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Teaser The regulatory frameworks for parenteral long-acting products differ between the European Union (EU) and USA. Here, we review the direction followed by Regulatory Agencies to evaluate the quality of drug release from such products.

Regulatory aspects and quality controls of polymer-based parenteral long-acting drug products: the challenge of approving copies

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To assure the safety and the efficacy of a medicinal product, quality and batch-to-batch reproducibility need to be guaranteed. In the case of parenteral long-acting products, the European Union (EU) and US Regulatory Authorities provide different indications, from the classification to the *in vitro* release assays related to such products. Despite their relevance, there are few *in vitro* experimental set-ups enabling researchers to discriminate among products with different *in vivo* behaviors. Consequently, most copies are authorized through hybrid instead of generic applications. Here, we review the actual regulatory frameworks to evaluate the *in vitro* release of drugs from polymer-based long-acting parenterals to highlight the directions followed by the Regulatory Agencies in the USA and EU.

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 for frequent dosing often associated with toxicity issues. For parenteral administration, long-acting implantable or injectable dosage forms (LAIs) are chosen to assure the constant blood concentration of a potent active pharmaceutical ingredient (API) over months or even years [1–3]. A variety of technologies have been proposed to control drug release, including crystal suspensions [4], emulsions, liposomes, implantable or injectable dosage forms based on nonbiodegradable and biodegradable polymers or *in situ* gelling systems.

All such technologies are a focus for global pharmaceutical companies because they can optimize the biopharmaceutical performance of an API or support the repurposing of established API and blockbusters after expiration of the exclusivity period. Among the available technologies, polymer-based LAI, which are of particular interest and complexity because of challenges associated with the product design, are considered to be 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 the pharmacokinetics (PK)

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of a LAI, which 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 conditions at the site of administration; and (iv) the PK-pharmacodynamics (PD) 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 complicated because of 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 reduced by the formation of a fibrous encapsulation through the host immune response [9–12] or steric hindrance by the extracellular matrix. Thus, *in vitro* tests might have a limited ability to properly predict the *in vivo* behavior of formulations with significant variation in the release profile.

Here, we focus on the regulatory pathway used 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 European Medicines Agency (EMA) and US Food and Drug Administration (FDA), we also analyze the potential applications of *in vitro* testing methods to discriminate the properties of a LAI and, possibly, to predict the *in vivo* response 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), allow us to highlight various critical factors that should be considered before moving towards the development of copies of polymer based LAIs.

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

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

As with other parenteral dosage forms, LAIs are required to be sterile, biocompatible, and non-immunogenic (Fig. 1). These characteristics are crucial for LAIs because they should remain at the injection and/or implantation site for weeks, months, or years without extruding outside of, or moving towards, other tissues or inducing local adverse effects. From a biopharmaceutical point of view, the composition and design of LAIs should assure the extended release of an API for a time period suitable to guarantee the therapeutically relevant concentration in the blood or locally

