Regulatory aspects and quality controls of polymer-based parenteral long-acting drug products: how challenging is approving copies?

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Teaser
The regulatory frameworks on parenteral long-acting products are different in the EU and USA. This article reviews the direction followed by the Regulatory Agencies to evaluate the quality of the drug release.

Keywords:
biorelevance, complex, generics, in vitro release, marketing authorization

Abstract

To assure the safety and the efficacy of a medicinal product, quality and batch-to-batch reproducibility need to be guaranteed. In case of parenteral long-acting products, the EU and US Authorities provide different indications, from the classification to the *in vitro* release assays. Despite their relevance, there are few *in vitro* experimental set-up enabling to discriminate among products with different *in vivo* behaviour. Consequently, most copies are authorised through hybrid applications, instead of generic ones.

The present work reviews the actual regulatory frameworks to evaluate the *in vitro* release tests of polymer-based long-acting parenteral aiming to outline the direction followed by the Regulatory Agencies.

Introduction

The therapeutic value of several pharmacological treatments is strictly related to the maintenance of a consistent plasmatic concentration for prolonged periods of time. This goal can be reached by developing prolonged release dosage forms, abolishing the need of frequent dosing often associated with toxicity issues. In case of parenteral administration, long-acting implantable or injectable dosage forms (LAI) are chosen to assure constant blood concentration of a potent active pharmaceutical ingredient (API) over months, or even years [1, 2, 3]. A wide variety of technologies have been proposed to control drug release, e.g. crystal suspensions [4], emulsions, liposomes, implantable or injectable dosage forms based on not-biodegradable and biodegradable polymers or *in situ* gelling systems.

All of them are actually being spotlighted by global pharmaceutical companies since they can optimize the biopharmaceutical performance or support the repurposing of established active ingredients and blockbusters after expiration of the exclusivity period. Among the available technologies, polymer-based LAI, which are of particular interest and complexity due to the challenges in the product design, are considered as *complex parenteral formulations* requiring dedicated regulations to assure their quality, safety and efficacy [5, 6]. The development of therapeutically equivalent copies necessitates taking into account that the pharmacokinetics of a LAI depends not only on the physicochemical properties of the excipients, but also on the manufacturing process. Here, the key parameters to be considered before moving towards a LAI concern i) the target quality attributes of the dosage form [7], ii) the influence of the critical process parameters in manufacturing, iii) the interactions between the LAI and the physiological condition at the site of administration and iv) the PKPD of the API.

Even if the regulatory pathway provides specific product guidelines aimed at proving the bioequivalence between the originator and the copy of a complex medicinal product, the identification of the critical attributes and the establishment of *in vitro*/*in vivo* correlations (IVIVC) are very complicated, due to the complex release characteristics and the lack of standardized, compendial in vitro release testing methods. For instance, the burst release observed under *in vitro* conditions can be masked by the in vivo absorption phase at the intramuscular site [8], or lowered by the formation of a fibrous encapsulation through the host immune response [9, 10, 11, 12] or steric hindrance by the extracellular matrix. Thus, in vitro tests might have a limited ability to properly predict the in vivo behaviour of formulations with significant variations in the release profile.

This review deals with the regulatory pathway to evaluate the quality of polymer-based LAI with a particular focus on the development of copies. As per the quality assessment required by the EMA and FDA, the potential applications of the *in vitro* testing methods to discriminate the properties of a LAI and, possibly, to predict the *in vivo* response is analysed also for waiver purposes. The knowledge and experience gained through decades of use of poly(lactic-co-glycolic acid) (PLGA) and/or poly(lactic acid) (PLA), allowed us to highline various critical factors which may be considered particularly prior to moving towards the development of copies of polymer based LAI.

To better understand the issues of quality testing, the technological aspects of polymer-based LAI available on the market are briefly discussed in the light of their definition according to the main Pharmacopoeias which consider different attributes in the classification. As a consequence, the requirements can be different according to the applied monograph.

Target product profile of long-acting products and technologies available on the market

As other parenteral dosage forms, LAI are required to be sterile, biocompatible and non-immunogenic (**Figure 1**). These characteristics are critical for LAI because they should remain at the injection/implantation site for weeks, months or years without being extruded outside or moving towards other tissues or inducing local adverse effects. From a biopharmaceutical point of view, the composition and design of LAI should assure the extended release of an API for a time period suitable to guarantee the therapeutic relevant concentration in the blood or locally in a specific tissue/organ (e.g., eye, or intra-articular cavity) for weeks, months or years. Moreover, the device required for injection and/or implantation should be optimized along with the implantation procedure.

