Novartis Pharma AG

A roadmap for production of drug loaded poly(lactic-co-glycolic acid) (PLGA) microparticles: challenges and opportunities

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Agenda

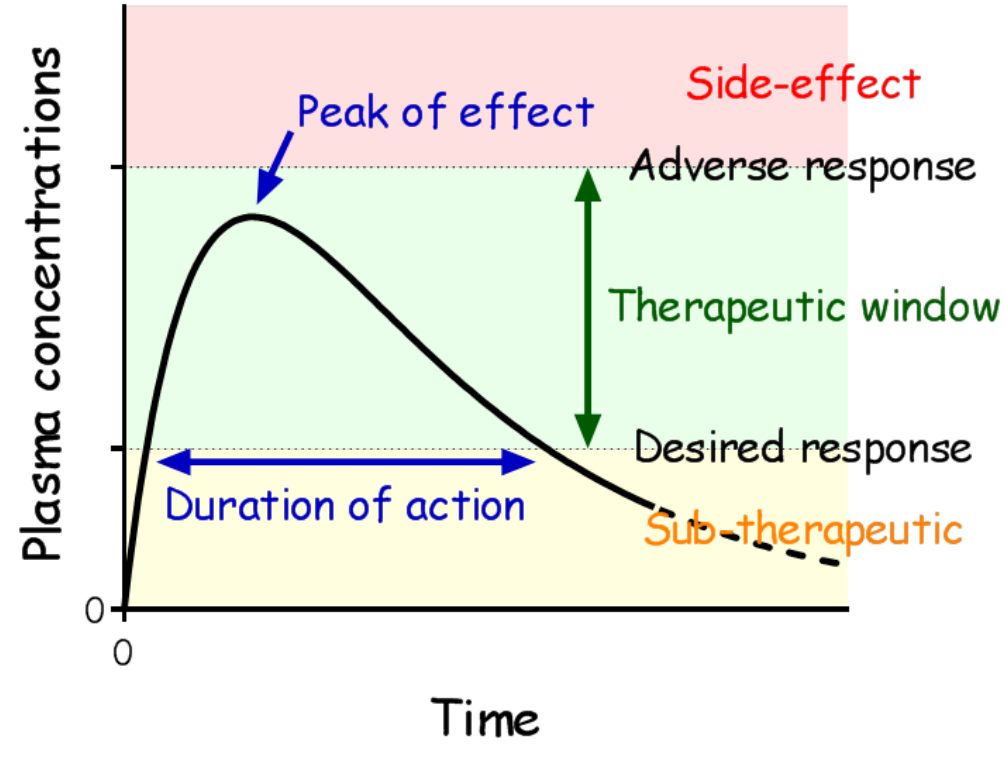
1. **Section 1: introduction**
   - General introduction
   - PLGA and PLGA based microparticles
   - Marketed product
   - Clinical trials
2. **Section 2: Challenges regarding development of PLGA MPs**
   - Road map for production of PLGA MPs
   - Drug substance properties
   - Formulations characterization (drug loading, drug release, scale up, sterilization etc.)
   - Administration

Revolutionizing Medicine: The Power of Long-Acting Injectables

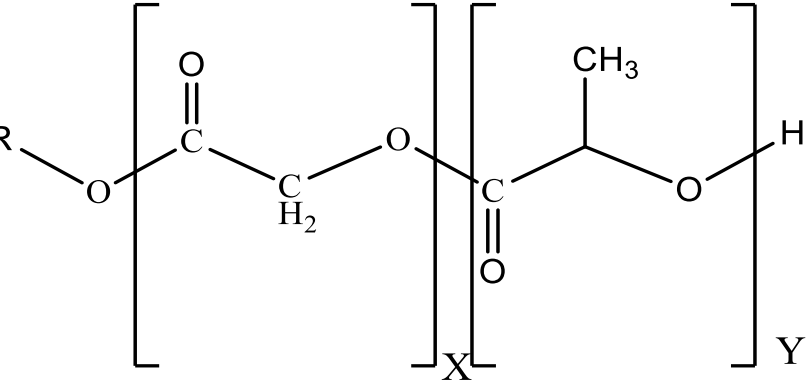
The Problem with Traditional Medications

