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"How difficult is it to manufacture a LAI formulation, really?"

"[Ease of manufacture] really depends on the technology that comes into play"

Background

Range of LAI technologies.

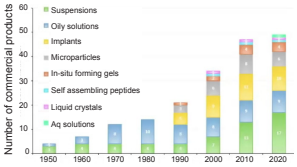
- Solutions: Haldol 5mg/mL.
- Microencapsulation: Risperdal CONSTA.
- Solid-state implants: Zoladex.
- In-situ forming depots: Eligard.
- Suspensions: Depo-Provera; Abilify Maintena; CABENUVA.

Each technology has a very different manufacturing plan.

- Delayed generic development of Risperdal CONSTA may have had more to do with manufacturability than IP.

Evolving landscape of commercial LAI products (1950-2024).

- Growing list of applied technologies.
  - ◊ 1950-1990. No major development beyond Suspensions and Oily solutions.
  - ◊ 1990s. Implants, Microparticles, & In-situ forming gels.
  - ◊ 2000- 2010. Self-assembling peptides & liquid crystals.
  - ◊ 2023. Aqueous solutions.



- Expanding therapeutic areas.
  - ◊ Schizophrenia (17); Oncology/palliative care (13); Contraception (6); Hormonal disorder/ deficiencies (8); Infectious diseases – Not HIV (4)/HIV(4); Opioid dependence (3); Diabetes-related disorders (3); Anti-inflammatory (2); Other (3).

How to select a LAI technology

Compound properties.

- Intrinsic properties for slow release (e.g., CAB). Compound can be injected "as is" as a suspension; Size can be adjusted.
- Need to control the release. Start working with polymer chemistry.

Advantages and limitations of each technology.*

	Advantages	Disadvantages
Solution	• **Process scale-up (Simple).** • **Manufacturability (Cost).** • **Sterilization strategies.** • Simple preparation & manufacturing	• Limited release duration. • Administration (Viscosity). • Drug loading.
Microencapsulation	• Drug-release modifications. • Hydrophobic & hydrophilic drugs	• **Process scale-up (Complex).** • **Manufacturability (Expensive).** • **Aseptic processing.** • Initial drug release. • Drug loading limitations.
Solid-state implant	• Drug-release modifications. • Hydrophobic & hydrophilic drugs	• **Manufacturability (Expensive).** • **Aseptic processing.** • Invasive administration. • Size/drug-loading limitations
In situ forming depot	• **Process scale-up (Relatively simple).** • **Manufacturability (Cost).** • **Sterilization strategies.** • Drug-release modifications. • Simpler preparation.	• Organic (Biocompatible solvents). • Initial drug release. • Stability (API, polymer). • Administration (Viscosity). • Drug-loading limitations.
In situ hydrophobic API depot	• Simple preparation. • Simple formulations. • High drug-loading possible.	• **Process scale-up (Particle size).** • Drug-release control. • Particle size. • API modifications.

* Blue indicates factors more relevant to manufacturing.

Consider product price in a price-sensitive market.

- Older, oil-based solutions are the cheapest products on the market.
  - ◊ Easiest to manufacture; Excipient is inexpensive; and Thermal sterilization is possible.

Aseptic processing costs & technical complications should not be underestimated.

- Consider the sterile manufacturing plan early.
  - ◊ Global sterilization guidelines are ethically aligned and enforced as of P1.
  - ◊ EMA (2019): 1. Autoclaving (Fastest & most effective); 2. Dry sterilization (Oil formulations); **3. Aseptic processing** (Selected technology/compound properties do not allow terminal sterilization).
- Aseptic processing and API sourcing requirements.
  - ◊ Sterile API requires infrastructure. Gamma-irradiation or sterile filtration and aseptic crystallization.
- Finding a plant that can generate cheap generics can be a challenge.
  - ◊ **Generic manufacturers are price-dependent and cannot install every technology.** They will focus on achieving excellence in a particular technology.
  - ◊ **Technologies created at universities are not restricted by infrastructure.** The process may not be installed in aseptic conditions.

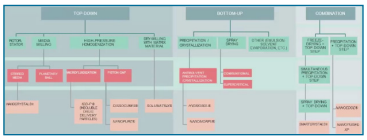
Manufacturing schema by technology

Solutions and in-situ forming gels (Low complexity).

- Dispensing; Mixing; Filling; Sterilization.
- Scale-up and sterilization are relatively easy. Scale up using mathematical models (i.e., From 1mL to 4 tons); Sterilization via autoclaving (Most manufacturers have this).

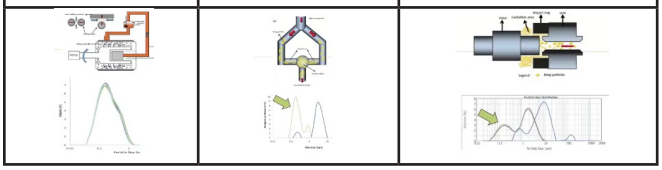
Suspensions (More complex).

- Many options for Top-down, Bottom-up, & Combination methods.
  - ◊ Top-down via media milling or high-pressure homogenization is ideal. (i.e, Used for commercial products).
  - ◊ Combination method adds to cost & complexity (i.e., Additional technologies).
  - ◊ Nanonization milling to target is robust and scalable (e.g., CAB).
    - * A 4L chamber can manufacture 150-200L. (Need to invest in the technology); Custom equipment for small (R&D) or large scale (Operations).
    - * Broad application to other LAIs.
    - * Key process parameters are understood: Agitator speed; Milling media (Type, size, charge); Milling Time; Suspension Flow; API (Particle size, concentration).



- The production approach for micro- and nano-suspensions matters.

Media Milling	Microfluidization	High-pressure homogenization
Most likely to be used	Not used commercially	Used for a few commercial products



  - ◊ **Different milling technologies yield different particle-size distributions (Same API).** Important for compounds with huge sensitivity on the release.
  - ◊ Scale-up is possible by modeling breakage behavior.
    1. Frontal impacts (Breakage) and Shear stresses (Break agglomerates/brittle material): Probability of stressing.
    2. Brittleness: Low stress energy (SE) values break all particle sizes for brittle materials.
    3. Stress number: Above a minimum SE value, breakage rate depends on the number of stress events.
  - ◊ **Technology interchange is not necessarily possible**. A copycat formulation can be difficult to obtain if not truly copied all the way.

Implants (Intermediate complexity).

- Dispensing; Mixing; Extrusion; Cutting; Sterilization. HME is often used.

Microspheres (Most complex).

- Manufacturing complexity can drive long generic timelines.
  - ◊ Systems are robust and well-understood, but many process parameters define the release.
  - ◊ Microfluidization yields more consistent production but is not widely implemented.
  - ◊ 20-year delay in generic Risperdol was likely due to manufacturing complexity.
    - * The first generic was an in-situ forming gel. (i.e., A "Short cut" when they could not make it work)