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Generic Long-acting Injectable Product Availability and Approval Standards

Krista Anim Anno, Lei Zhang, and Wenlei Jiang

Office of Research and Standards, Office of Generic Drugs, U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring, Maryland 20993

Corresponding Author: wenlei.jiang@fda.hhs.gov

PURPOSE

- Long-acting injectable (LAI) drug products enable the controlled release of a drug over an extended duration of time to achieve a prolonged therapeutic effect.
- Extended therapeutic effects offer several benefits including:
  - Increased medication adherence
  - Improved safety and efficacy
  - Decreased healthcare costs
  - Improved patient outcomes
- LAIs have numerous advantages, yet there is limited generic availability in the United States (US). Understanding of the LAI availability on the European market and approval standards between US and Europe will help identify market gap and pinpoint the divergences of approval criteria, in turn, strategize approaches to improve global LAI access.

OBJECTIVE(S)

The objective of this study is to survey generic LAI approvals by European and the US regulatory agencies and compare the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval standards for generic LAIs.

METHOD(S)

PRODUCT AVAILABILITY

Drugs@FDA

- **505(b)(1) and 505(b)(2):** New Drug Application (NDA)
- **505(j):** Abbreviated New Drug Application (ANDA)

EMA Medicines Database

- **Article 8(3):** Full or full-mixed application
- **Article 10(1):** Generic medicinal product application
- **Article 10(3):** Hybrid medicinal product application

EMA National Registers of Authorised Medicines

Swissmedic Authorised Human Medicinal Products

APPROVAL STANDARDS

Identified Product-Specific Guidances (PSGs) and General Guidances for LAIs published by U.S. FDA and EMA

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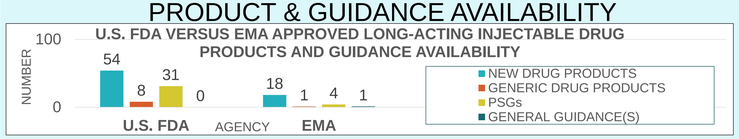
Compared and contrasted recommendations between agencies

RESULT(S)

PRODUCT & GUIDANCE AVAILABILITY



EMA or U.S. FDA Approved Long-acting Injectables

EMA – Approved via Article 8(3) (Based on EMA Medicines Database)	U.S. FDA – Approved via 505(b)(1) or 505(b)(2) (Duplicate Active Pharmaceutical Ingredients (APIs) Not Repetitively Listed)	
• Afamelanotide • Aripiprazole • Bupivacaine • Bupivacaine; Meloxicam • Buprenorphine • Buprenorphine hydrochloride • Cabotegravir • Cytarabine[1] • Degarelix acetate • Exenatide • Fulvestrant • Olanzapine pamoate • Paliperidone palmitate • Pasireotide pamoate • Rilpivirine • Risperidone	• Afamelanotide • Aripiprazole • Aripiprazole lauroxil • Bimatoprost • Bupivacaine • Bupivacaine; Meloxicam • Buprenorphine • Buprenorphine hydrochloride[1] • Cabotegravir • Cabotegravir; Rilpivirine • Cytarabine[1] • Degarelix acetate • Doxycycline hyclate[1] • Exenatide[2] • Fluocinolone acetonide • Fulvestrant • Goserelin acetate • Granisetron • Haloperidol decanoate • Hydroxyprogesterone caproate • Lanreotide acetate	• Leuprolide acetate • Leuprolide acetate; Norethindrone acetate[1] • Leuprolide mesylate • Medroxyprogesterone acetate • Methylprednisolone acetate • Mitomycin • Mometasone furoate • Morphine sulfate[1] • Naltrexone • Octreotide acetate • Olanzapine pamoate • Paliperidone palmitate • Pasireotide pamoate • Penicillin G benzathine • Risperidone • Testosterone cypionate • Testosterone enanthate • Testosterone undecanoate • Triamcinolone acetonide • Triptorelin pamoate

[1]Withdrawn
[2] One NDA withdrawn; One NDA marketed

EMA Long-acting Injectables Approved via Article 10(1) (Based on EMA Medicines Database)	U.S. FDA Long-acting Injectable Approved via 505(j) (Active Pharmaceutical Ingredients Listed)	
• Fulvestrant	• Fulvestrant • Haloperidol decanoate • Hydroxyprogesterone caproate • Medroxyprogesterone acetate	• Methylprednisolone acetate • Paliperidone palmitate • Testosterone cypionate • Triamcinolone acetonide

