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Review Article

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Pre-filled syringes in developed and developing region: An insight into Regulatory considerations

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Abstract

A Pre-filled syringe is a disposable syringe that is supplied already loaded with the substance to be injected. It is a unit dose of parenteral medication to which a needle has been fixed by a producer. They are small which make them easy to carry and are dependable for delivering a precise dose of medication. These reasons are leading to growth of parenteral medication in pharmaceutical market. The intent of this review article is to provide information on regulatory guidelines involved in submission approach for marketing authorization of pre-filled syringe in developed region (USA, EU) and developing region (India). It also further explains about complexities associated with Pre-filled syringes in terms of regulations, submission approaches and quality development considerations in developing region. There is a need to develop an effective regulatory framework to make regulations of Pre-filled syringes more comprehensive for regulatory bodies. A harmonized forum to be made through which single application can be made and single review process can be followed to avoid deviations in regulatory pathways.

Keywords: Pre-filled syringes, regulations, combination products, Primary Mode of Action (PMOA), parenteral products

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1. Introduction

For parenteral administration of medications, Pre-filled syringes (PFS) have become preferred choice of delivery systems in healthcare facilities. They are unit dose preparations with already loaded medication in it. Pre-filled syringes offer several advantages to patients and a healthcare provider such as less time is required for administration of the medicine. An accurate dose is accessible for conveyance to the patient, no overload volume, minimal wastage so beneficial for highly potent and expensive drugs such as controlled substances (e.g. Morphine).

Pre-filled syringes are gaining solid acknowledgment as a favoured device for parenteral administration for injectable biologics and biotechnology drugs, protein-based medications, sustained release formulations, and other parenteral medicines like antithrombotic medications, immunizations, blood stimulants, interferons, and other treatment of perpetual conditions like rheumatoid joint pain expecting patients to self-control medicine several times each week.

2. Regulations for Pre-filled syringes in USA

In United States of America (USA), PFS are combination products {21 CFR 3.2e (i)}. Historically Pre-filled syringes were generally registered as container closure system for the medicinal product contained in it. Pre-filled syringes are a "single entity combination product consist of two or more regulated medical products that are marketed as a single unit" (1).

21 CFR part 4 elucidated intentions to authorize Pre-filled syringes as combination products subject to current Good Manufacturing Practices (cGMPs). "Syringe is a device used to deliver medical product. Accordingly, a pre-filled syringe is a combination product and subject to this rule" (preamble) (2).

Congress previously recognized the requirement for explicit guideline on combination products in Safe Medical Devices Act of 1990 (SMDA).

The Office of Combination Products (OCP) was set up in 2002 which is a part of Food and Drug Administration (FDA's) implementation of Medical device user fee and modernization act of 2002. OCP is in charge of (3, 4):

- Assigning a centre with primary jurisdiction for combination products
- Ensuring opportune pre-market review of combination products
- Ensuring consistency of post market regulations of combination products
- Reviewing and modifying guidance documents and regulations pertaining to combination products.

As drug-device combination products, Pre-filled syringes are subject to cGMP requirements for drugs and devices (21 CFR part 4). In the US, the Final Rule for cGMPs for Combination Products was published by the FDA on January 22, 2013 and issued under 21 CFR Part 4. Within the new guidance was the concept of a 'streamlined approach' to the application of the good manufacturing practices or quality system regulation (QSR) (Figure 1). To ensure full compliance with quality system requirements for Pre-filled 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 (5).

