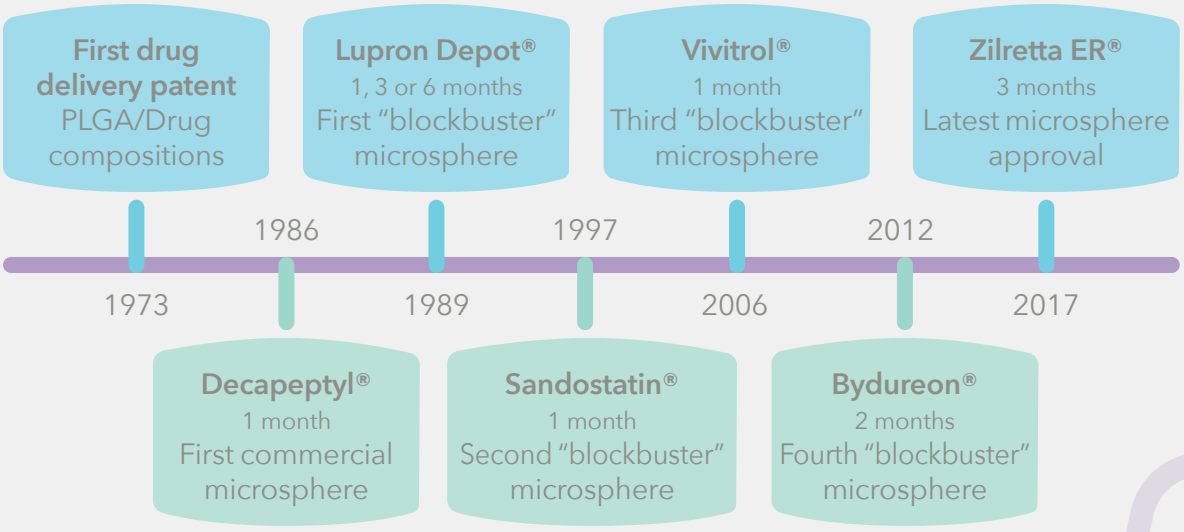
LUBRIZOL LIFE SCIENCE

LLS Health Whitepaper

Overcoming the Knowledge Gap — Long-Acting Injectables and Implantables

Introduction

The market for long-acting injectable (LAI) and implantable drug products is growing rapidly. The implantable drug delivery market alone was valued at USD 22.85 Billion in 2020 and is projected to reach USD 45.82 Billion by 2028, growing at a CAGR of 8.0% from 2021 to 2028.[1] Meanwhile, the LAI market was valued at USD 30.5 Billion in 2019 and is projected to reach USD 40.7 Billion by 2025, at a CAGR of 6.0% during the forecast period.[2]



Microsphere depot injections are **complex to formulate and manufacture**. Twenty nine (29) long-acting injectable products have FDA approval, but **only one** has a generic.

Figure 1: Key Microsphere Depot Injections over the years

Long-acting products, such as LAIs and implantables, have been available on the market for many decades, but market growth has accelerated in recent years. Both have become increasingly popular among drug developers for a number of reasons:

- **Improved patient adherence** – by reducing the number of doses that patients need to take, they can help eliminate the risk of missed doses, enhancing patient compliance.
- **Reduced side effects** – by avoiding first-pass oral metabolism and providing consistent drug release over time, long-acting products are able to minimize toxicity and side effects of APIs. A well-designed long-acting product stays within the therapeutic window and avoids the dosing fluctuations of daily pills or injections, enhancing the patient experience.
- **Harnessing of HPAPIs** – the controlled release of highly potent APIs (HPAPIs), even at small quantities, is possible with LAIs and implantables. This makes them an important option for drugs incorporating a wide range of compounds, such as sex hormones, enhancing their performance and prolonging effectiveness.
- **Streamlined development and IP protection** – both LAIs and implantables can utilize existing APIs through the simplified 505(b)(2) regulatory pathway in the United States, meaning they can be used to develop novel, IP-protected dosage forms or extend the product lifecycle for an existing drug.

The development of new long-acting formulation techniques has enabled the rapid expansion and diversification of LAI and implantable drug products to treat a wide range of health issues.

Examples include:

- Cancers
- Diabetes
- Central nervous system (CNS) disorders such as schizophrenia
- Substance abuse and addiction
- Eye diseases
- HIV treatment and prevention
- Contraception
- And more

Examples of long-acting products now available on the market

CNS Disorders – Janssen's Invega LAI product line consists of injectable nanosuspensions developed to treat schizophrenia. Reformulation every six years has significantly improved not just drug performance, but the duration of therapeutic action too. For instance:

- 2009: Invega Sustenna® was approved for 1-month injection
- 2015: Invega Trinza® was approved for 3-month injection
- 2021: Invega Hafyera™ was approved for 6-month injection[3]

HIV Treatment and Prevention – Several drug developers are exploring the potential of LAIs to treat and prevent HIV.

- Gilead and Merck have partnered to co-develop long-acting HIV treatments.[4]
- LLS Health and the International Partnership for Microbicides co-developed the dapivirine vaginal ring as a new option for HIV prevention – a product that was recommended by the World Health Organization (WHO) in 2021.[5]
- The Bill & Melinda Gates Foundation has also issued grants of more than $200 million to develop, scale up and clinically validate long-acting technologies for HIV prevention and treatment, as well as for other global health issues.[6]

Contraception – A number of drug developers have also considered long-acting technologies for contraception and family planning in recent years. For example:

- NuvaRing was the first contraceptive vaginal ring to be FDA-approved in 2001, providing up to 1 month of drug release.
- Lubrizol was part of the development of Ornibel® which was approved in Europe in 2017 as a second-generation contraceptive vaginal ring. It was developed to be bioequivalent to NuvaRing® but employed thermoplastic polyurethane (TPU) to differentiate the design and gain approval.
- Annovera® was FDA-approved in 2018 and greatly extended the contraceptive protection, providing 1-year of therapy from a single ring.[7]
- Other novel rings are currently in clinical trials around the world with a range of designs, excipients, and target indications.