Moreover, LAI should also be easily removed from the administration site at the end of the release period or in case of harmful events. To avoid tissue damages after the extraction procedure biodegradable polymers (e.g. PLA and PLGA) subject to complete degradation in biocompatible byproducts, are generally used. Based on all target product profiles listed in **Figure 1**, the majority of polymer-based LAI are diffusion/erosion-controlled systems (e.g., microspheres or implants) depending on the feature of the material forming matrix [13]. Microparticles (or microspheres) are sphere-shaped matrices sizing from 20 to 100 µm in which the API is dispersed throughout [14]. They are injected by intramuscular or subcutaneous routes to obtain a systemic effect, or inserted in a specific site of the body (e.g., sinus, Sinuva®; eye, Ozurdex®; bones, InductOs®; intra-articular cavity, Zilretta®) to localize the drug release and/or to limit the systemic concentration [14, 15].

Implants designed as diffusion-controlled systems consist of non-biodegradable cylinders capped at both ends by poly(vinyl alcohol) [PVA] or silicon, which governs the drug release. Examples of polymers used to this purpose are ethyl vinyl alcohol (e.g., Nexplanon®, Retisert®) and polyimide (e.g., Iluvien®).

Alternatively, in situ gel systems consist in solution of an API and PLGA in N-methyl pyrrolidone administered subcutaneously. Upon injection a sustained release depot (e.g., Atridox®, Eligard®) is formed because the solvent diffusion in the surrounding extra-cellular matrix causes the precipitation of the polymer entrapping the API [16].

Definition of LAI in the main Pharmacopoeias

A comparison of the three main Pharmacopoeias shows that LAI classification and monographs are not harmonized. In the European Pharmacopoeia (Ph. Eur.) "parenteral preparations" are divided in two categories depending on the physical state of the dosage form, namely "Implants" and "Gels for injections" [17]. Because no specific information on the size and shape of "Implants" are reported, all implantable dosage forms are included (**Figure 2**).

According to the Japanese Pharmacopeia (JP) LAI are listed among "Preparations for injection" and their classification is primarily based on the administration process [18]. "Implant/pellets" are solid or gel-like form injections administered subcutaneously or intramuscularly by a specific device or chirurgical procedure. Biodegradable microspheres which are resuspended before administration, are considered among "Prolonged release injections" generally prepared by dissolving or suspending active substance(s) in a non-aqueous vehicle, such as vegetable oil.

The United States Pharmacopoeia (USP) includes LAI in two different monographs, namely "Suspension" and "Implant". The former includes both *in situ* gelling systems and biodegradable microspheres administered as aqueous suspension by injection using a conventional syringe and needle (**Figure 2**). "Implant" refers to single-shaped mass made of bioabsorbable or non-bioabsorbable polymers administered by means of a suitable special injector or procedure. Typical duration of these long-acting dosage forms is 2 and 3 months for bioabsorbable and up to 3 years for non-bioabsorbable implants. "Implant" is a comprehensive term including also "pellets" and "drug substance-eluting stents" [19]. However, the criticality of drug-eluting stents, which are medical devices in consideration of the prevalent mechanical effect, fall outside the scope of this review despite the release rate of the ancillary API has to be controlled [20].

Regarding the compendial assays, the Ph. Eur. general monograph on "*Parenteral preparation*" only specifies that sterility and particulate contamination should be evaluated for implants, and an appropriate test to properly demonstrate the release of the active substances should be performed [17].

In the USP monograph "*<1> Injections and implanted drug products (parenterals) – product quality tests*" [19], both general and class-specific quality tests are provided The first part includes "universal tests" for all parenterals related to identification assays, API impurities, particulate matter, sterility, bacterial endotoxins, container content, packaging systems, container-closure integrity and labelling. The uniformity of dosage units is required for all types of LAI, whereas the water content should be determined for freeze-dried products (i.e., microspheres).

The JP specifies that "Implants/Pellets" meet the requirements of Uniformity of Dosage Units, but tests of foreign insoluble matter and extractable volume are enlisted in the general chapter "Tests for preparations".

Considerations on the drug release evaluation in the EU and US

As with most dosage forms, an *in vitro* drug release test provides the fundamental information required to assess the product quality and, therefore, to support the batch release. Moreover, due to the expense, time, labor, and need for human subjects and/or animals to test *in vitro* performance, *in vitro* release is also gaining attention as a surrogate for product performance.