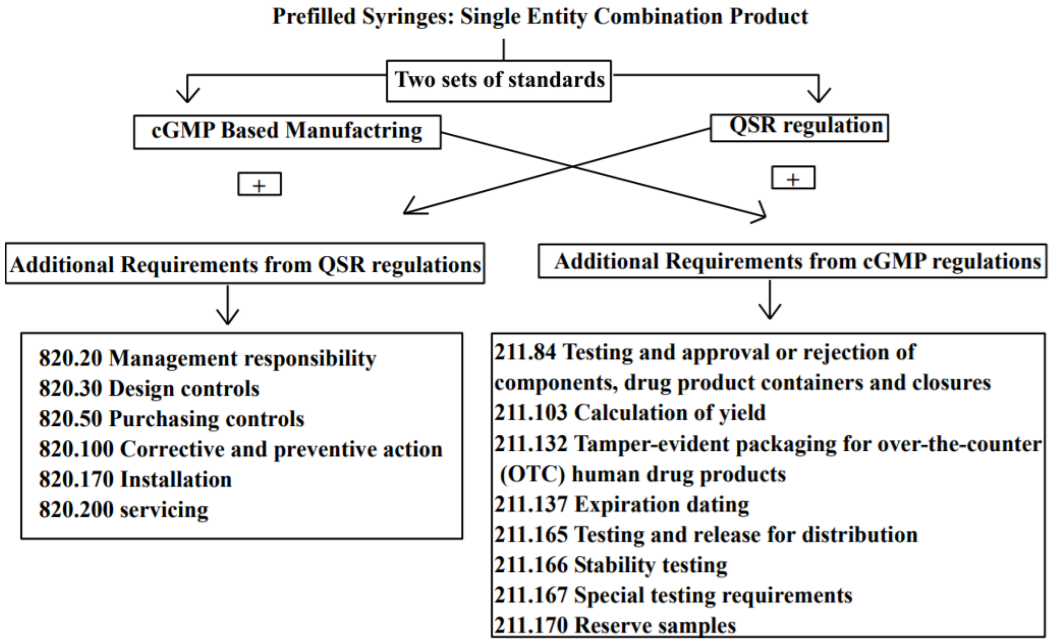

Figure 1. Stream-lined system for Pre-filled syringes (5)

Process for marketing authorization

Combination products such as Pre-filled syringes are allocated to CDER or CBER as lead centre due to Primary Mode of Action (PMOA) (therapeutic action on the body) (21 CFR part 3-PMOA is defined as single mode of action of a combination product that gives most imperative therapeutic activity of the product). OCP is in charge for prompt assignment of a new combination product to lead FDA review centre which might be CDER, CBER or CDRH. For example, Drug eluting stents are regulated as devices while Pre-filled syringes (PFS) are regulated as drug.

Three step process to obtain a marketing approval for pre-filled syringes

Figure 2. Process to obtain a marketing approval for pre-filled syringe

Lead centre assignment

PMOA standard defines Lead Centre. The process for assigning lead centre is illustrated in Figure 3. (6, 7)

