Recommendation of Partial Area Under the Curve (pAUC) Metrics in Product-Specific Guidance for Long-Acting Injectable (LAI) Drug Products

SBIA 2022: Advancing Generic Drug Development: Translating Science to Approval

Day 1, Session 4: Scientific Challenges and Advancements of Long-Acting Injectables (LAIs)

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Disclaimer

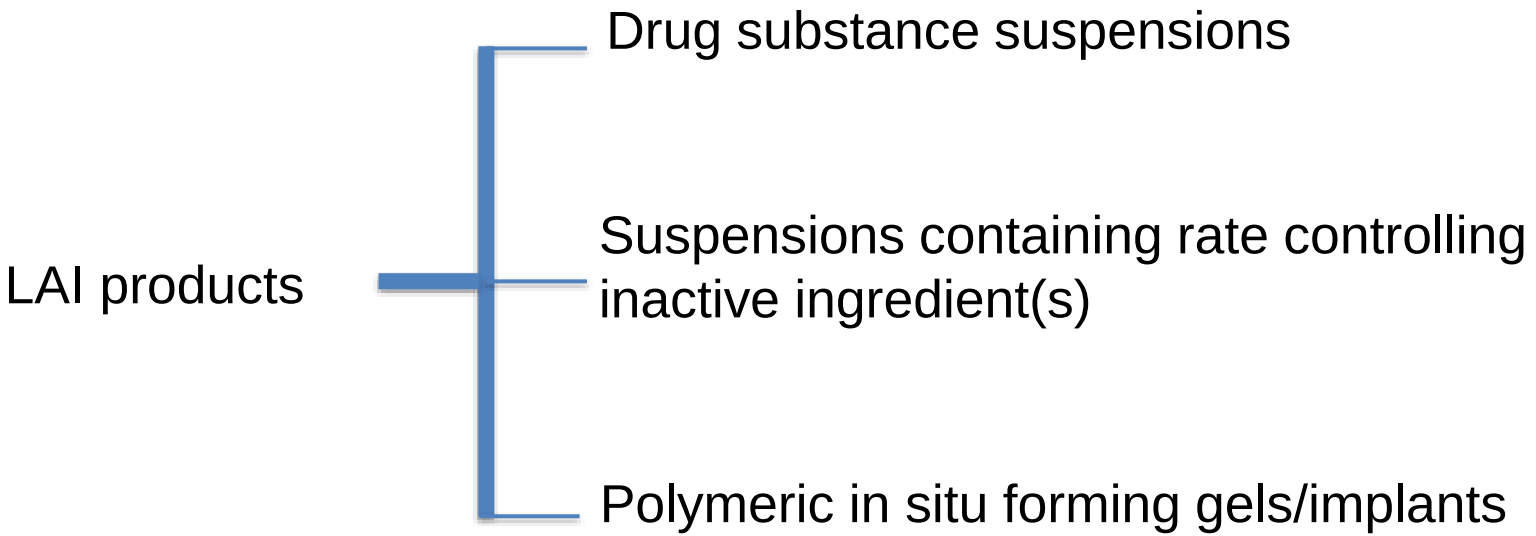
This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

Learning Objective

- Describe formulations for LAIs with pAUC recommendation
- Understand scientific rationale for pAUC recommendations
- Describe few case examples for LAIs with pAUC recommendation

Long Acting Injectable (LAI) Products

Long-acting drug products for injection, implantation, and insertion are formulated to achieve sustained drug release and action for extended time from days to years.