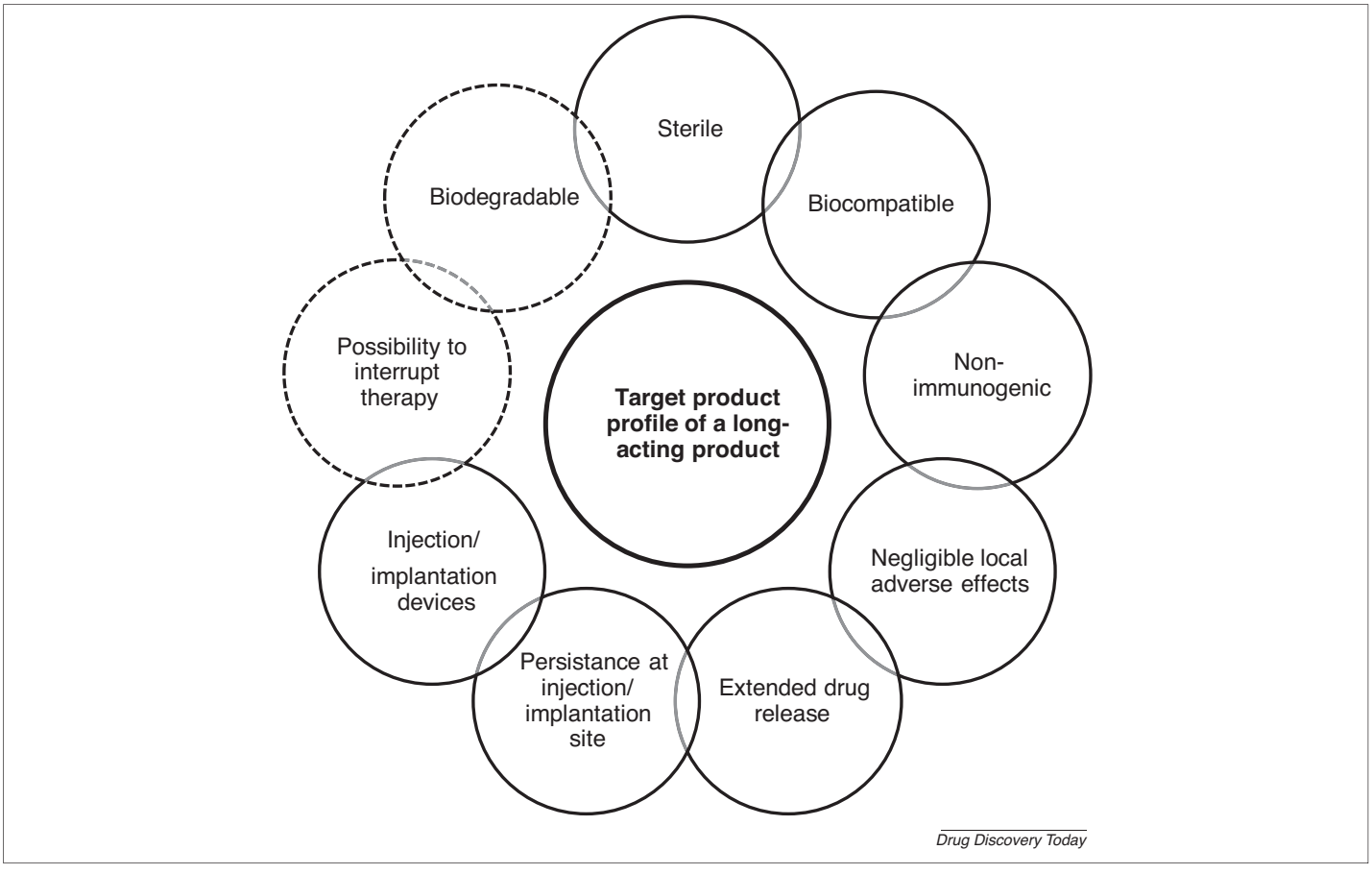

FIGURE 1

Target product profile of a long-acting implantable (LAI). The mandatory attributes are in solid circles, whereas the desirable ones in dotted circles.

in a specific tissue and/or 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 damage 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 Fig. 1, most polymer-based LAIs are diffusion and/or erosion-controlled systems (e.g., microspheres or implants) depending on the feature of the material forming the matrix [13]. Microparticles (or microspheres) are sphere-shaped matrices ranging in size from 20 to 100 μm in which the API is dispersed throughout [14]. They are injected via the intramuscular or subcutaneous routes to obtain a systemic effect, or are inserted into a specific site of the body (e.g., sinus, Sinuva®; eye, Ozurdex®; bones, InductOs®; or intra-articular cavity, Zilretta®) to localize the drug release and/or to limit the systemic concentration [14,15]. Implants designed as diffusion-controlled systems comprise nonbiodegradable cylinders capped at both ends by poly(vinyl alcohol) [PVA] or silicon, which govern the drug release. Examples of polymers used for this purpose are ethyl vinyl alcohol (e.g., Nexplanon® and Retisert®) and polyimide (e.g., Iluvien®).