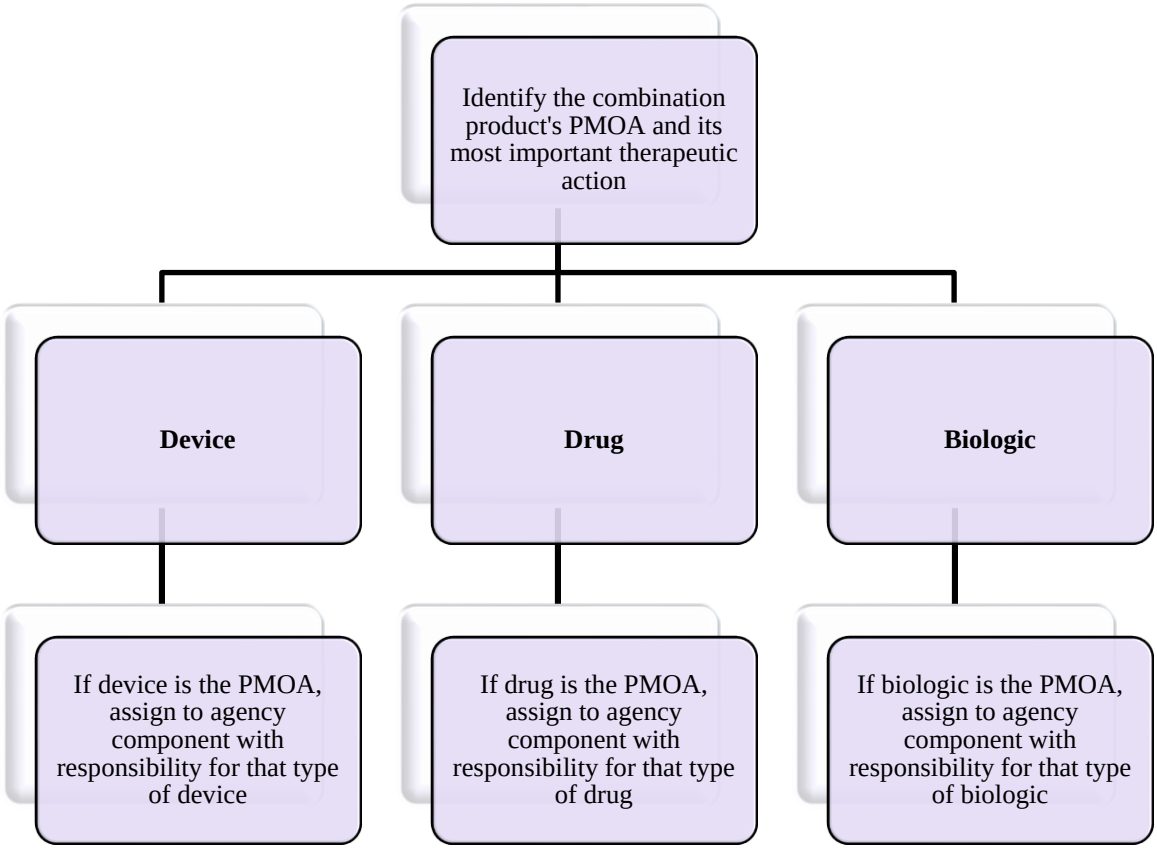

Figure 3. Decision algorithm for assignment of lead centre (6)

If necessary, submit a request for designation (RFD) to the FDA office of combination products.

Premarket Review Process

The conformity assessment is done by the US FDA Centres:

- Based on safety and effectiveness—constituent parts & interaction of constituent parts
- Combined/coordinated analysis and decision-making by Centres, with OCP input as needed

Varying pathways to market depending on technology and PMOA

Consistent procedure and standards to review process

Marketing application

- Once submitted the product application has a coordinated review by centres
- Generally, only one marketing application needed
- If two are appropriate (may be the case for cross-labelled combination products), authorize marketing only when/if both are ready for approval/clearance
- Facility inspections by staff is conducted with appropriate expertise for all constituent parts:
  - ✓ Strong business relationships can be essential, e.g., to ensure success
  - ✓ Ongoing reliance on proprietary data
  - ✓ Appropriate coordination of post marketing changes to constituent parts

After the assignment of lead centre, the product developer can approach the lead centre for market authorization by following the required market application to the lead centre (6-8).

For pre-filled syringe, the lead centre is CDER/CBER so the product should be submitted under NDA (New Drug Applications) (9, 10).

Generally, drug or biological product information for Pre-filled syringes product information and related engineering and manufacturing information should be located in the same eCTD sections that would provide similar information for the drug or biological product alone. Specific sections in eCTD for PFS are as follows:

- **Section 3.2. P.3 Manufacture:** PFS manufacturing applies to the entire combination product (e.g., drug –device combination) in accordance with 21 CFR Part 4. It includes applicable device information pertaining to manufacturing or assembly of PFS as a whole. As applicable, this section may hyperlink to unique device constituent manufacturing information in 3.2.R.
- **Section 3.2.P.3.1 Manufacturer(s)**
  - ➢ For each facility identify the type of manufacturing and testing activities required.
  - ➢ For each facility that is subject to 21 CFR part 4, identity whether it follows the combination product streamlined manufacturing approach and identify the

base set of regulations (i.e., 21 CFR 211 or 820).

- Provide a detailed list of all manufacturing facilities; what activities occur at the site (e.g., assembly, filling, sterilization, testing, other); what constituents are at the site (e.g., drug only, device only, both drug and device). For the facilities that have both the drug and device, identify which combination product operating system is used at the site.