In both cases, the definition of a suitable protocol is critical for a LAI. Among the reasons, is the duration of drug release being 30-90 days or even longer. Hence, many efforts also focused on shortening the time span of *in vitro* release experiments, to provide a quick and reliable method for assessing and predicting drug release. The variation of different parameters (i.e. temperature, solvent, ionic strength, pH, enzymes, surfactant and agitation rate) and apparatus (i.e. sample-and-separate methods, continuous flow cell methods and dialysis methods [21]) were proposed to determine *in vitro* release profile in reasonable experimental time [21, 22].

Beside these differences, the proper methodological approach should be carefully selected according to the mechanism of release. As an example, it is well-recognized that diffusion and erosion/degradation processes control the drug release from PLGA-based LAI. Indeed, the water diffusion into the PLGA matrix allows the API solubilization and its diffusion outside the system. Concomitantly, when the water activity causes the hydrolysis of ester bonds of the PLGA and the degradation products reach a molecular weight lower than about 1 KDa, the matrix starts to erode.

Both phenomena are influenced by the polymer molecular weight, the ratio between monomers and the presence of an end-capping group [23, 24]. Being prone to acid- and base-catalysed degradation [25], *in vitro* experimental parameters should be carefully defined because (un)expected changes may also alter the release mechanism and/or polymer degradation. For example, the release mechanism of triamcinolone acetonide and risperidone from PLGA microparticles was significantly influenced by pH [26] and temperature and apparatus [27], respectively.

Regarding the compendial test, there are very few regulatory standards for LAI. Only the USP and BP monographs on goserelin implants recommend an *in vitro* method to test the drug release from the two commercially available dosages at 3.6 mg and 10.8 mg [28, 2928] (**Table 1**). For a LAI that does not have a dissolution test method in the USP, the FDA prepared a databased enlisting recommended *in vitro* methods to aid of developing generic drug products (**Table 1**). In another words, the reported protocols allowed to rationalize the comparison of *in vitro* performances between drug products.

In the EU, the lack of specific and harmonized protocols leaves room for different interpretations and the EMA evaluates the appropriateness of the chosen method during the assessment of the marketing authorization application. However, the availability of harmonized dissolution protocols could accelerate the development of new and generic products, other than post-marketing variations because the comparison between products would be facilitate.

As already mentioned, *in vitro* release studies can also be designed to establish an *in-vitro-in-vivo* correlation (IVIVC), namely "a predictive mathematical model describing the relationship between an *in vitro* property of a dosage form and a relevant *in vivo* response" [30]. Generally, IVIVC can be categorized into five different levels: Levels A, B, C, D, and multiple Level C [31]. If a point-to-point relationship between *in vitro* and *in vivo* data (i.e. Level A IVIVC) is established and validated, the *in vitro* release method can be used as a surrogate for bioequivalence studies during approval and when post-approval changes are required (*e.g.* formulation composition, as well as manufacturing process, equipment and site) [11, 32, 33]. The applicant can introduce post-approval changes in all the parts of the authorized version of CTD. Both the EMA and the FDA established multiple-level classification for post-approval changes based on their major/minor impact on the drug product benefit/risk balance [34, 35]. As a general rule, if the dosage form is particularly critical or the variation may influence the clinical pattern, changes are classified as major by both the Agencies. In the case of LAI, the EMA classifies as Type II variation changes in the (i) concentration of a single

dose parenteral product where the strength remains the same or (ii) coating if it is critical for the release mechanism [36]. Also the FDA considers "major variations" in the manufacturing process of implants or microparticles when they can impact on the quality, safety and efficacy of the medicinal product [34, 37]. Emblematic cases are the risperidone- or naltrexone-loaded microparticles since modifications in the manufacturing process affect significantly the feature of microspheres [37] and the API bioavailability [38, 39].

Since no regulatory IVIVC guidance is available for complex non-oral drug products, the same principles of developing IVIVC for extended release oral dosage forms have been applied. It is a complicated process, due not only to the complex characteristics of LAI (*e.g.* multi-phasic release), but also to the lack of suitable *in vitro* release testing methods. Authors considered variables accounting for the methodology (i.e. apparatus [40]) and for the physiological (or physio-pathologic) environment, such as body temperature, vascularity, pH, buffer capacity, osmolarity, volumes or any tissue responses [2, 41, 42, 43]. Bio-relevant *in vitro* protocols should not alter the mechanism(s) of *in vivo* drug release and are applicable only when the drug release (dissolution) is the rate-limiting step for its absorption [44]. On the other hand, it is a hard task to simulate the conditions occurring in the biological environment or to identify which variables are significant [2] and the Level A IVIVC, demonstrated only for a few LAI [38, 39], cannot be generalized.