- **Adherence Issues**
- **Fluctuating Drug Levels**

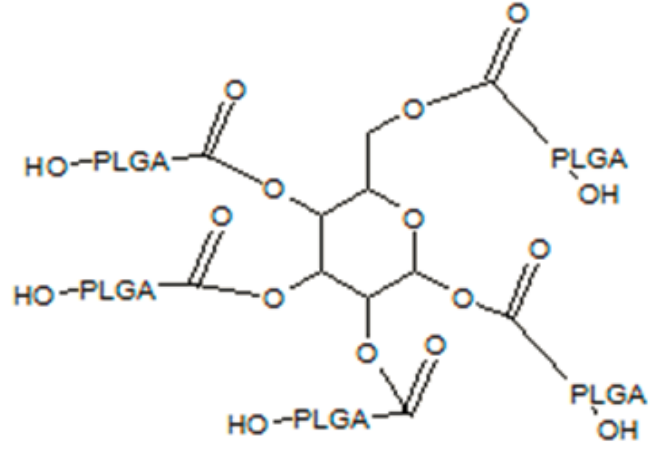
What are Long-Acting Injectables?



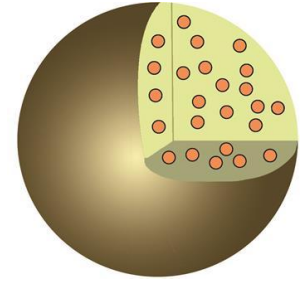
Poly (lactic-co-glycolic acid) co-polymer (PLGA) : Linear and branched



Linear PLGA



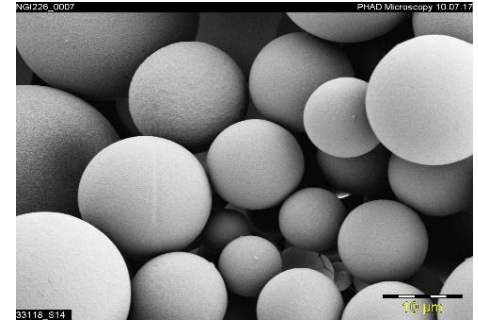
Branched PLGA



Drug physical state:

1) Molecularly dispersed
2) Solid particle dispersed
3) Combination of Both

Example of SEM image of PLGA microparticles



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Microparticles Manufacturing Methods

Established Methods

- **Emulsion Solvent Evaporation:** Most common; suitable for both hydrophilic and lipophilic drugs. Includes single (O/W) and double (W1/O/W2) emulsion techniques. Key challenges: encapsulation efficiency and particle size control.
- **Spray Drying:** Simple and scalable, but high temperatures may limit use for sensitive drugs.
- **Spinning Disk:** Used for specific drugs (e.g., Zilretta®); relies on centrifugal force for particle formation.

Novel Methods

- **Membrane Emulsification:** Produces monodisperse MPs with precise size control; scalable by increasing membrane size or parallelization.
- **Microfluidics:** Enables reproducible, monodisperse MPs; scalable by parallelizing devices. Used in large-scale vaccine production.
- **Inkjet Printing:** Allows for tailored particle shapes and sizes; scalable via nozzle arrays.