- **Section 3.2.R Regional information**

  This section may be used for device engineering design documentation and narrative explanations that are not otherwise provided in Section 3.2.P.7. Examples of the information include the following:

  - Design Input Requirement
  - Design Output Specifications (e.g., device description, drawings, specifications, bill of materials, etc.)
  - Design Verification Plan/Summary Report and supporting data (e.g., software, electromechanical conformance, bench testing, biocompatibility)
  - Design Validation Plan/Summary Report and supporting data (e.g., performance testing, narrative discussion of the applicability of data provided in Module 5)
  - Risk Management File
  - Traceability Matrix

3. Regulations for Pre-filled syringes in European Union (EU)

With the publication of the new regulation on medical devices (MDR, regulation (EU) 2017/745) comes an important amendment to the medicines legislation, in article 117, for integral drug-device combinations in Article 1.9 (chapter 1 scope and definition of the MDR) gives the definition of a single integral product as:

"If the device intended to administer a medicinal product and the medicinal product are placed on the market in such a way that they form a single integral product which is intended exclusively for use in the given combination and which is not reusable, that single integral product shall be governed by directive 2001/83/EC or regulation (EC) no 726/2004, as applicable" (11).

In that case, the relevant general safety and performance requirements set out in Annex I to this Regulation shall apply as far as the safety and performance of the device part of the single integral product are concerned.

Examples of integral products which are not reusable are Pre-filled syringes, pre-filled pens, nebulizers pre-charged with a specific medicinal product, patches for transdermal drug delivery and pre-filled inhalers.

So, Pre-filled syringes can be defined as single, not reusable integral drug-device combination which is intended exclusively for use in the given combination (11).

As per new guidance documents published by EMA on 28 February, 2019, Medicines can be marketed for use in combination with a medical device, usually to enable the delivery of the medicine.

If the principle intended action of the combination product is achieved by the medicine, the entire product is regulated as a medicinal product under Directive 2001/83/EC or Regulation (EC) No 726/2004. So PFS is regulated as a medicinal product by CHMP.

Process for marketing authorisation

Within Europe, PFS (Pre-filled syringes), which are regulated as medicinal products but which contain a delivery device and form a single integral product, are primarily the scope of the EBE (European Biopharmaceutical Enterprises) working group.

The group has a broad scope with emphasis being on understanding specifically technical requirements and information required to achieve successful Marketing Application registrations and Life Cycle Management filings and on the emerging requirements from Europe.

Article 117 of the Medical Devices Regulation (MDR) (Regulation (EU) 2017/745) amends the Directive on medicinal products for human use (MPD) (Directive 2001/83/EC). This will significantly affect pharmaceutical manufacturers supplying drug delivery devices in combination with their medicinal products (such as Pre-filled syringes). It will also impact device manufacturers supplying these drug-delivery devices to pharmaceutical manufacturers for inclusion in medicinal products (such as empty syringes). Notified bodies will also be affected.

This change affects medicinal products that incorporate a device that would be covered by the MDR if supplied separately. The dossier for a marketing authorisation under the MPD will have to include evidence of the conformity of the device part with the applicable general safety and performance requirements in Annex I to the MDR. This could be either:

- an EU declaration of conformity or the relevant certificate issued by a notified body that allows a CE mark to be affixed to the device, or
- an opinion on the conformity of the device with the general safety and performance requirements in the MDR. This has to be issued by an appropriately-designated notified body, if the conformity assessment of the device, if used separately, requires the involvement of a notified body (12).

For Pre-filled syringe, drug is principal action, medicinal product directive 2001/83/EC drives approval through medicinal competent authority; filed as a single

MAA. For device elements, annex I of MDD to be followed as far as safety and performance of the device is concerned (13).

Within the current regulatory landscape, guidance which covers requirements for registration of pharmaceuticals such as ICH M4Q, does not sufficiently address the Module 3 considerations to ensure registration of an integral drug-device combination product. In the absence of such key guidance, it is known that location of information related to the device component, as well as specifically what level of details is submitted, is variable across companies.