How to reach the market: the regulatory approval pathways in the EU and US

Considering the current clinical landscape, technologies for LAI production can be also applied to re-formulate "old drug substances" into new pharmaceutical dosage forms or formulations, generally with the same indication(s), but a different efficacy/safety profile, due to the modification of drug pharmacokinetics. Sometimes this strategy would also favour the repositioning (or repurposing) of a drug as a new medicinal product. In both scenarios, the applicant will submit a standard document of common elements (Common Technical Document, CTD), demonstrating of quality, safety and efficacy profiles of the product, but the supporting data required by a Regulatory Agency will vary according to the application type.

Therapeutically equivalent copies

In case of a LAI containing an already-authorized API for the same or similar therapeutic indications and if both the pharmaceutical form and strength are the same, the marketing authorization relies upon the demonstration of therapeutic equivalence with respect to the originator. If it is

demonstrated by bioequivalence studies, a simplified dossier can be submitted to the FDA, EMA or a national Regulatory Agency.

Since patent protection of LAI has generally expired, copies allow to reduce costs sustained by patients and healthcare systems. In the case of LAI, a 10-year period of data exclusivity is granted after marketing authorisation. Afterwards, even if the formulation is still protected by a patent, the application for marketing authorisation for a generic product based on a different technology can be submitted. As an example, risperidone has been approved as biodegradable microspheres (Risperidal® Consta®) and in-situ gelling system (Perseris Kit®) in both cases using PLGA as controlling release polymer.

In the US, the procedure to be followed is the Abbreviated New Drug Application (ANDA), while in EU a generic application should be submitted through a centralized, decentralized or mutual recognition procedure. In both cases, the application does generally not requires preclinical and clinical data to establish safety and efficacy. Instead, the applicant must scientifically demonstrate that the therapeutics performance of the generic and innovator are equivalent. Therefore, chemical, pharmaceutical and biological documentation provided by Module 3 is the most critical, as the formulation design plays a crucial role in controlling release technologies. Both in the EU and the US, products can be considered therapeutically equivalent only if they have identical active ingredient(s), dosage form, strength, route of administration and they are bioequivalent to the reference product [45, 46]. In case of parenteral administration, the regulatory approvals can be made through a waiver for “exception excipient regulations,” which covers preservatives, buffers, and antioxidants used in parenteral drug products. As an example, a biowaiver can be generally accepted for generics of injectable aqueous solution.

For all other inactive ingredients, namely those interacting with the API or influencing its biodistribution, However, two different situations are envisaged by the two main Regulatory Agencies. The EMA still considers biowaivers if the test and the reference products contain the same excipients in very similar quantity and proper justifications are provided to demonstrate that the pharmacokinetics is not affected [47]. Conversely, FDA states that the regulatory pathway of an ANDA can be submitted to the FDA only if the copy contains contain the same inactive ingredients (Q1) and in the same concentration (Q2) as the reference listed drug [48]. But LAI are considered as complex dosage forms [49], and therefore, they must fulfil the Q1/Q2 sameness requirement [50]. As an example, the controlled correspondence to request a Q1/Q2 evaluation of proposed formulations based on PLGA and/or PLGA regards the polymer composition (ratio

between glycolic and lactic acids), molecular weight, weight distribution and polymer architecture (*e.g.,* linear or star-branched) [51]. The application of these standards makes the pathway towards the marketing authorization of a generic LAI more difficult in the US than in the EU. To the best of our knowledge, LAI copies are authorized and marketed in several EU countries, but none of them have been either authorised by ANDA procedure or classified as bioequivalent in the FDA Orange book. One of the possible explanations of this difference is the difficulties in demonstrating the Q1/Q2 sameness requirement for all inactive ingredients because the exact qualitative and quantitative composition of excipients may not be known or available at the moment of the drug product development. To solve this problem, a rigorous approach of reverse engineering can be proposed to describe product attributes useful to develop generic leuprolide-PLGA microspheres, as recently proposed on 1-month Lupron-Depot® [7].

Even so, criticality of materials, product design and manufacturing method may lead to differences in the biopharmaceutical properties and bioavailability [52, 53]. As an example, compositionally equivalent PLGA microparticles loaded by risperidone with manufacturing differences , presented distinctly different physicochemical properties which were also confirmed by PK data in rabbits [38].