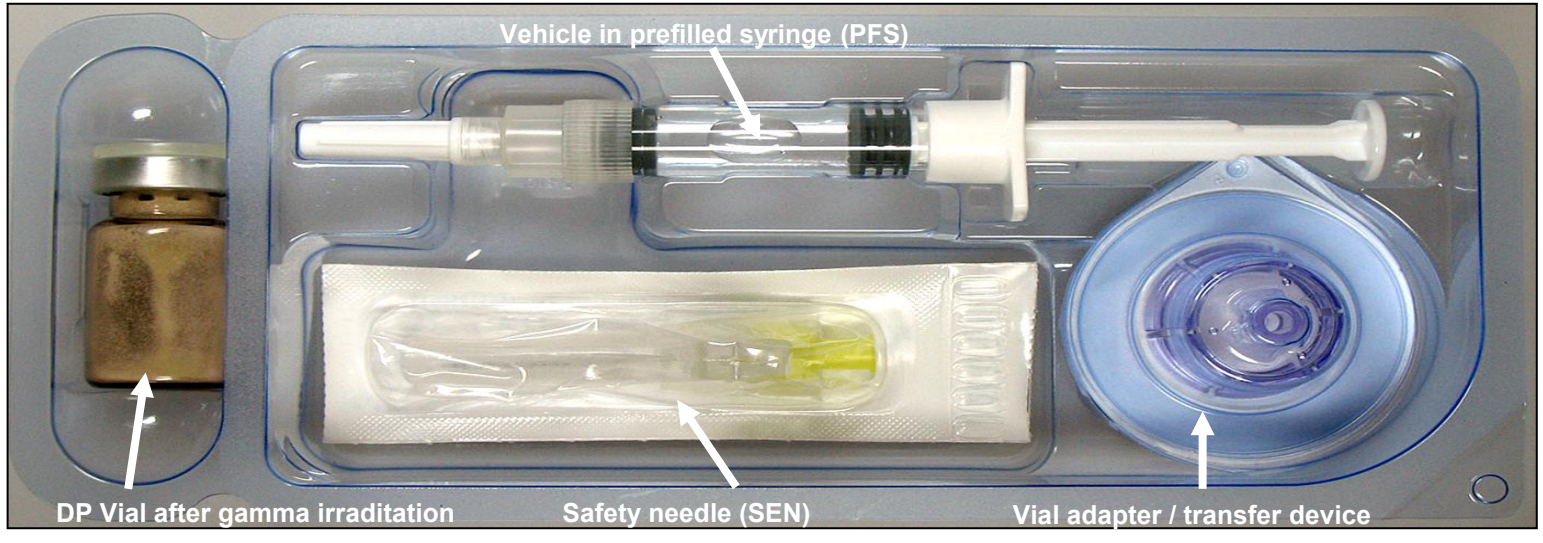
Marketed PLGA-based microparticle formulations: 11

Registered name	Drug	Manufacturer	Indication	Route of administration	Dosing interval (week)	Log P	Water solubility (mg/mL)	PLGA type (L/G ratio)	Highest dosage (mg)	Drug loading% (w/w)
Arestin®	Minocycline hydrochloride	OraPharma	Gum infection	subgingival	12	0.5	50.00	PLGA	1.0	Not found
Bydureon®	Exenatide	AstraZeneca	Type 2 diabetes mellitus	SC	1	- 2.1	1.00	PLGA 75:25	2.0	5.0
Lupron Depot®	Leuprolide acetate	Takeda, Abbott	Breast and prostatic cancer	IM	4–26	1.1	0.50	PLA*	45.0	17.0
Nutropin Depot®	Somatotropin	Genentech Inc.	GH deficiency	SC	4–5	–	5.00	Not found	22.5	12.0
Risperdal Consta®	Risperidone	Alkermes & Janssen	Schizophrenia, Psychotic disorders	IM	2	3.0	0.003	PLGA 75:25	52.0	32.9
Sandostatin® LAR	Octreotide acetate	Novartis	Acromegaly, Carcinoid Tumors	IM	4	0.4	1.20	PLGA 55/45 star polymer	30.0	4.17
Signifor® LAR	Pasireotide pamoate	Novartis	Acromegaly	IM	4	3.0	0.01	PLGA 55/45 star polymer + PLGA 50:50	60.0	25
Somatuline® LA	Lanreotide acetate	Ipsen Pharma Biotech	Acromegaly	IM	2	1.1	0.50	PLGA 75: 25	30.0	24.6**
Trelstar® LA	Triptorelin pamoate	Debiopharm, Ipsen, Vifor	Prostatic cancer	IM	4–26	1.7	0.03	Not found	22.5	7.3
Vivitro®	Naltrexone	Alkermes & Janssen	Alcohol Opioid dependence	IM	4	1.9	1.63	PLGA 75:25	380.0	33.7
Zilretta®	Triamcinolone acetonide	Flexion	Pain killer	intra-articular	12	2.5	0.04	PLGA 75:25	32.0	25.0

* Poly(lactic acid) polymer (it is not known whether it is poly(L-Lactic acid) or poly(DL-Lactic acid). Solubility and logP values obtained from drug bank [89].
** From FDA data base [90]; other data are from PharmaCircle® data base [14].