Location of quality information and data on safety and performance of the device component of PFS for eCTD Module 3:

- **3.2 P** All Quality information related to device component and combination product safety and performance
- **3.2 R** Compliance with MDD Annex 1 – mentioning applicable studies performed to demonstrate compliance
- **3.2.P** sections May cross refer studies handled in the QMS not provided in the dossier

Regarding Module 3 dossier content strategy, it is the Industry position that Module 3 shall be built around a high-level package on the manufacture and control of the medical device component in Module 3 that is focused on: -

- Manufacturing and controls
- Compatibility/interaction between the drug product and the device
- Container closure integrity
- Accuracy of dosing
- Functional performance
- Usability of the product

In case device components may be utilized for a number of different injectable products (e.g. PFS and pre-filled pens), a system similar to the US Device Master File could be proposed in case a Notified Body review is required, e.g. where

- a general Technical file is maintained (with the optional support of the component suppliers).
- a specific section is developed for the individual combination products.

Regulatory review process

The review process for drug-device combinations like Pre-filled syringes follows Centralised procedure in EU (Figure 4) (14).

- Firstly, the applicant submits Marketing Authorisation Application (MAA) for drug-device combination (e.g. PFS) to CHMP and device file to NB (Notified Body) for assessment.
- The review of medicinal product and delivery device takes place simultaneously.
- It takes about one day by CHMP to validate the application.
- Within time period of 80 days, NB gives opinion on acceptance or rejection of delivery device.
- After 120 days, CHMP submits review on medicinal product along with NB opinion to CA (Competent Authority).
- Then, a query response phase conducted between CHMP and applicant.
- Then, finally after time period of 210 days, CHMP gives opinion/decision on approval of MAA for a pre-filled syringe in European Union.

4. Regulatory system in India

In India, combination products regulation is not clear; some products of this category are treated as drugs irrespective of the device component associated with it; e.g., drug eluting stent (15).

As per CDSCO, there are two factors which decide whether a product is to be regulated as either drug or device i.e.

- Regulatory status of product in country of origin
- Mechanism of action/ primary mode of action

PFS are pre-measured single -dose ready-to-use injectables for parenteral drug. Tracing its history in early 80's, PFS, presently is the most preferred drug delivery system for parenteral purposes. Countries like US, Europe and Japan, pre-dominantly use PFS, while its usage is expanding in developing countries as well like in India and China. For Pre-filled syringes, there are no well-defined definition and regulations as such issued by DCGI.

However, there are three categories which are important to explain:

i. Prefillable glass barrel (without needle):

This category consists of a glass barrel, plunger. These are non-regulated in India and are mainly considered as container-closure system because there is no drug molecule filled in it and they are without any needle (16).

ii. Prefillable glass barrel (with needle):

These consist of glass barrel, plunger, needle and are intended for the automatic self-administration of drugs and biologics from standard glass barrel.

As per CDSCO guidance for medical devices, 2018, these are regulated as notified medical device under class B. (17, 18).

iii. Pre-filled syringe:

This category consists of glass barrel, plunger, needle, needle shield along with active drug in it.

They can be regulated as either drug or device depending on their intended use or action (19).