Moreover, the lack of compendial *in vitro* release testing and validated IVIVC may limit the use of waivers in the marketing authorisation of LAI copies. The applicants can refer to the FDA database of dissolution methods (**Table 1**) or product-specific bioequivalence guidance (**Table 2**) which depicts three scenarios:

i. bioequivalence studies should be performed for all strengths available;
ii. bioequivalence studies should be performed for some strengths, but waivers can be accepted for other strengths available (a linear relationship between the strength and the pharmacokinetic data are needed);
iii. both bioequivalence studies and *in vitro* release studies should be performed to support the equivalence between test and reference products (*e.g.,* risperidone).

The EMA issued only a bioequivalence guideline on octreotide acetate *depot* powder (**Table 2**) [54] at the highest strength (*i.e.*, 30 mg) without providing details on the study design for lower strengths (*i.e.*, 10 mg, 20 mg).

However, therapeutically equivalent copies of a LAI cannot be authorized following the procedure used for generics when:

a) the test product does not fulfil the Q1/Q2 sameness requirement or the generic definition in the US and UE, respectively (*e.g.*, changes in active substance, strength, pharmaceutical form);
b) bioequivalence cannot be considered as a surrogate of the therapeutic equivalence (*e.g.*, locally-applied and locally-acting drug products);
c) the route of administration is changed with respect to the reference product, but a therapeutic improvement is not expected.

In these conditions, the hybrid application includes preclinical and clinical data to demonstrate the therapeutically equivalence of test and the reference product. The body of data included in the comparability studies varies case-by-case according to the complexity of the drug product or the therapeutic indications.

Therapeutic improvement and repurposing of old drug substances

An "old" API, even if no longer on the market, can be re-formulated in order to improve its benefit/risk balance for the same/similar therapeutic indication or totally new ones. Leuprolide acetate is one of the most well-known examples: short-term use of GnRH agonists stimulates pituitary gonadotropin release, while long-term administration leads to inhibition of the pituitary-gonadal axis due to downregulation of the GnRH pituitary receptors. Hence, the switching from the "one-shot" subcutaneous injection of the conventional parenteral solution to biodegradable microspheres allowed to obtain a therapy to treat a variety of endocrine disorders that are responsive to reductions in gonadal steroids [55].

In case of repurposing, the data required by the Regulatory Agency can be reduced since the API has already been authorized for the same or similar therapeutic indications. Indeed, even if a therapeutic improvement is expected, the efficacy and safety may be partially derived from literature data or provided by medicinal products already on the market even if in a different pharmaceutical form. Consequently, the information required will vary, based on the complexity of the benefit/risk balance assessment and on the differences (or similarities) with a reference medicinal product already authorized. However, detailed information is required on substances, both the API and the excipients, on pharmaceutical development and on *in vitro* and *in vivo* biopharmaceutical performances [56]. The critical quality attributes of the product should be also identified and studied as a function of its intended use and route of administration.

In the US, a repurposed drug is not eligible for an Abbreviated New Drug Application (ANDA), but the applicant can follow the 505(b)(2) New Drug Application (NDA) which allows the use of non-proprietary studies that have previously achieved a high standard of quality and safety to support any part of an application [57].

On the contrary, in the EU this condition falls in the "hybrid" procedure described by Article 10(3) of Directive 2001/83/EC. In this situation, the application relies, in part, upon the dossier of a reference medicinal product and the results of appropriate own non-clinical and/or clinical studies. As an example, EMA recently approved a buprenorphine-loaded implant for the substitution treatment of opioid dependence in clinically stable adult patients [58], based on a dossier that contain reduced less preclinical data, since the pharmacodynamic of buprenorphine is well-known and the clinical data included the comparison between the clinical and pharmacokinetic performance of the implant and the existing authorized medicinal product (i.e. sublingual tablets).

However, repurposing is not just a matter to find a new use for an "old" API: to support a new indication, the regulatory approval requires a detailed research and development process. Indeed, the different pharmacokinetics and the pharmacodynamics with respect to the reference product, can change the benefit/risk balance. Even if a hybrid application is still feasible, the safety and efficacy of a repurposed API may not be extrapolated, or supplemented, from data available in the public domain, but supporting studies should be required. Therefore, the amount of clinical data to be provided may be so huge to make the preparation of a complete dossier necessary.