Formulation: Polymer Microspheres

- Polymer microspheres are controlled release systems that consist of polymeric materials that encapsulate active pharmaceutical ingredients (APIs) in a dispersion or as an API core surrounded by a polymer shell.
- A multiphasic release profile:
  - Initial burst release - release of API adsorbed to the particle surface or near the surface driven by diffusion.
  - Lag phase - time required for polymer degradation and erosion to occur as a result of release media penetration and polymeric matrix swelling.
  - Extended-release phase - polymer degrades enough to become water soluble, the polymer microspheres will undergo mass loss and matrix erosion continuously releasing API until depletion.
- Each of the above release phases can result in distinct phases and peaks in the PK profile for the LAI drug product

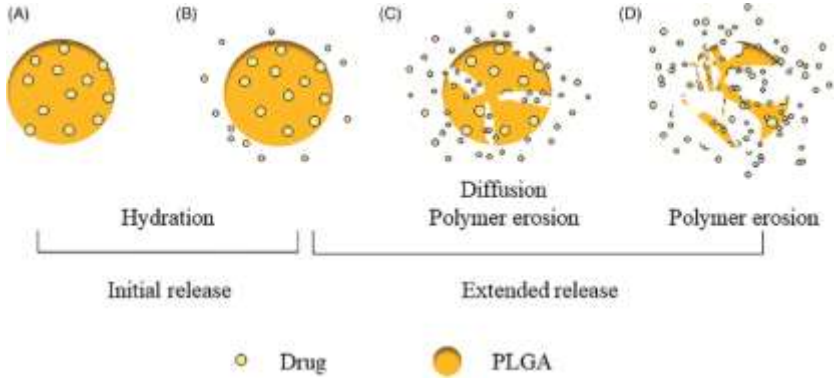


Figure: Schematic representation of degradation mechanism of PLGA microspheres
Hua Y et al. Poly(lactic-co-glycolic acid) microsphere production based on quality by design: a review. Drug Delivery. 2021;28(1):1342-55.

Formulation: In-situ Gel

- In situ forming implants are an injectable liquid dosage form which consists of drug, water-insoluble biodegradable copolymer, and a biocompatible organic solvent to dissolve the polymer and deliver the drug in the form of solution or suspension.
- Upon injection, the aqueous body fluid triggers phase separation and polymer precipitation leaving a biodegradable solid depot.
- Multi-phasic drug release
  - Initial burst release caused by phase separation as solid depot is formed
  - Diffusion facilitated release phase
  - Degradation facilitated release phase

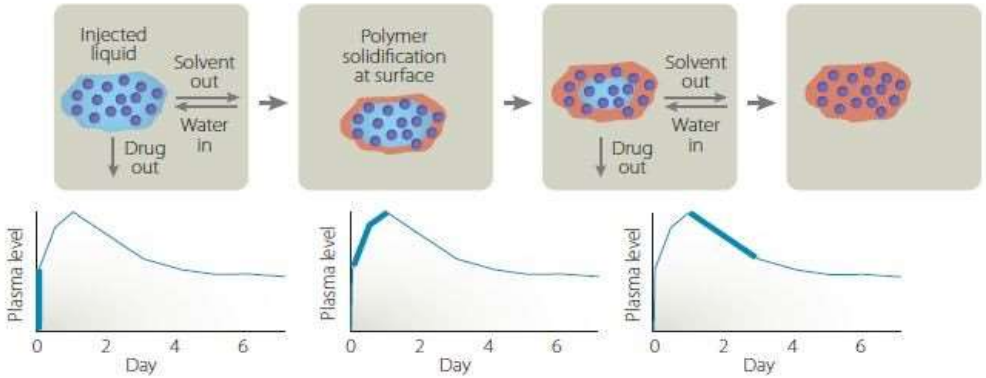


Figure: Indivior's RBP-6000 sustained-release formulation of buprenorphine containing ATRIGEL delivery system. Indivior Inc. Driving Innovation in Addiction Medicine. Advertisement feature in Nature – Biopharma dealmakers. 2017.

Partial AUC for LAI

What warrants partial AUC for assessing bioequivalence of LAI?