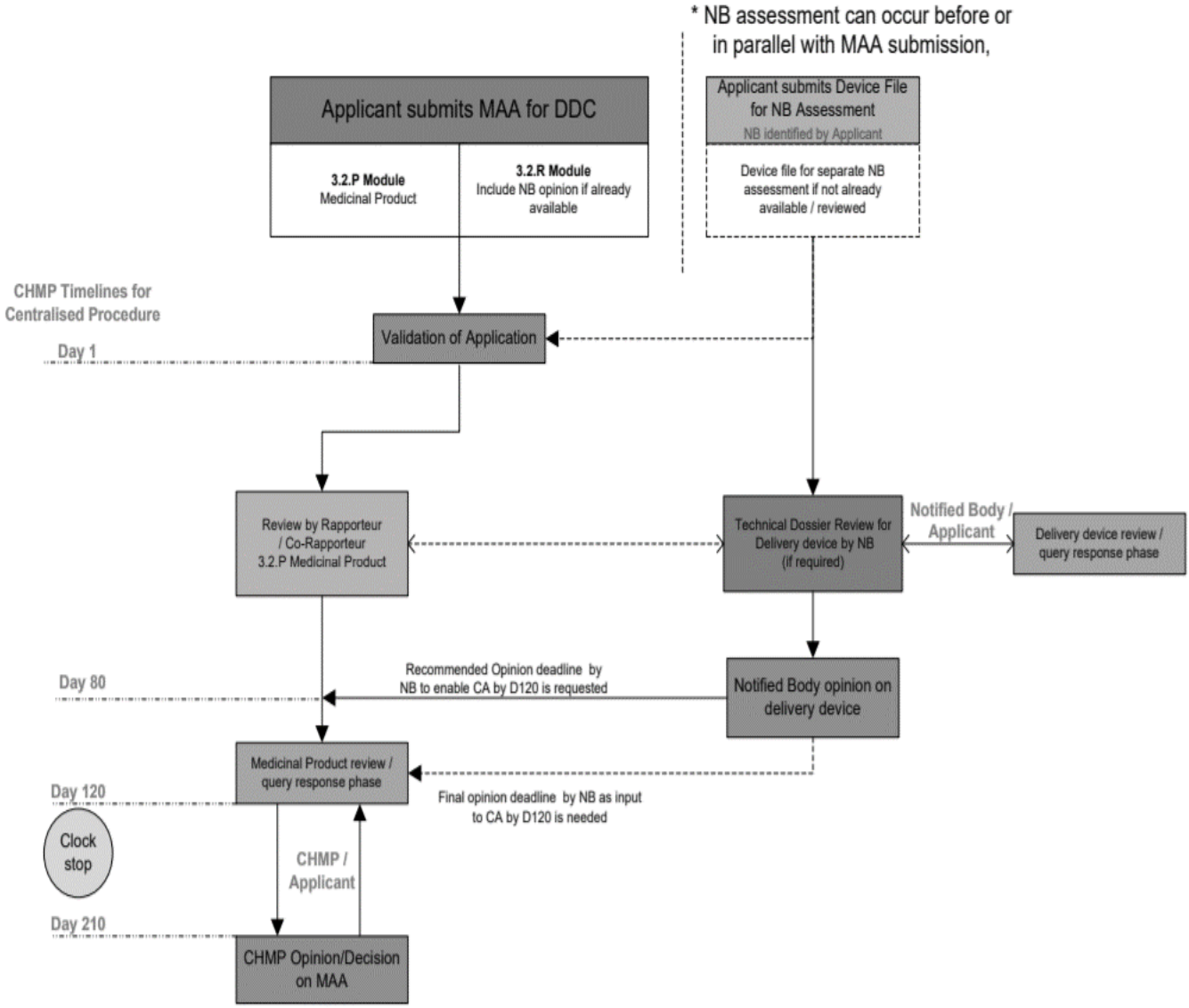

Figure 4. MAA review and approval of integral drug-device combinations (14)

Globally, there are six companies manufacturing PFS - Becton, Dickinson & Co (BD), SCHOTT, Stevanato Group, Weigao, Gerresheimer and Nipro. However, these companies only make empty Pre-filled syringes (PFS) and then sell to the drug manufactures to be filled with the parenteral medicine/drug into it. While Ahmedabad-based Roselabs Biosciences claims to the first fully integrated PFS manufacturer in the world, to manufacture empty PFS, its components and then fill it with own formulated parenteral drug, before it can be put in the market for sell.

The pre-filled syringe manufacturers supply non-sterilized bulk Pre-filled syringes to contract fillers or pharma companies. Many of the suppliers are packaging only glass Pre-filled syringes, which have been in use much longer than plastic Pre-filled syringes. However, the trend is now shifting towards the manufacture of plastic Pre-filled syringes.

