilot
- pivotal

Exempt from QSRs

Number of required studies product-dependent

No direct mapping to IND phases

No concept of clinical hold

Need to demonstrate “relative safety” prior to initiation

Non clinical studies

Types of data is the same between Centers but the timing of data and conditions for initiating clinical trials are different

CDRH

- Specific upfront data submission with commitments for subsequent data submissions during studies
- All necessary data submitted upfront as part of "relative safety" demonstration
- Usually no additional data submitted after approval

Human Factor Studies

Formative Usability Testing

Identifies strengths and weaknesses

–How can it be made better?

–Should be conducted while device is still under development Iterative Process

Summative Usability Testing

Final product testing

- Tested by representative user under realistic conditions
- Develop mitigation strategy for failures or problems that arise Modify the design interface
- User instructions/training
- Re-test to show effectiveness of mitigation

Quality System Requirements for Drugs, Biologics, Medical Devices and Combination Products

According to FDA's combination product definitions in the *Product Jurisdiction Regulation*,11 prefilled drug delivery devices such as prefilled syringes, auto-injectors and pens containing drugs or biologics are combination products. Some manufacturers prefer to consider syringe components as components of a pharmaceutical container closure or primary parenteral packaging system. While the syringe constituent part of a prefilled syringe is a container closure system, syringe components, once assembled, form a syringe, which is a medical device. Filling a medical device with a drug formulation creates a combination product. FDA has the authority to apply drug, biologic and medical device regulations to any product composed of a drug or biologic and medical device constituent parts. Thus, FDA can require medical device, drug or biologic manufacturers of combination products and/ or their constituent parts to comply with applicable requirements of the both QSR and the CGMP regulations. According to the proposed quality system rule for combination products, when the constituent parts of a combination product are manufactured separately and remain

separate, each is subject only to the regulation that pertains to that type of constituent part. When the constituent parts of a combination product are combined to form a single-entity combination product, or are co-packaged to form a kit combination product, the constituent parts retain their regulatory status both before and after they are combined. When the constituent parts are combined or co-packaged, quality system requirements that apply separately to each constituent part also apply to the entire combination product. FDA considers the QSR and CGMP regulations to be similar and overlapping. Each regulation is designed to fit the characteristics of the products it regulates. The proposed quality system rule for combination products suggests specific requirements of one regulation can be satisfied, perhaps with some fine tuning, by complying with a general requirement of the counterpart regulation. For manufacturers of single-entity and kit combination products containing drug (or biologic) and device constituent parts, rather than implementing multiple and potentially redundant quality systems, the proposed rule allows compliance with either the CGMP or the QSR to satisfy most requirements. There are gaps where the regulations do not overlap. To ensure full compliance with quality system requirements for single-entity or kit combination product development and manufacture involving drug (or biologic) and device constituent parts, missing QSR elements may be added to an existing CGMP-based quality system (and vice versa in the case of a medicated device developed under a QSR-based quality system) to form a "streamlined" (i.e., hybrid) quality system.

The proposed rule identifies six gaps between a CGMP-based quality system and the QSR: management responsibility, corrective and preventive actions, design controls, purchasing controls, installation and servicing Installation and servicing usually do not usually apply to drug delivery systems. With some fine tuning, the management responsibility and corrective and preventative action requirements of the QSR can be satisfied by conformance to the ICH Q10 guideline that defines CGMP best practices. This leaves design controls and purchasing controls as truly unique elements of the QSR, for which there are no counterparts in the CGMP regulation. Design controls are interrelated practices and procedures intended to control medical device design development throughout the product lifecycle. They are first applied during establishment of the initial device design requirements specification. The QSR requires established and maintained formal procedures defining the design planning process activities and responsibilities. Procedures also are required to assure design inputs appropriately satisfy performance specifications and user needs and design outputs allow adequate evaluation of conformance with design inputs. Design reviews must be conducted