National Agencies	Long-acting Injectables Approved via National Agencies (Not an exhaustive list)			
Germany	• Fluocinolone acetonide • Goserelin acetate • Haloperidol decanoate	• Leuprorelin (with acetic acid)[1] • Leuproreline mesylate[2]	• Medroxyprogesterone acetate • Mitomycin • Octreotide acetate	• Testosterone enanthate • Testosterone undecanoate • Triptorelin embonate[3]
France	• Doxycycline hyclate • Fluocinolone acetonide • Goserelin acetate • Haloperidol decanoate	• Lanreotide acetate • Leuprorelin acetate[1] • Medroxyprogesterone acetate	• Methylprednisolone acetate • Mitomycin • Octreotide acetate	• Testosterone undecanoate • Triptorelin embonate[3] • Triptorelin pamoate
Spain	• Fluocinolone acetonide • Goserelin acetate[4] • Lanreotide acetate • Leuprorelin acetate[1]	• Medroxyprogesterone acetate • Mitomycin • Octreotide acetate	• Testosterone cypionate • Testosterone undecanoate	• Triptorellin acetate • Triptorellin pamoate[3]
Netherlands	• Fluocinolone acetonide • Goserelin acetate • Haloperidol decanoate • Leuprorelin acetate[1]	• Leuprorelin mesilate[2] • Medroxyprogesterone acetate	• Methylprednisolone acetate • Mitomycin • Octreotide acetate	• Testosterone esters[5] • Testosterone undecanoate • Triptorelin pamoate
Sweden	• Doxycycline hyclate • Fluocinolone acetonide • Goserelin acetate • Haloperidol decanoate • Lanreotide acetate	• Leuprorelin acetate[1] • Leuprorelin mesilate[2] • Medroxyprogesterone acetate	• Methylprednisolone acetate • Mitomycin • Octreotide acetate	• Testosterone enanthate • Testosterone undecanoate • Triamcinolone acetonide • Triptorelin embonate[3]

Approved Long-acting Injectables in Switzerland (Not an exhaustive list)

• Aripiprazole • Buprenorphine • Cabotegravir • Degarelix acetate • Exenatide	• Fulvestrant • Goserelin acetate • Haloperidol decanoate • Lanreotide acetate • Leuprorelin acetate[1]	• Medroxyprogesterone acetate • Methylprednisolone acetate • Octreotide acetate • Paliperidone palmitate • Pasireotide pamoate	• Rilpivirine • Risperidone • Testosterone enanthate • Triamcinolone acetonide

[1]Equivalent to Leuprolide acetate; [2] Equivalent to Leuprolide mesylate; [3] Equivalent to Triptorelin pamoate; [4] Equivalent to Goserelin acetate; [5] Testosterone esters includes: Testosterone decanoate; Testosterone isocaproate ; Testosterone phenylpropionate; Testosterone proprionate; Products approved by U.S. FDA but not by European Agencies are indicated in Orange. Products approved by European Agencies but not by U.S. FDA are indicated in Blue.

APPROVAL STANDARDS

EMA General Guidance: Guideline on the Pharmacokinetic (PK) and Clinical Evaluation of Modified Release Dosage Forms

- For intramuscular/subcutaneous depot formulations, it is recommended to conduct both a single dose study and multiple dose study* comparing test and reference products
- Only one strength must be investigated if the different strengths are proportional in composition and exhibit a similar in vitro dissolution profile

*Multiple dose may be waived if single dose demonstrates, with highest strength, that mean $AUC_{(0-t)}$ after first dose covers more than 90% of mean $AUC_{(0-\infty)}$ for both test and reference

EMA and U.S. FDA PSGs Comparison

Exenatide subcutaneous extended-release for suspension/suspension (U.S. RLD 022200; 209210)

	Similarity	Difference
Study Design	Both recommend parallel	• EMA also recommends crossover • EMA recommends **both** single dose study in healthy subjects and multiple dose study in patients* while U.S. FDA recommends **either** single dose study in healthy subjects** or multiple dose study in patients*** *Possible waiver of multiple dose study with low risk of accumulation shown with single dose study **Single dose subjects with a family history of medullary thyroid carcinoma should be excluded ***Multiple dose patients with type II diabetes already receiving a stable regimen of exenatide
Study drug strength	2 mg	N.A.
Analyte to measure	Both recommend exenatide in plasma	N.A.
PK parameters for bioequivalence (BE) evaluation	**Single Dose:** • AUC_{0-t} • $AUC_{0-\infty}$ **Multiple Dose:** • $C_{max,ss}$* • AUC_t* *U.S. FDA recommends both individual and mean	**Single Dose:** • **EMA**: C_{max} (initial burst); C_{max} (extended release phase) • **U.S. FDA**: C_{max}; $AUC_{weekl-t}$ (supportive data) **Multiple Dose** • **EMA**: $C_{t,ss}$ • **U.S. FDA** (individual and mean): Blood drug concentration levels once at steady state; $C_{min,ss}$; Percent fluctuation; Time to peak concentration
Device considerations	N.A.	U.S. FDA provides recommendations on device component while EMA did not specify

Octreotide acetate depot powder and solvent for suspension for injection (U.S. RLD 021008)