Alternatively, *in situ* gel systems comprise a solution of an API and PLGA in *N*-methyl pyrrolidone administered subcutaneously. Upon injection, a sustained-release depot (e.g., Atridox® and Eligard®) is formed because solvent diffusion in the surrounding extracellular 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 into two categories depending on the physical state of the dosage form, namely 'Implants' and 'Gels for injections' [17]. Given that no specific information on the size and shape of 'Implants' is reported, all implantable dosage forms are included (Fig. 2).

According to the Japanese Pharmacopeia (JP), LAIs are listed among 'Preparations for injection' and their classification is based primarily on the administration process [18]. 'Implant/pellets' are either solid or gel-like form injections administered subcutaneously or intramuscularly by a specific device or surgical 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 nonaqueous vehicle, such as vegetable oil.

The United States Pharmacopoeia (USP) includes LAIs in two different monographs, namely 'Suspension' and 'Implant'. The former includes both *in situ* gelling systems and biodegradable microspheres administered as aqueous suspensions by injection

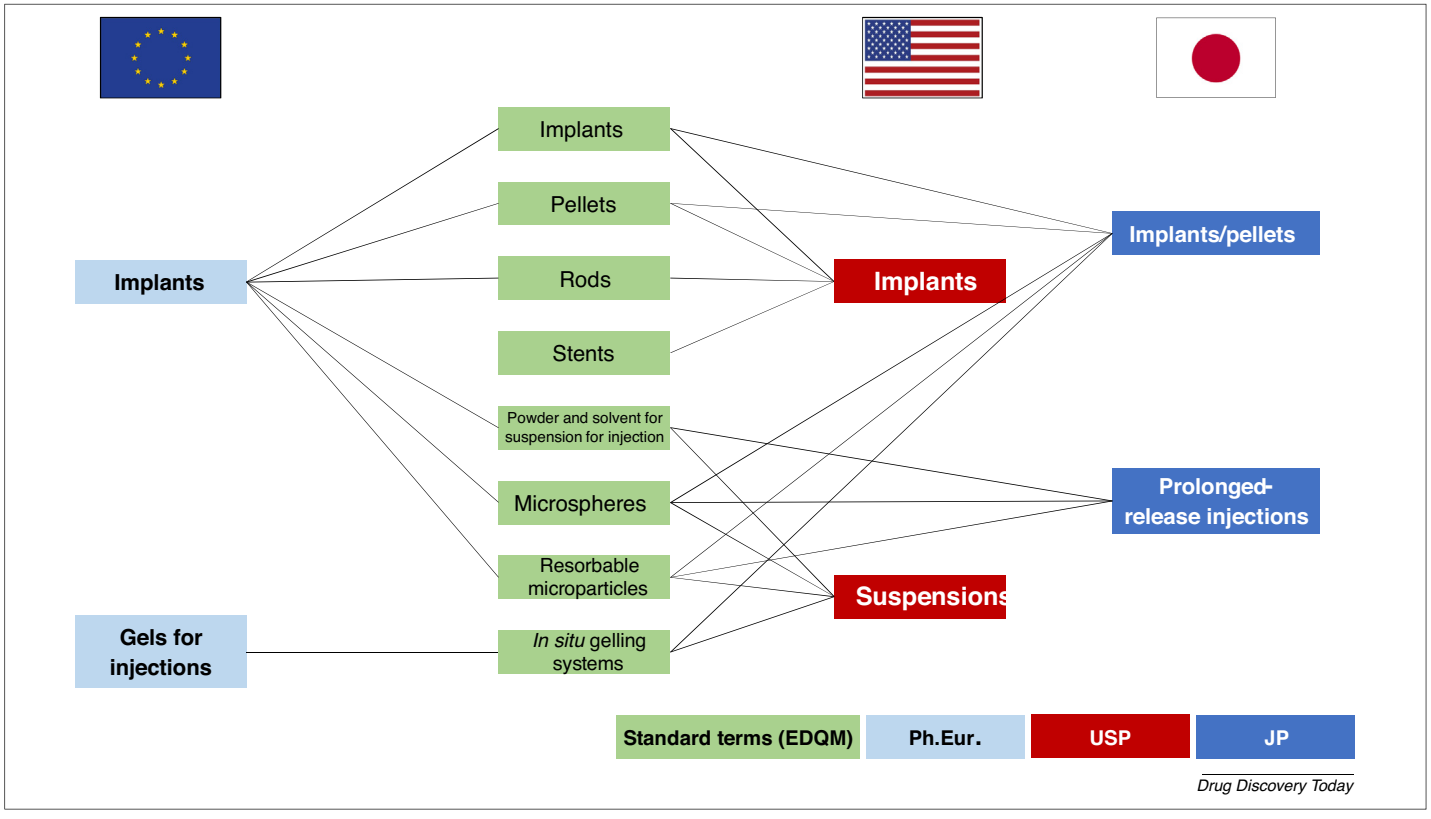

FIGURE 2

Schematic classifications of long-acting implantables (LAIs) according to the main Pharmacopoeias with respect to the standard terms proposed by European Directorate for the Quality of Medicines & HealthCare (EDQM) Abbreviations: JP, Japanese Pharmacopeia; Ph.Eur., European Pharmacopoeia; USP, United States Pharmacopoeia.

using a conventional syringe and needle (Fig. 2). 'Implant' refers to single-shaped masses comprising bioabsorbable or nonbioabsorbable polymers administered by means of a suitable special injector or procedure. The typical duration of these long-acting dosage forms is 2–3 months for bioabsorbable and up to 3 years for nonbioabsorbable implants. 'Implant' is a comprehensive term that also includes 'pellets' and 'drug substance-eluting stents' [19]. However, the criticality of drug-eluting stents, which are medical devices in terms of the prevalent mechanical effect, fall outside the scope of this review even though the release rate of the ancillary API has to be controlled [20].

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

In the USP monograph 'Injections and implanted drug products (parenterals) – product quality tests' [19], both general and class-specific quality tests are provided The first 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 labeling. The uniformity of dosage units is required for all types of LAIs, 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 included in the general chapter 'Tests for preparations'.