by appropriately structured multidisciplinary teams at appropriate times throughout design development. Design verification testing procedures must be established and maintained to determine whether the design output satisfies the design input requirements. Procedures must be established and maintained for validating production units under use conditions to demonstrate that the product's intended use and user needs are satisfied. Design changes and manufacturing transfer from prototypes to production and beyond are also controlled through design control procedures. Finally, all records needed to demonstrate that the product was developed in accordance with the design plan are archived in a Design History File, which differs from a Pharmaceutical Development Report. Purchasing controls are a set of interrelated practices intended to ensure purchased products, components and services conform to specifications; and selected suppliers, contractors and consultants are qualified; their performance is periodically assessed; and appropriate quality controls are established and maintained based on supplier performance. Purchasing controls can be viewed as a design control system for purchasing. Both follow the same basic principles, methodically establishing input requirements and verifying performance outputs. Vendor selection must be based on an evaluation of their ability to meet specified requirements (viz., design input) and appropriate controls (viz., design verification) must be established on the basis of this evaluation (viz., design output). Records of acceptable suppliers must be established and maintained (viz., Design History File). Communication of requirements, including quality requirements, must be documented (viz., Design History File). Purchasing documents should include, where possible, an agreement that the vendor will notify the device manufacturer of changes to the product, processes or services to enable the impact of the change on overall product quality to be evaluated (viz., design changes). Typically, pharmaceutical manufacturers establish quality systems that comply with the CGMP regulation, and medical device manufacturers establish quality systems that comply with the QSR. Medical device manufacturers may obtain certification of conformance to the international quality system standard for medical devices, ISO 13485 (Medical Devices—Quality management Systems—Requirements for Regulatory Purposes). Medical device manufacturers that consider their drug delivery products to be pharmaceutical packaging system components may obtain certification of their quality system's conformance to the international standard ISO 15378 (Primary Packaging Materials for Medicinal Products—Particular Requirements for the Application of ISO 9001:2000). It remains to be seen, once the final rule is in place, whether FDA will consider conformance to these standards to be sufficient for vendor compliance

with quality system regulatory requirements for combination products, device constituents and component part

Industry Concerns

Pharmaceutical and medical device companies expressed their concerns about the proposed rule by providing comments directly to FDA or through their trade or professional associations. Some of the key issues raised in these comments concern FDA's expectations on the applicability of the QSR to component manufacturers of combination product device constituent parts. Clarification also was requested on how FDA expects combination product manufacturers to apply device quality system requirements to combination product constituent parts before and after arrival at the manufacturing facility where the combination product is formed. Pharmaceutical companies manufacturing prefilled drug delivery systems that consider prefillable syringe components to be pharmaceutical packaging or container closure systems subject only to CGMP regulations have sought clarification from FDA on the need to apply design controls to their pharmaceutical formulation and packaging development activities.

Others have sought clarification of what FDA expects combination product manufacturers to do to document the compliance of a "streamlined quality system" to 21 CFR 4, Sub-part A. Pharmaceutical and medical device manufacturers also would like to understand how FDA will apply these new quality system requirements to legacy products. These and other issues are expected to be addressed in the final rule and preamble and in anticipated guidance documents.

REFERENCES

1. Pre-filled syringes: a review of the history, manufacturing and challenges, Sacha G[1], Rogers JA, Miller RL. Pharmaceutical development technology.2015 JAN 20 (1).
2. world journal of pharmaceutical sciences issn (print):2321-3310; issn (online) :- drug prefilled non re usable syringes as drug device by Nupur s .kale, asim kazi and shantanu s. kale
3. prefilled syringes: an innovation in parenteral packaging by sagar makwana, biswajit basu, yogita makasana,[1] and abhay dharamsi ,int j pharm investig. 2011 oct-dec; 1(4): 200–206.
4. prefilled syringe device training: novel approaches & technologies to increase patient confidence & decrease anxiety

5. Regulatory Submission Strategies for Pre-filled Syringes by Biogen (5th Annual Pre-filled Syringes Summit, San Diego, CA, Pre-Conference Workshop, 23 June 2015).
6. supplement to the september 2009 issue, pharmaceutical technology, apli synthesis and formulations
7. Development of an adequate strategy for a global change in the primary container closure system of a parenteral herbal drug, BONN 2013.
8. Recent Developments in Prefilled Syringes,The review of american pharmaceutical business & Technology October 03, 2012,BY Patty H. Kiang, Ph.D.
9. https://www.yumpu.com/en/document/view/4550315/prefilled-syringes-ondrugdelivery/3
10. prefilled syringes and usability of opthalmic viscosurgical devices by shiba t, tsuneoka h june 2014.
11. James c Boylan; Steven L Nail. Parenteral Products. In: Banker GS, Rhodes CT, eds. Modern Pharmaceutics. New York: Marcel Dekker, 2002; 360-410
12. Pre filled syringe-ready to use drug delivery system :a review by ingle RG, Agarwal AS,pubmed. Gov 2014 sep ;11(9)
13. Michael NE. West Prefillable Syringe Solutions Glass and plastic based system. [Last accessed on 2011 Jul 14]; Am Pharm Rev. 2012; 4: 12–6. Available from: http://www.westpfssolutions.com/en/prefsys .
14. Drug prefilled non – reusable syringes as drug device by Nupur S.Kale, Asim kazi and shantanu s.kale ; world journal of pharmaceutical science ISSN print 2321-3086(online);2015
15. Prefilled syringes: in the operation room & the home , from emergency medications to long term biotherapeutics – on drug delivery FEB 2013 issue ISSN- 2049-145 X
16. Glenn AT. Prefillable syringes: Trends and growth strategies. Cedar cottage, Newtimber Place Lane, West Sussex, BN6 9BU, United Kingdom: ON drug delivery Ltd; 2006. Registered in England: No 05314696