- Complex drug release mechanisms
  - Drug substance suspensions – diffusion control
  - Polymeric systems – a combination of several mechanisms (e.g., diffusion, erosion…)
- When a single dose in vivo bioequivalence study can be recommended, the traditional metrics of AUC and Cmax may not be sufficient to
  - capture potential impact of formulation and/or manufacturing parameters on drug release kinetics in vivo
  - ensure comparable drug absorption/exposure for some LAI drug products

PSGs recommended pAUCs for LAI

PSG	Route	pAUC	Study design	Subject	Formulation	RLD Number	PSG link
Leuprolide Acetate	Injectable Depot IM	Day 7-t	fasting, parallel, single-dose	Patient	Polymer microsphere	203696	https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_203696.pdf
Leuprolide Acetate	Powder SC	Day 7-t	fasting, parallel, single-dose	Patient	Polymer ATRIGEL® system	021343	https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021343.pdf
Triptorelin pamoate	Injectable	Day 7-t	fasting, parallel, single-dose	Patient	Polymer microsphere	20715 21288 22437	https://www.accessdata.fda.gov/drugsatfda_docs/psg/Triptorelin pamoate_IMinj_20715_21288_22437_RV02-14.pdf
Buprenorphine	Solution SC	Week 3-4	fasting, parallel, single-dose	Patient	Polymer ATRIGEL® system	209819	https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_209819.pdf
Octreotide	Injectable	Day 0-28, 28-56	fasting, parallel, single-dose	Healthy subject	Polymer microsphere	21008	https://www.accessdata.fda.gov/drugsatfda_docs/psg/Octreotide acetate_inj_21008_RV02-14.pdf
Naltrexone	Injectable IM	Day 1-10, 10-28	fasting, parallel, single-dose	Healthy subject	Polymer microsphere	021897	https://www.accessdata.fda.gov/drugsatfda_docs/psg/Naltrexone_ER intramuscular inj. suspension_021897_RV09-15.pdf

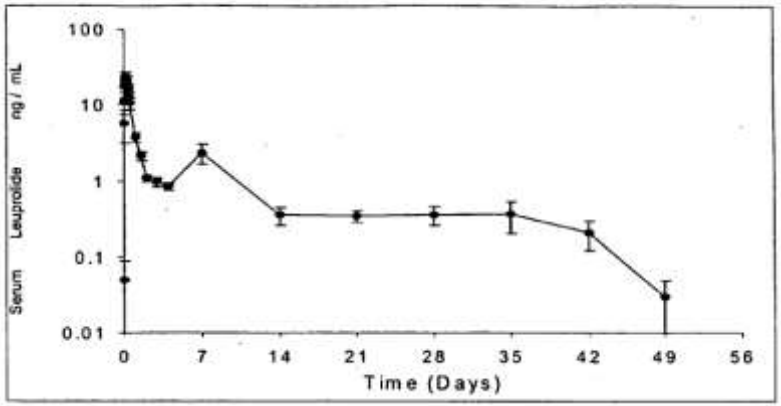
Case 1: Leuprolide and Triptorelin

- Leuprolide and Triptorelin are Gonadotropin-releasing hormone (GnRH) agonists
- pAUC recommendation: day 7-t
- Day 7-t represents sustained release phase or plateau phase of PK profile

Pharmacokinetics

- The PK curve for the drug product (Eligard® 7.5 mg) is characterized by two main phases which include an initial burst release of drug product followed by a sustained-release “plateau” phase for several days.
- The initial burst release from Eligard formulation is complete within the first 2-3 days.
- The plateau phase lasts from 1-6 months based on strength.

Figure 1. Serum Leuprolide Concentrations (Mean, SEM) Following a Single SC Injection of ELIGARD™ 7.5 mg in 8 Orchiectomized Subjects (Study AGL 9802).