"Sanofi, GlaxoSmithKline, and Pfizer are the major buyers of pre-filled syringe that are used for the delivery of insulin, anticoagulants, and vaccines. Many underdeveloped and developing countries rely on developed countries to meet their demand for Pre-filled syringes. For instance, India meets most its Pre-filled syringes demand via imports from the countries such as the US and France,

Pre-filled syringe as medical device

Many of the PFS in India are imported as medical device from regulated countries such as USA, Europe and others. Examples include Pre-filled syringes containing hyaluronic acid, glycerol and other inactive components which do not give any pharmacological effect to human body. Since, such PFS does not contain any active drug substance so they will be regulated as Class B medical devices and related imported regulations associated with it. The procedure for import

of Pre-filled syringes as medical device is presented through Figure 5 (20).

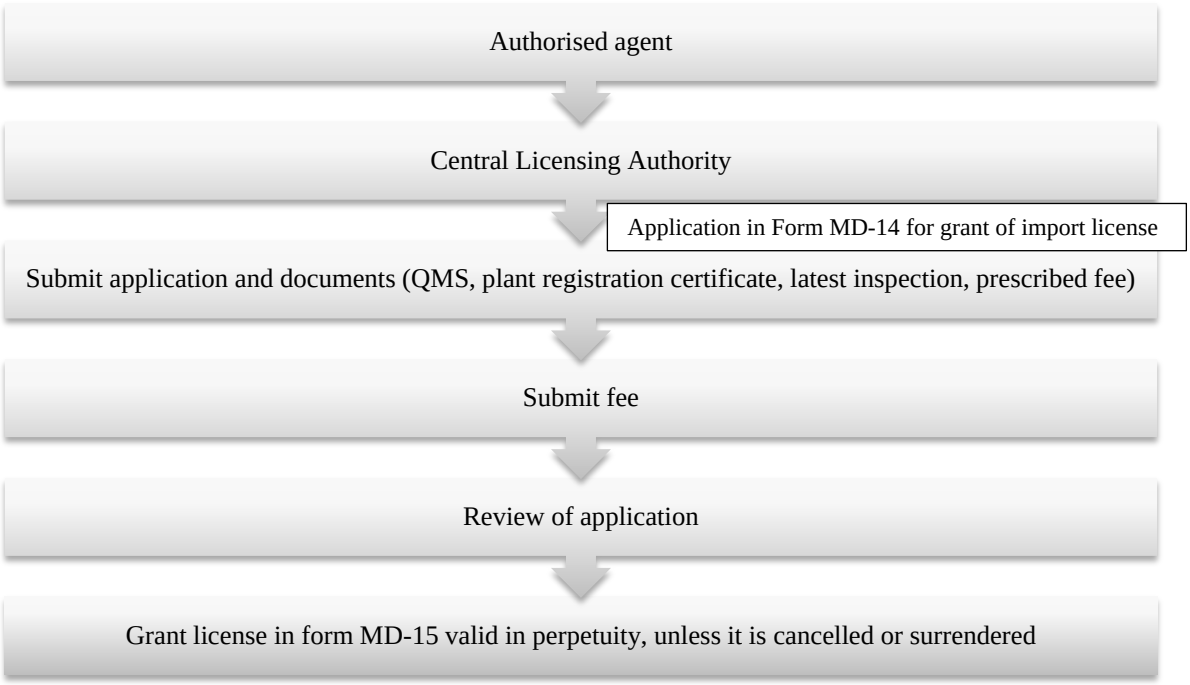

Figure 5. Procedure for import of Pre-filled syringes as a device (20)

Documents required with application for grant of license for import of medical device

- Notarized copy of overseas manufacturing site and Free Sale Certificate (FSC)
- Notarized copy of QMS (Quality Management System) or full Quality Assurance certificate
- Self-attested copy of whole sale license or manufacturing licence
- Copy of latest inspection/audit report carried out by Notified Bodies/NRA

It takes about 9 months by Central Licensing Authority to review the application for grant of import license. The medical device(s) shall conform to the standards/specifications mentioned in the Second Schedule of the Drugs and Cosmetics Act. ISO/MDD/ or such other standards or specifications approved by Directorate (21).

Pre-filled syringe as drug

Pre-filled syringes containing active drug components with some therapeutic or pharmacological effect are regulated as drug in India.