As mentioned, comparative *in vitro* (*e.g.,* release studies) or *in vivo* studies (*e.g.,* bioequivalence) may be also performed to compare the performances of formulation(s) used in clinical studies to those of commercial formulation(s) or to support changes of formulation or its manufacturing process in the late stage of pharmaceutical development. In this context, only Level A IVIVC are relevant from a regulatory point of view for wavering bioequivalence studies [59, 60].

In case of old API repurposed as new formulations, clinical studies are required to characterize the *in vivo* performance. For example, the EMA requires pharmacokinetic studies aimed at evaluating the drug diffusion from the implantation site, which is the rate-limiting steps determining the systemic availability and the risks of dose-dumping [60]. In particular, the single-dose or multiple-dose studies are focused on clinical aspects, e.g. the site-dependent absorption pattern, the fluctuation in drug concentration and lag-times. When more than one strength is considered, the possible proportionality in absorption profile should be investigated. Moreover, the applicant should perform at least single-dose and multi-dose studies to compare *in vivo* performances after

intramuscular and subcutaneous administration with respect to an authorized reference [60]. The multi-dose study is needed unless the bioavailability after the single-dose (expressed as AUC_{0-t}) is higher than 90% of the global bioavailability (expressed as $AUC_{0-\infty}$) in both test and reference. The investigations should be performed using only one strength, only if the others are proportional in composition, exhibit a similar *in vitro* profile and there is a linear correlation between the strength and the pharmacokinetic profile.

Conclusions

The variety and complexity of the technologies used to produce LAI which are designed to meet specific medical needs, dictate an assessment of *in vitro* testing on a case-by-case basis. To speed-up their development, more product-dedicated guidelines or *in vitro* compendial tests should be elaborated to support formulation, testing and approval. By increasing our understanding, the number of copies of LAI on the market could also increase. In any case, the lack of standardized *in vitro* methods shall limit the market entry of copies of a LAI, but "in-house" methods should be accepted when and whether are able to predict the biopharmaceutical behaviour.

There are at least two other challenges to the development generic products. First the US and the EU requirements are substantially different: the FDA considers sameness of specific components, namely identity and quantity, as the reference listed drug; in the EU a simplified procedure can be followed when relevant analytical methods are established and the characteristic properties of active and inactive ingredients are well-known. Next, in the EU issues related to those products approved before the introduction of the centralized procedure need to be addressed since the approval through applications to single European Member States determined the lack or, at least, the impossibility to find public information on the *in vitro* characterization of marketed products.

Table 1 – Protocols for release tests included in a Pharmacopeia monograph or accepted by Regulatory Agencies.

Drug product	Dose	Apparatus	Sample	Medium	Volume	Temp.	Stirring	Sampling time
Dexamethasone IMT (FDA [61])	NA	USP VII (with reciprocating 50 mesh baskets	NA	PBS + 0.05 g/L SDS	30 mL	45 °C	30 cycles/min	12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240 h
Goserelin implant (USP [28] BP [29])	3.6 mg/ 10.8 mg	Flat-bottomed, borosilicate glass jar (120 mL) with a tight plastic cap	1/5 unit (3.6/10.8 mg)	pH 7.4 phosphate/ citrate buffer	50 mL	39 °C	NA	7, 14, 17, 21 and 28 days (3.6mg) 3, 14, 35, 56, 84 days (10.8 mg)
Goserelin implant (FDA [61])	3.6 mg/ 10.8 mg	120 mL Wheaton jar	NA	pH 7.4 PBS	50 mL	39 °C	Swirl orbit at 205 rpm for 6 s	7, 14, 17, 21 and 28 days (3.6mg) 3, 14, 35, 56, 84 days (10.8 mg)
Leuprolide acetate ERS (FDA [61])	NA	USP II or IV	NA	NA	NA	NA	NA	NA
Naltrexone ERS (FDA [62])	380 mg	250 mL HDPE plastic bottle	600 mg	pH 7.4 PBS + 0.02% Tween 20 + 0.02% sodium azide (osmolarity: 270 mOsm/kg)	200 mL	37 °C	NA	1, 7, 14, 28 days
Octreotide ERS (FDA [61])	NA	USP II or IV	NA	NA	NA	NA	NA	NA
Risperidone MP (FDA [63])	25 mg	Cylinder bottle	NA	pH 7.4 HEPES buffer + sodium azide + NaCl + Tween 20	200 mL	37 and 45 °C	NA	1, 21 days (37 °C) Multiple time points from 0 to 8 days (45 °C)
Triamcinolone acetonide MP (Zilretta® PQR [64])	40 mg	USP II	160 mg of MPs	pH 7.2 PBS (10 mM) + 0.3% SDS + 0.02% sodium azide	1000 mL	35 °C	75 rpm	4, 24, 48, 120 h
Triptorelin pamoate ERS (FDA [61])	NA	USP II	NA	50 mL methanol to 950 mL water	950 mL	NA	75 rpm	1, 8, 24, 96, 168 h