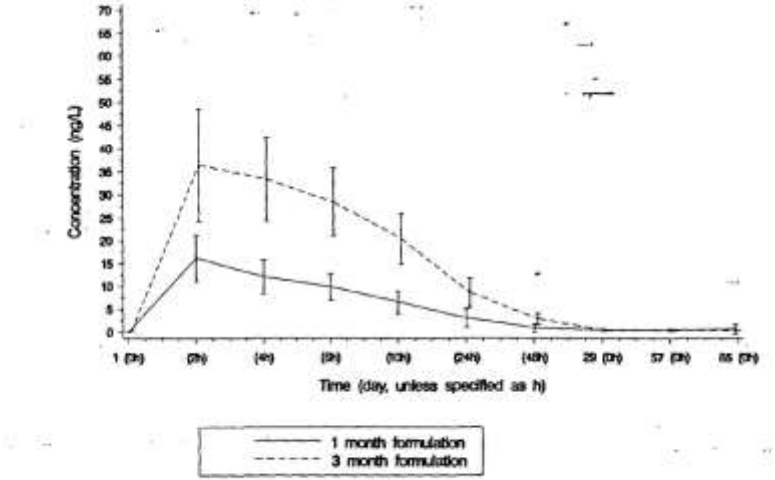


Fig 2. Comparison of serum triptorelin concentrations following first IM injection of 1-month vs 3-month formulations

Figure source: Clinical Pharmacology and Biopharmaceutics review document from Drugs@FDA for ELIGARD KIT (NDA 021343) and TRELSTAR

Reasons for pAUC Recommendation

Formulation consideration:

- Once the serum level of testosterone is < 50 ng/dL (associated with surgical castration), the PK profile does not impact the pharmacodynamic (PD) result.

- PK curve is characterized by a large initial peak due to high burst release which constitutes a significant portion of the total AUC. By day 7, this initial release is completed.

- The sustained release portion of the PK profile from day 7-t is the most relevant period to compare rate and extent of absorption of drug released from test and reference products.

Reasons for pAUC Recommendation

Clinical relevance:

- Mean testosterone levels increased above baseline during the first week following the initial injection, declining thereafter to baseline levels or below by the end of the second week of treatment.

- Therefore, a transient increase in clinical signs and symptoms of puberty may be observed during the first weeks of therapy or after subsequent doses. This is consistent across all GnRH agonists.

- This suggests importance of plasma concentrations at the start of therapy. AUC Day 7-t parameter is clinically relevant based on this mode of action. The sustained release portion impacts clinical performance.

Case 2: Buprenorphine

- Buprenorphine is a partial opioid agonist used in treatment of opioid addiction

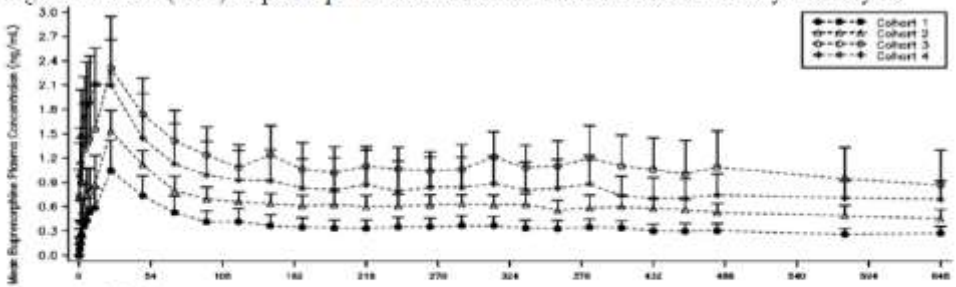
- LAI Buprenorphine pAUC: Week 3-4

- pAUC represents for terminal portion of plateau phase of PK curve. pAUC recommended in lieu of Cmin as BE criteria

Pharmacokinetics

- The buprenorphine ATRIGEL Delivery System allows for extended release by formation of in situ gel.
- The PK curve for the drug product is characterized by two main phases which include an initial release of drug product characterized by a single peak (days 0-3). The initial burst release is small and does not constitute a significant portion of the total AUC.
- This is followed by a sustained-release “plateau” phase (days 3-28) for several days.