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, because of the expense, time, labor, and need for human subjects and/or animals to test *in vivo* performance, *in vitro* release is also gaining attention as a surrogate for product performance.

In both cases, the definition of a suitable protocol is crucial for a LAI. One of the reasons is a duration of drug release of 30–90 days or longer. Hence, many efforts are 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 profiles in a reasonable experimental time [21,22].

In addition to 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 and/or degradation processes control drug release from PLGA-based LAIs. Indeed, water diffusion into the PLGA matrix enables API solubilization and its diffusion outside the system. Concomitantly, when the water activity causes the hydrolysis of ester bonds of PLGA and the degradation products reach a molecular weight lower than ~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-catalyzed degradation [25], *in vitro* experimental parameters should be carefully defined because (un)expected changes can 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 by temperature and apparatus [27], respectively.

In terms of the compendial test, there are few regulatory standards for LAIs. Only the USP and the British Pharmacopoeia (BP) monographs on goserelin implants recommend an *in vitro* method to test drug release from the two commercially available dosages at 3.6 mg and 10.8 mg [28,29] (Table 1). For a LAI without a dissolution test method described in the USP, the FDA has prepared a database listing the recommended *in vitro* methods to aid the development of generic drug products (Table 1). Thus, the reported protocols allow researchers 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 of postmarketing 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 postapproval changes are required (e.g., formulation composition, as well as manufacturing process, equipment, and site) [11,32,33]. The applicant can introduce postapproval changes to all parts of the authorized version of common technical document (CTD). Both the EMA and the FDA have established multiple-level classifications for post-approval changes based on their major and/or minor impacts on the drug product benefit:risk balance [34,35]. As a general rule, if the dosage form is particularly crucial or if a variation might influence the clinical pattern, changes are classified as major by both Agencies. In the case of LAIs, 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 crucial for the release mechanism [36]. In addition, the FDA considers 'major variations' in the manufacturing process of implants or microparticles when they can impact the quality, safety, and efficacy of the medicinal product [34,37]. Examples include risperidone- or naltrexone-loaded microparticles because modifications in the manufacturing process affect significantly the features of microspheres [37] and API bioavailability [38,39].