The main legislation governing drug registrations, manufacture, import, sale or distribution is as per Drugs and Cosmetics Act, 1940 and Rules, 1945. All generic drug manufactures must follow Guidelines for bioavailability and bioequivalence studies as per CDSCO. Regulations for clinical trials on Human subjects are regulated by Schedule Y of the act and GCP guidelines as per CDSCO.

There are no specific safety and efficacy guidelines for Pre-filled syringes issued by DCGI. However, most of the pre-filled syringes are imported as finished formulation from regulated countries like USA.

Procedure for import of PFS

Generally, PFS are imported as finished formulation in India. The procedure followed for import of PFS to India resembles the import of drugs from other countries as discussed below (22):

Import license: An application for an import License shall be made to the licensing authority in Form 8 for drugs, either by the Manufacturer or by the Manufacturer's agent in India who is having the wholesale license for sale or distribution of drugs and shall be accompanied by a License fee of one thousand rupees for a single drug and one hundred rupees for each additional drug and by an undertaking in Form 9 duly signed by or on behalf of the manufacturer.

Any application for import licence in Form 8 which shall be accompanied by a copy of Registration Certificate issued in Form 41 under Rule 27-A.

On receipt of an application for an import License in the form and manner prescribed in Rule 24, the licensing authority shall on being satisfied, that, if granted, the conditions of the License will be observed, issue an import License in Form 10 or Form 10-A, as the case may be.

A License, unless, it is sooner suspended or cancelled, shall be valid for a period of three years from date of its issue and for a fresh license is made three months before the expiry.

Format for import license in form 10 of finished formulation

- Covering letter
- An authorization letter

- **Form 8:** Application in Form 8 duly signed and stamped by the applicant with name and designation for licence to import drugs.
- **Form 9:** Original Form 9 duly filled & issued by the manufacturer/Indian agent.
- Requisite Fee- Rs.1000 for 1 proposed Drug and Rs.100 for each additional Drug to be imported.
- A duly attested (by gazetted officer)/notarized (in India) and valid copy of wholesale License for sale or distribution of drugs or manufacturing License (should be enclosed with the product permission list), under Drugs and Cosmetics Rules issued by the State Licensing Authority.
- A Valid copy of Registration Certificate in Form 41 issued by CDSCO with respect to proposed Drug, duly authenticated by Indian Agent.
- The required documents as per Registration Certificate in Form 41 issued by the CDSCO. (If Applicable) (23).

Regulatory challenges associated with Pre-filled syringes

i. Applicability of appropriate regulations

ii. Determination of the PMOA (predicated on intended use)

iii. New regulations

iv. Rest of world countries that will have different approaches to combination products.

v. Each review centre has different set of laws, regulations and guidance. Each may differ in the amount of data required to support and successfully clear a submission approval

vi. Challenges with the acceptance of clinical trial data for FDA review

vii. Risks of submission delay due to the lack of supporting data in the areas of clinical, toxicology; ADME/PK studies

viii. The impact of product and process changes both during and after submission

ix. Understanding how the product will be regulated globally

x. Lack of clarity on how regulatory agencies review these products

5. Recommendations

For effective legislation for combination products like Pre-filled syringes, it should be recommended by government regulatory bodies to develop a process that ensures flexibility on overall authorization application review and approval process. There is a need for effective internal inter-disciplinary collaboration between regulatory bodies and industry to build a common framework to regulate Pre-filled syringes at a global scale. For that, more dialogue and discussion are required between industry & regulatory agencies to develop this framework. Consequently, more groups and forums focused on the regulatory aspects of Pre-filled syringes are required.

6. Conclusion

This article thesis thoroughly analyzed the pre-filled syringe regulations and submission approaches relevant in different regions. From this article, some important facts stood out such as pre-filled syringe is gaining high acceptance in the pharmaceutical industry due to its benefits offered when compared with traditional drug containers such as vials and ampoules. On the other side, regulators are also facing challenges in filing application for authorization of Pre-filled syringes particularly in developing region, because there is no single application applicable unlike in USA and Europe. So, there is lack of clarity in reviewing Pre-filled syringes in Indian market.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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