Novartis marketed products based on PLGA

- Signifor ® and Sandostatine LAR commercial tray /IFU



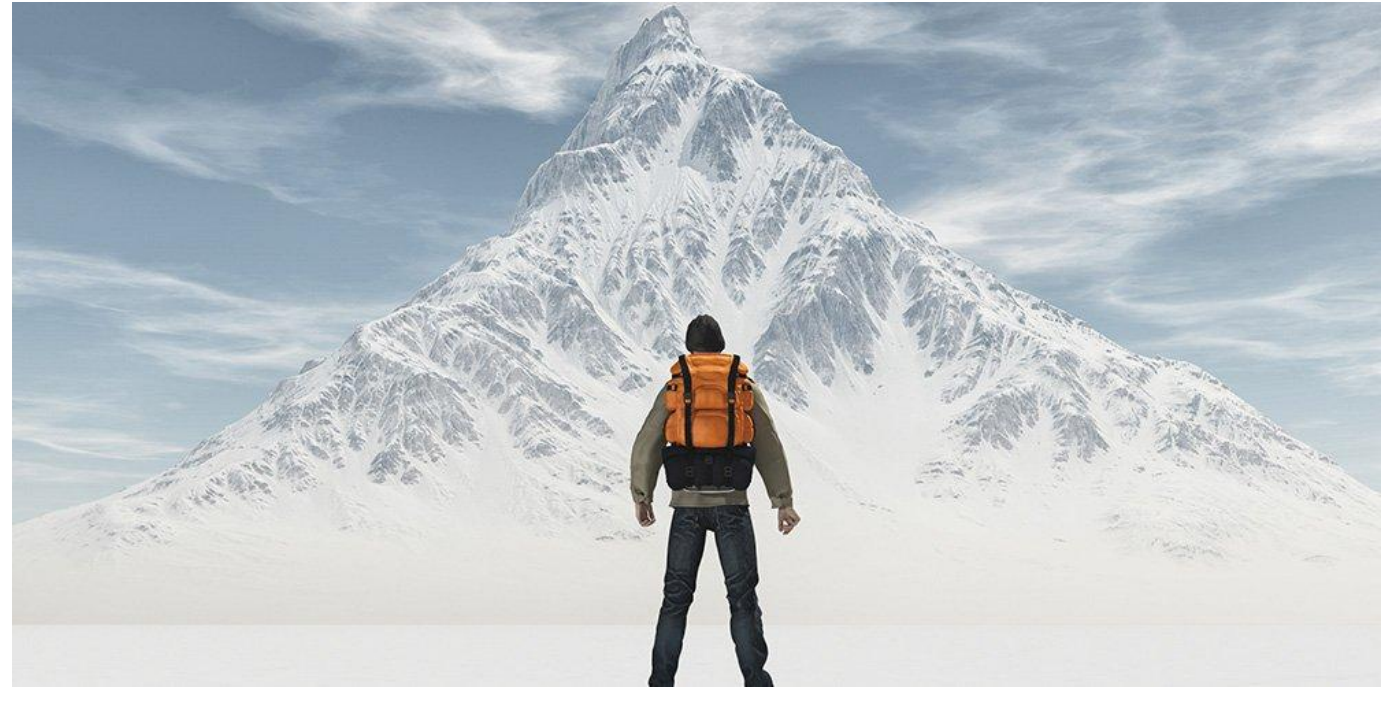
For patient with acromegaly Cushing's disease