Given that no regulatory guidance on IVIVC is available for complex non-oral drug products, the same principles for developing IVIVC for extended-release oral dosage forms have been applied. It is a complicated process, due to not only the complex

TABLE 1

Protocols for release tests included in a Pharmacopeia monograph or accepted by Regulatory Agencies[a]

Drug product (Regulatory Authority)	Dose	Apparatus	Sample	Medium	Volume	Temperature	Stirring	Sampling time	Refs
Dexamethasone IMT (FDA)	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	[61]
Goserelin implant (USP, BP)	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 (3.6 mg) 3, 14, 35, 56, 84 days (10.8 mg)	[28,29]
Goserelin implant (FDA)	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 (3.6 mg); 3, 14, 35, 56, 84 days (10.8 mg)	[61]
Leuprolide acetate ERS (FDA)	NA	USP II or IV	NA	NA	NA	NA	NA	NA	[61]
Naltrexone ERS (FDA)	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	[62]
Octreotide ERS (FDA)	NA	USP II or IV	NA	NA	NA	NA	NA	NA	[61]
Risperidone MP (FDA)	25 mg	Cylinder bottle	NA	pH 7.4 HEPES buffer + sodium azide + NaCl + Tween 20	200 ml	37 °C and 45 °C	NA	1, 21 days (37 °C) Multiple time points from 0 to 8 days (45 °C)	[63]
Triamcinolone acetonide MP (Zilretta® PQR)	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	[64]
Triptorelin pamoate ERS (FDA)	NA	USP II	NA	50 ml methanol:950 ml water	950 ml	NA	75 rpm	1, 8, 24, 96, 168 h	[61]

[a] Abbreviations: 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.

characteristics of LAI (e.g., multiphasic release), but also the lack of suitable *in vitro* release testing methods. Researchers have considered variables accounting for the methodology (i.e., apparatus [40]) and the physiological (or physio-pathological) environment, such as body temperature, vascularity, pH, buffer capacity, osmolarity, volume, or any tissue responses [2,41–43]. Biorelevant *in vitro* protocols should not alter the mechanism(s) of the *in vivo* drug release and are applicable only when the drug release (i.e., dissolution) is the rate-limiting step for its absorption [44]. By contrast, it is difficult 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 LAIs [38,39], cannot be generalized.

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

Given the current clinical landscape, technologies for LAI production can be also applied to reformulate 'old drug substances' into new pharmaceutical dosage forms or formulations, generally with the same indication(s), but a different efficacy and/or safety profile because of the modification of drug PK. Sometimes, this strategy can also favor the repositioning (or repurposing) of a drug as a new medicinal product. In both scenarios, the applicant submits a standard document of common elements (CTD), demonstrating of the quality, safety, and efficacy profiles of the product; however, the supporting data required by a Regulatory Agency vary according to the application type.

Therapeutically equivalent copies

For 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.

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

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

For all other inactive ingredients, namely those interacting with the API or influencing its biodistribution, 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 similar quantities and if proper justifications are provided to demonstrate that the PK is not affected [47]. Conversely, the FDA states that the regulatory pathway of an ANDA can be submitted only if the copy contains the same inactive ingredients (Q1) and in the same concentration (Q2) as the reference listed drug [48]. However, LAIs are considered to be 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 regards the polymer composition (i.e., 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 USA 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 an ANDA procedure or classified as bioequivalent in the FDA Orange book. One possible explanation for 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 might 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 that are useful for developing genericPLGA microspheres, as recently proposed for 1-month Lupron-Depot® [7].