Figure 24 Mean (±SD) Buprenorphine Plasma Concentrations versus Time Day 1 to Day 28



SD = standard deviation
Cohort 1 = a single SC injection of RBP-6000 containing 50 mg buprenorphine.
Cohort 2 = a single SC injection of RBP-6000 containing 100 mg buprenorphine.
Cohort 3 = a single SC injection of RBP-6000 containing 200 mg buprenorphine.
Cohort 4 = QD dosing with SUBOXONE SL, 8 mg (two 4 mg doses approximately 3 hours apart) on Day -7 and 12 mg on Days -6 through -1.

Figure 25 Plot of Mean (+ SD) Buprenorphine Plasma Concentrations versus Time on a Linear Scale for All Cohorts: Day 1 to Day 3

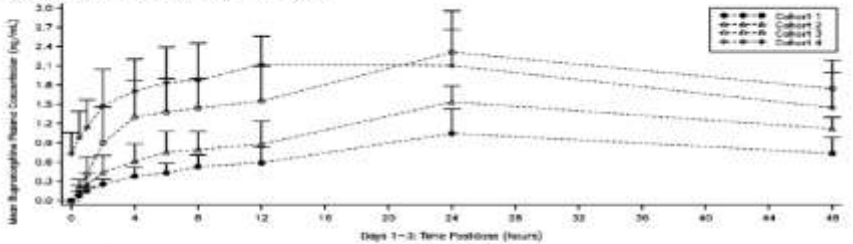


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Figure source: Clinical Pharmacology and Biopharmaceutics review document from Drugs@FDA for SUBLOCADE (NDA 209819)

Reasons for pAUC Recommendation

- Exposure response analysis shows a trend of drug-liking reduction with increasing buprenorphine exposure. A comparable minimum plasma concentration (Cmin) for potential generic formulation to the reference listed drug (RLD) during plateau phase is important.

- Cmin and shape of the PK curve should be monitored in the end stage of plateau phase (Days 21-28) such that Cmin for a generic product would not be less than the equivalent concentration of the reference product at the same time point.

- Due to difficulties of proper characterization and BE assessment on Cmin (high intra-subject variability), pAUC 3 - 4 week in place of Cmin was included.

Case 3: Octreotide and Naltrexone

- Octreotide is a somatostatin analog.
  LAI Octreotide pAUC: Day 0-28, 28-56

- Naltrexone is opioid antagonist.
  LAI Naltrexone pAUC: Day 1-10, 10-28

- pAUC recommendation for multiple peaks in PK curve

Octreotide

- The single dose profile is characterized by a transient initial peak within 1 hour after administration, progressively declining over the following 3-5 days, then slowly increasing and reaching a plateau about 2-3 weeks.

- Since the dosing interval is 28 days, exposure from 0 to 28 days is important.

- Octreotide levels continue to increase even after 28 days. Equivalence in exposure during the time interval from 28-56 days will help to ensure similarity in steady-state profiles.

Figure 9: Mean,sd octreotide (upper panel) and growth hormone concentrations (lower panel) after a single IM injection of LAR in acromegalic patients

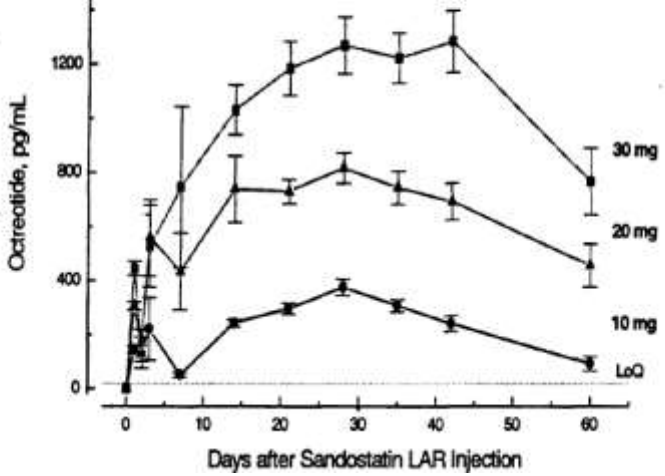

Figure source: Clinical Pharmacology and Biopharmaceutics review document from Drugs@FDA for SANDOSTATIN LAR (NDA 21008)