ERS: extended release suspension; ID: Injectable Depot; IM: Intramuscular suspension/injection; IMT: Implant; MP: microparticles; NA: not available; PBS: phosphate buffer solution; PQR: product quality review.

Table 2 – Guidelines issued by the EMA and FDA on long-acting parenteral products.

API	Dosage forms	Source	Recommended study to assess bioequivalence	Strengths	Waiver	Ref.
Goserelin acetate	IMT	FDA	2 single-dose, parallel in vivo studies	3.6, 10.8 mg	--*	[65]
Leuprolide acetate	ID	FDA	2 single-dose, randomized, parallel in vivo studies	30, 45 mg/vial	For 11.25 and 22.5 mg/vial (vs 30 mg/vial)	[66]
Leuprolide acetate	IMT	FDA	1 single-dose, parallel, crossover in vivo study	Equivalent to 65 mg of base	--*	[67]
Leuprolide acetate, Norethindrone acetate	ID + oral tablet	FDA	2 single-dose, randomized, parallel in vivo studies	11.25, 3.75mg/vial leuprolide acetate ID	--*	[51]
			1 steady state, crossover in vivo study	5 mg Norethindrone acetate tablet		
Naltrexone	ERS	FDA	1 parallel in vivo study	380 mg/vial	--*	[62]
Octreotide acetate	MPs	EMA	1 single-dose, parallel design in vivo study	30 mg	--*	[54]
Octreotide acetate	MPs	FDA	1 single-dose, parallel design in vivo study	30 mg	For 10, 20 mg (vs 30 mg)	[68]
Risperidone	MPs	FDA	1 in vitro drug release	25 mg/vial	For 12.5, 37.5, 50 mg/vial (vs 25 mg/vial)	[63]
			1 in vivo, two period, crossover, steady-state study	12.5, 25, 37.5, 50 mg/vial		
Triptorelin pamoate	IM	FDA	3 single-dose, parallel design in vivo with pharmacokinetics endpoints	3.75, 11.5, 22.5 mg base/vial	--*	[69]

ERS: extended release suspension; ID: Injectable *Depot*; IM: Intramuscular Injection/suspension; IMT: Implant; IS: Injectable suspension; MPs: microparticles; NA: not available.

* not reported in the guideline.

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Figure legends:

Figure 1 – Target product profile of a LAI. The mandatory attributes are reported in solid circles, whereas the desirable ones in dotted circles.

Figure 2 – Schematic classifications of LAI according to the main Pharmacopoeia with respect to the standard terms proposed by EDQM.