Even so, the criticality of materials, product design, and manufacturing method can lead to differences in the biopharmaceutical properties and bioavailability [52,53]. As an example, compositionally equivalent PLGA microparticles loaded with 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 can limit the use of waivers in the marketing authorization 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 PK data is needed); and (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 has issued only a bioequivalence guideline on octreotide acetate depot powder (Table 2) [54] at the highest strength

TABLE 2

Guidelines issued by the EMA and the FDA on long-acting parenteral products[a]

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

[a] Abbreviations: ERS, extended release suspension; ID, injectable depot; IM, intramuscular Injection/suspension; IMT, implant; IS, injectable suspension; MPs, microparticles; NA, not available.
[b] Not reported in the Guideline.

(i.e., 30 mg) without providing details on the study design for lower strengths (i.e., 10 or 20 mg). However, therapeutically equivalent copies of a LAI cannot be authorized following the procedure used for generics when: (i) the test product does not fulfil the Q1/Q2 sameness requirement or the generic definition in the USA and EU, respectively (e.g., changes in active substance, strength, pharmaceutical form); (ii) bioequivalence cannot be considered as a surrogate of the therapeutic equivalence (e.g., locally applied and locally acting drug products); and (iii) 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 the test and reference products. 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 reformulated to improve its benefit:risk balance for the same and/or 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, whereas long-term administration leads to inhibition of the pituitary–gonadal axis because of downregulation of the GnRH pituitary receptors. Hence, the switching from a 'one-shot' subcutaneous injection of the conventional parenteral solution to biodegradable microspheres resulted in a therapy to treat a variety of endocrine disorders that are responsive to reductions in gonadal steroids [55].

In the case of repurposing, data required by the Regulatory Agency can be reduced because 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 might 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 can 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 USA, a repurposed drug is not eligible for an ANDA, but the applicant can follow the 505(b)(2) New Drug Application (NDA), which allows the use of nonproprietary studies that have previously achieved a high standard of quality and safety to support any part of an application [57].

By contrast, in the EU, this condition falls in the 'hybrid' procedure described by the 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 nonclinical and/or clinical studies. As an example, the EMA recently approved a buprenorphine-loaded implant for the substitution treatment of opioid dependence in clinically stable adults [58], based on a dossier that contained fewer preclinical data,

because the PD of buprenorphine is well-known and the clinical data included the comparison between the clinical and PK performance of the implant and the existing authorized medicinal product (i.e., sublingual tablets).

However, repurposing is not just a matter of finding 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 PK and PD 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 might 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 might be so huge to make a complete CTD necessary.

As mentioned earlier, comparative *in vitro* (e.g., release studies) or *in vivo* studies (e.g., bioequivalence) can 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 during the late stage of pharmaceutical development. In this context, only Level A IVIVCs are relevant from a regulatory point of view for wavering bioequivalence studies [59,60].

For old APIs repurposed as new formulations, clinical studies are required to characterize the *in vivo* performance. For example, the EMA requires PK studies aimed at evaluating 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, single-dose or multiple-dose studies focus on clinical aspects, such as 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 multidose study is needed unless the bioavailability after the single-dose (expressed as $AUC_{0\text{-}t}$) is >90% of the global bioavailability (expressed as $AUC_{0\text{-}\infty}$) in both test and reference. The investigations should be performed using a single 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 PK profile.

Concluding remarks

The variety and complexity of technologies used to produce LAIs that 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 LAIs on the market could also increase. In any case, the lack of standardized *in vitro* methods limits the market entry of copies of a LAI, but 'in-house' methods should be accepted when and if they are able to predict the biopharmaceutical behavior.

There are at least two other challenges to the development of generic products. First, the US and EU requirements are substantially different: the FDA considers the 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 because the approval through applications to single European Member States determines the lack or, at least, the impossibility of finding public information on the *in vitro* characterization of marketed products.

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