	Similarity	Difference
Study Design	Both recommend single dose study with parallel design in healthy subjects	EMA also recommends a multiple dose study* *Multiple dose study may be waived if single dose PK is well characterized
Study drug strength	30 mg* *U.S. FDA recommends a waiver request of in vivo testing for 10 mg and 20 mg strengths. Test product and reference standard should be qualitatively (Q1) and quantitatively (Q2) the same	N.A.
Administration	N.A.	U.S. FDA recommends to administer as an intramuscular (IM) injection intragluteally while EMA does not specify
Analyte to measure	Both recommend octreotide in plasma	N.A.
PK parameters for BE evaluation	Both recommend measuring: • AUC_{0-28} • AUC_{28-56} • AUC_t • $AUC_{0-\infty}$ • C_{max} *U.S. FDA specifies for the data to be log-transformed	EMA also recommends measuring: • C_t • AUC_{0-24h} • T_{lag} • $C_{max\ per\ partial\ AUC}$ • $C_{max\ initial\ release}$

Lanreotide acetate prolonged-release solution for subcutaneous injection (U.S. RLD 022074)

	Similarity	Difference
Study Design	Single dose, parallel in vivo study in healthy subjects	• EMA also recommends a multiple dose study* • EMA recommends the use of one gender OR the exact same number of males and females while U.S. FDA recommends both males and females *Multiple dose study may be waived if single dose PK is well characterized
Study drug strength	120 mg	U.S. FDA recommends in vivo waiver for 60 mg and 90 mg based on the 120 mg
Administration sites	N.A.	U.S. FDA specifies deep subcutaneous injection at superior external quadrant of the buttock while EMA has no specifics
Analyte to Measure	Both recommend lanreotide in plasma	N.A.
PK parameters for BE evaluation	N.A.	• U.S. FDA did not provide specifics for in vivo PK studies EMA recommends: • AUC_{0-t} • $AUC_{0-\infty}$ • AUC_{0-168h} • $AUC_{168-672h}$ • AUC_{672h-t} • C_{max} • C_t
Waiver of in vivo BE study	Both agencies may grant a waiver if test product has the same qualitative (Q1) and quantitative (Q2) composition as the reference listed drug (RLD) and demonstrates equivalent molecular, structural, and thermodynamic properties	• EMA recommends specific tests with detailed analytical methods while U.S. FDA recommends tests without specific analytical methods • EMA recommends at least 5 batches of the test and reference products should be included in the comparability studies while U.S. FDA recommends 3 lots of both test product and reference standard

Paliperidone palmitate extended-release suspension for intramuscular injection (U.S. RLD 022264)

	Similarity	Difference
Study Design	Both recommend parallel or crossover study design	EMA recommends **both** a single dose study in healthy subjects or in patients stabilized on other antipsychotic medication and a multiple dose study in patients* while U.S. FDA recommends a multiple dose study in patients with the disease state on a stable regimen or maintenance dose of paliperidone *Possible waiver of multiple dose study with low risk of accumulation shown
Study drug strength	39 mg; 78 mg; 117 mg; 156 mg*; 234 mg** *U.S. FDA recommends in vivo waiver for other strengths based on 156 mg/mL **Strengths are equivalent to 25, 50, 75, 100, 150 mg eq, respectively	EMA recommends testing any dose/strength so long as the test product has the same concentration of active substance as the reference for all the strengths while U.S. FDA offers a waiver for other strengths if there is an acceptable BE study on the 156 mg/mL strength
Administration sites	N.A.	U.S. FDA recommends to administer in gluteal **and** deltoid muscle while EMA does not specify
Analyte to Measure	Both recommend paliperidone in plasma	N.A.
PK parameters for BE evaluation	**Multiple Dose:** • $C_{max,ss}$* • AUC_t* *U.S. FDA recommends both individual and mean	**Single Dose:** • **EMA**: AUC_{0-t}; AUC_∞; C_{max}; T_{max} • **U.S. FDA**: N.A. **Multiple Dose** • **EMA**: $C_{t,ss}$ • **U.S. FDA** (individual and mean): Plasma drug concentration levels once at steady state; $C_{min,ss}$; Percent fluctuation; Time to peak concentration

CONCLUSION(S)

- Similar to the U.S., there are limited generic LAIs approved by the EMA via centralized procedure.
- U.S. FDA has approved more brand name LAI drug products than those approved by the EMA centralized procedure, but there are many LAI products approved by National Agencies on the European market.
- The EMA has one general guidance to aid in the development of LAIs, while the U.S. FDA does not. However, the U.S. FDA has published more PSGs to assist generic LAI development than the EMA.
- For LAI products that have PSGs from both U.S. FDA and EMA, there are differences in recommendations between agencies. Understanding the rationales behind these differences can help harmonize the recommendations to facilitate global development of generic LAI products.
- Further work can be done to understand the European national agencies approval standards of LAIs.

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