Example of recent/ongoing clinical trials using PLGA MPs

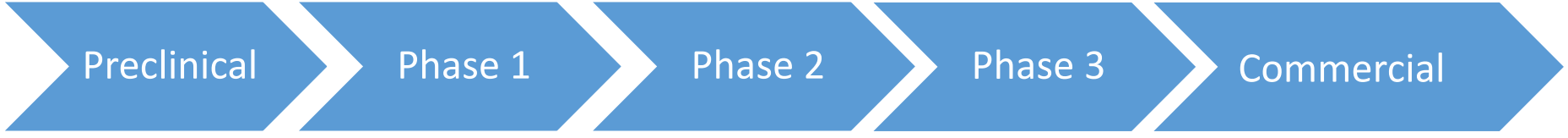
- **Tendon Injuries (Phase 2 ongoing)**
  - NGI226 loaded PLGA MPs
  - Injected close to the tendon (Novartis)
- **Lumbosacral radiculopathy or sciatica (phase 2 completed)**
  - Clonidine loaded PLGA MPs (Sollis Therapeutics)
  - Injected close to impacted nerve via applicator, conducted by fluoroscopy for accurate placement
- **Aneurysmal subarachnoid hemorrhage**
  - Nimodipine loaded PLGA intraventricular or intracisternal administration (Edge therapeutic)
  - Comparing to systemic administration→ discontinued as unlikely to meet the primary endpoint

Section 2:
Challenges regarding development of long acting Injectables

- Road map
- Formulations characterization (drug loading, drug release, scale up, sterilization etc.)
- Manufacturing
- Administration
- Local tolerability



Establishing the roadmap for development of drug product



Early Phase: Focus on formulation screening, stability, toxicology, and initial scale-up.
Quality by Design (QbD): Systematic approach starting with defining the quality target product profile (QTPP), identifying critical quality attributes (CQAs), and controlling material/process parameters.
Late Phase: Emphasizes process qualification, container/closure selection, and regulatory compliance.
Commercialization: Finalizes CQAs, validates processes, and ensures supply chain robustness.

Critical Formulation Challenges

- **Drug Substance Properties:** Lipophilicity, potency, and stability are crucial for successful encapsulation and release.
- **Drug Product Quality Attributes:** Drug loading capacity, particle size distribution, drug release kinetics, residual solvent, sterility, and injectability must be tightly controlled.
- **Sterilization:** Gamma irradiation, X-ray, and electron beam are preferred methods; impact on drug and polymer must be evaluated.

Manufacturing processes for LAI development

- Complex manufacturing process that needs extensive process development and scale up
- Early investment in scalable equipment (from lab scale through full production scale)
- Close collaboration between formulation team and manufacturing team needed
- Implementation of process analytical technology (PAT) tools
- LAI need to be produced with high quality, purity, and sterility, including being essentially free from foreign visible particles (20% batch recall due to foreign visible particle)

Syringeability and injectability of LAI formulations

- **Formulation effect**
  - Particle size, shape, density
  - Viscosity of vehicle
  - Suspension concentration
- **Geometry of the syringe and needle**
- **Rout of administration**
  - IM, SC, IA etc

In vitro and *in vivo* release from LAI formulations

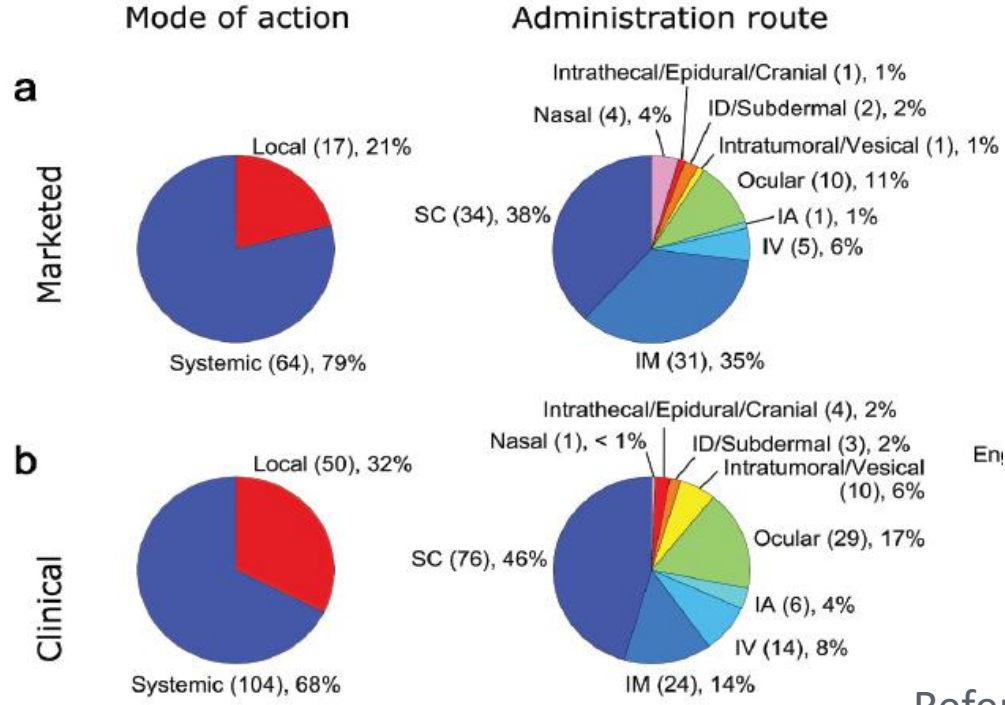
- **Aim of *in vitro* release study**
  - Formulation selection and process optimization
  - Batch-to-batch quality control evaluation
  - No official guideline or requirement about in vitro release set up (recent chapter from USP)
- **Release methods**
  - Sample-and-separate approach (small scale)
  - Continuous flow (USP IV) (no agglomerations of samples)
  - etc.
- **Release medium**
  - Biological mimicking fluid with addition of proteins or enzymes representing different tissues
  - Simple PBS buffer pH 7.4 (addition of surfactant for low water soluble drugs)
- **Final goal of in vitro release:**
- Establishment of IVIVC