Naltrexone

- The single dose profile is characterized by a transient initial peak which occurs approximately 2 hours after injection, followed by a second peak approximately 2 days later and a slow decline approximately 14 days post-dose.
- Days 1-10 captures the large second peak in PK profile. Drug release from days 1-10 constitutes a significant portion of the AUC.
- Days 10-28 captures the sustained release phase of the PK profile. Prolonged concentrations below 1ng/mL is not clinically efficacious for alcohol dependence.
- The above two pAUCs ensure similar rate and extent of release between a proposed generic product and the reference product.

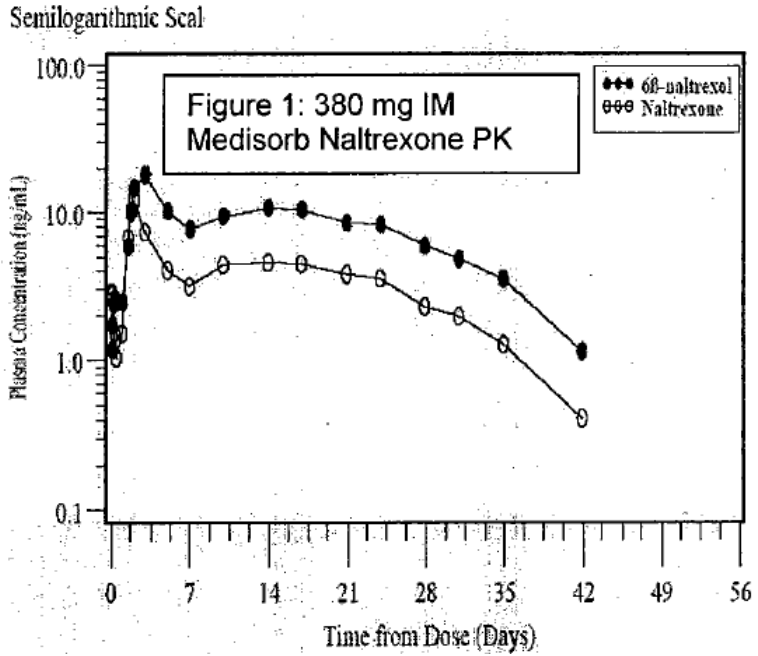

Figure source: Clinical Pharmacology and Biopharmaceutics review document from Drugs@FDA for VIVITROL (NDA 021897)

Regulatory Considerations for Use of pAUC for LAI

1) **Clinical Relevance**:
   - Sustained clinical effect resulting from control of API plasma concentrations within a therapeutic window for an extended duration e.g., buprenorphine

2) Formulation/Dosage form:
   - Complex PK shape resulting from multi-phasic release. Time window relevant to match plasma profile must be considered e.g., leuprolide acetate

Challenge Question #1

Which of the following LAI formulations has pAUC recommendation in PSG?

A. Leuprolide Acetate
B. Medroxyprogesterone acetate
C. Olanzapine pamoate
D. Penicillin G Benzathine

Challenge Question #2

Which of the following is the reason for pAUC of 3-4 week recommendation for Buprenorphine LAI?

A. Comparable plateau phase
B. Identical initial burst release
C. Comparable Cmin during plateau phase
D. Multiple peaks in PK curve

Summary

- LAI products have complex, multiphasic drug release mechanism.
- When a single dose in vivo bioequivalence study can be recommended, pAUC can be considered, as traditional metrics of AUC and Cmax may not be sufficient to ensure comparable drug absorption/exposure.
- Clinical relevance of API plasma concentrations and the multiphasic release from drug products are the major regulatory considerations for pAUC recommendation.

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