Figure 1

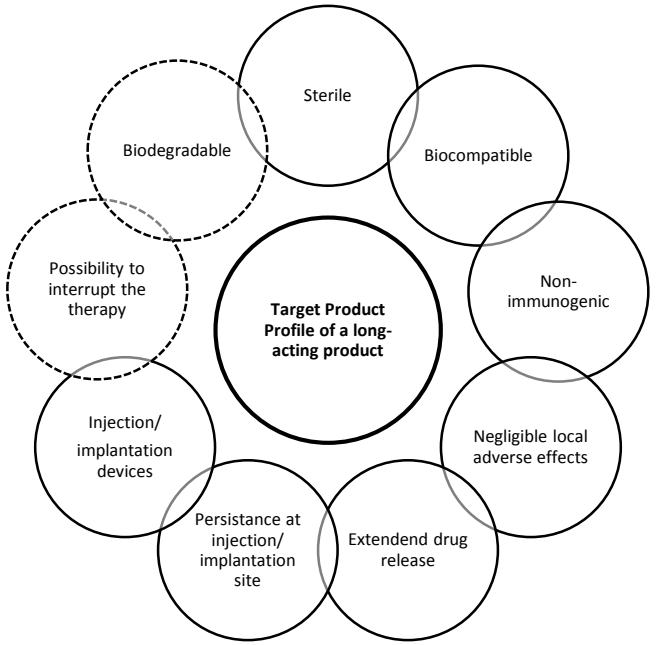
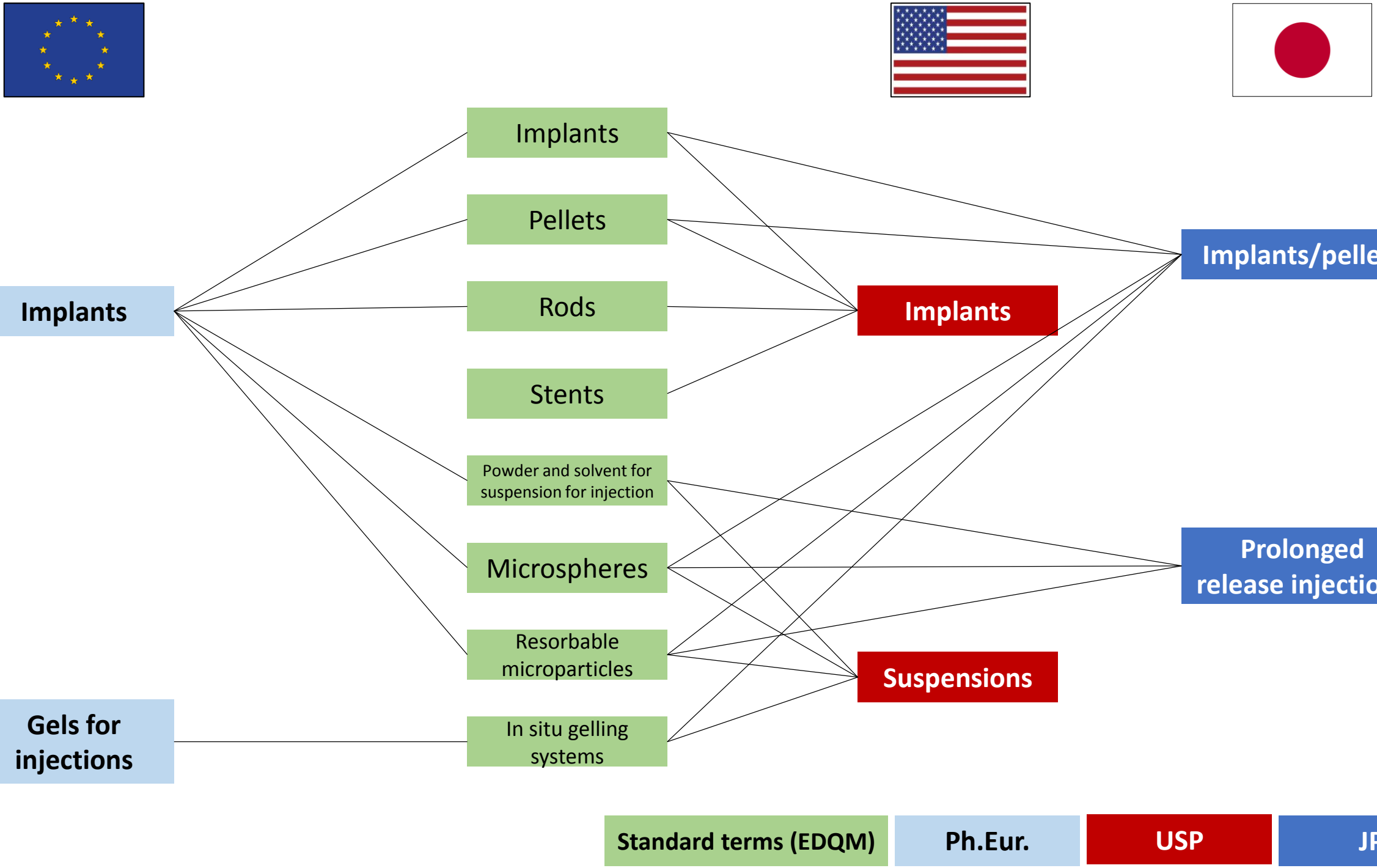

Sterile
Biocompatible
Non-immunogenic
Negligible local adverse effects
Extendend drug release
Persistance at injection/ implantation site
Injection/ implantation devices
Possibility to interrupt the therapy
Biodegradable
Target Product Profile of a long-acting product

Figure 2


Implants
Pellets
Rods
Stents
Powder and solvent for suspension for injection
Microspheres
Resorbable microparticles
In situ gelling systems
Implants
Gels for injections
Implants/pellets
Implants
Prolonged release injections
Suspensions
Standard terms (EDQM)
Ph.Eur.
USP
JP

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