In vivo behavior and tolerance of LAI formulations

- **Immune system response**
  - Repair tissue injury
  - Remove the foreign material by foreign body response (FBR).
- **Immune responses is described in 3 phases**
  - An active response to a more chronic response of particle uptake and breakdown
  - Immediately after tissue injury: protein release from blood cells and ECM triggers a signaling cascade leading to acute inflammation with neutrophils
  - Over time, when initial tissue damage is repaired, the process becomes more chronic, with macrophages as dominant cell type.
  - Activation of ECM and fibroblasts, granuloma and fibrous capsule formation may occur at the site of depot which can alter drug release
- **Particles having sizes < 5µm are taken up easily by phagocytosis suggesting materials of > 10 µm size to be able to escape the phagocytosis**

Opportunities

- **Local drug delivery** → less systemic drug exposure and high drug concentration at the site of action
- Transition from intramuscular (IM) to subcutaneous (SC) delivery is driven by convenience and reduced healthcare



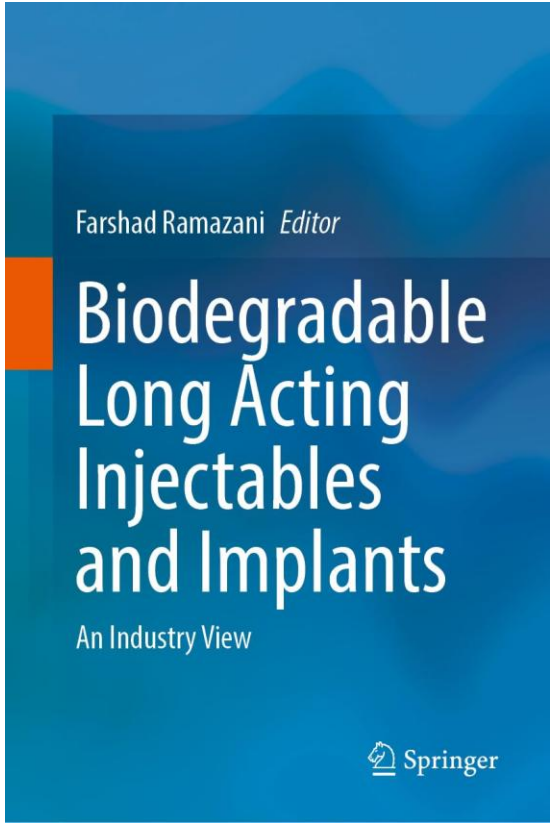
Reference: doi: 10.1080/17425247.2022.2106213.

Conclusion

- Development of LAI: Complex and time consuming
  - Benefit for patient and sustained sale for pharma
  - Early on collaboration between research and development teams is required to design ideal drug molecules with suitable delivery systems.
  - Manufacturing issues (e.g., scale up production, sterilization, syringeability and injectability)
  - Local tolerability and *in vivo* fate of the formulations.

Thank you all for your attention

Reference for further information



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Back up slides

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