Despite great progress in the industry, the development of LAIs and implantables does pose challenges for pharmaceutical companies, particularly if they are embarking on a long-acting project for the first time. Carefully considering these challenges is key to ensuring successful development.

In this whitepaper, we will explore the challenges of long-acting drug development and discuss how to overcome these to maximize the success of any development project.

Section 1: Understanding LAIs And Implantables

The benefits

Implantable drug delivery systems are designed to be implanted or inserted via several different routes of administration, including intravaginal, subcutaneous, intraocular and intra-articular. Implants are used to provide sustained drug release over a period of weeks, months, or even years.

While many implants offer controlled, systemic drug release, they can also be used for localized, site-specific drug delivery to areas like the brain or tumor. This enables treatment of conditions such as inflammation without the drug passing through the rest of the body.

Implantables in action

- **Intravaginal rings (IVRs)** provide steady release of highly potent drugs over several months. IVRs have been developed for contraception (NuvaRing, Ornibel, etc…), HIV prevention (IPM's Dapivirine Ring), or even a combination of both (CONRAD's Multipurpose Ring).
- **Ozurdex** is a microscopic, rod-shaped implant that is placed directly into the eye of a patient to treat local inflammation and replace monthly injections.
- **Implants for oncology treatment** include solid tumor implants or site-specific devices such as bladder implants designed to deliver cancer treatments directly to the site of the disease, avoiding systemic exposure and minimizing adverse effects.

A key benefit of implantables is that they offer fewer unwanted side effects than traditional dosage forms.

There are several reasons for this:

- **Avoid first-pass metabolism** associated with the oral route of administration. With localized drug delivery, the API is not circulated throughout the body or metabolized by the liver, helping to reduce unpleasant side effects and increasing bioavailability.
- **Lower dosage:** smaller doses of API are required for implantables because the drug is delivered more efficiently when compared with other routes of administration. Localized implants can use less drug because they are placed at the site of action, and implants for systemic delivery can also deliver lower levels of API within the therapeutic window. This reduces the side effects caused by high levels of API in the body. In addition, in the case of very expensive APIs, can help reduce the manufacturing cost for a drug product as less API is needed per dose.
- **Consistent dose over time** due to the controlled release of the drug from the implantable. This means that drug levels consistently remain within the therapeutic window, rather than peaking and declining throughout the course of the treatment. This helps minimize toxicity and side effects.

Achieving controlled release

When designing implantables, it is possible to achieve control over drug release through several design variables. These include:

Polymer selection: to alter the properties of the device, as well as interactions with the API. The choice of polymer will depend on the system chosen for the implantable. For example:

- **Bioresorbable systems:** these degrade within the body to release the drug and do not require explantation. They are typically used for up to six months of delivery. Bioresorbable implants are typically made of poly(lactic-co-glycolic acid) (PLGA) polymers, as they can be safely broken down by the body. Examples of bioresorbable implants are found in several routes of administration, including:
  - Ozurdex: Intravitreal (eye) implant
  - Zoladex: Subcutaneous rod-shaped implant
  - Propel: Stent-like sinus implant
  - Gliadel wafer: Brain implant

- **Biodurable systems:** these products are made from polymers that do not degrade within the body and rely on diffusion to deliver drugs. While their non-biodegradable nature means these products must be removed at the end of treatment, they also offer the benefit of reversible drug delivery. If a patient experiences side effects or wants to stop treatment, biodurable implants and inserts can be removed at any time. Such systems also enable longer delivery timeframes of up to several years. They are usually made from thermoplastic polyurethane (TPU), ethylene-vinyl acetate (EVA), or silicone, due to their long history of use in medical products and control over drug loading/release. Examples of biodurable products include:
  - Nexplanon: Subcutaneous rod-shaped implant
  - Probuphine: Set of four subcutaneous rod-shaped implants
  - NuvaRing: Intravaginal ring
  - Iluvien: Ophthalmic implant

- **Device design:** depending on the specific design of the implantable device, a range of different drug release kinetics can be obtained:
  - **Matrix systems:** in matrix-type implants, the API is uniformly dispersed throughout the polymer. As such, they often exhibit first-order drug release, with a burst followed by a tapering drug release rate (see Figure 3).
  - **Reservoir or core-sheath systems:** a drug-loaded core is surrounded by a rate-controlling polymer membrane. As a result, reservoir systems exhibit zero-order drug release, meaning they provide a steady release rate over time (see Figure 3). These are especially useful for the delivery of hormones, which require consistent, steady dosing over time.
  - **Coating systems:** these systems involve the application of a drug-loaded layer to the surface of a device. They can be used to incorporate drugs into existing medical devices, such as drug-eluting stents.

Drug Incorporation Techniques for Implantable Devices

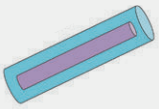
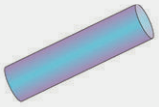
		Description	Examples
Matrix		Drug uniformly dispersed throughout polymer	Zoladex® Ozurdex®
Reservoir		Drug core surrounded by polymer membrane	Nexplanon® NuvaRing®
Coating		Drug-containing layer applied to the surface	Drug-Eluting Stents

Figure 2: Different drug incorporation techniques for implantables

Various Types of Drug Release Profiles

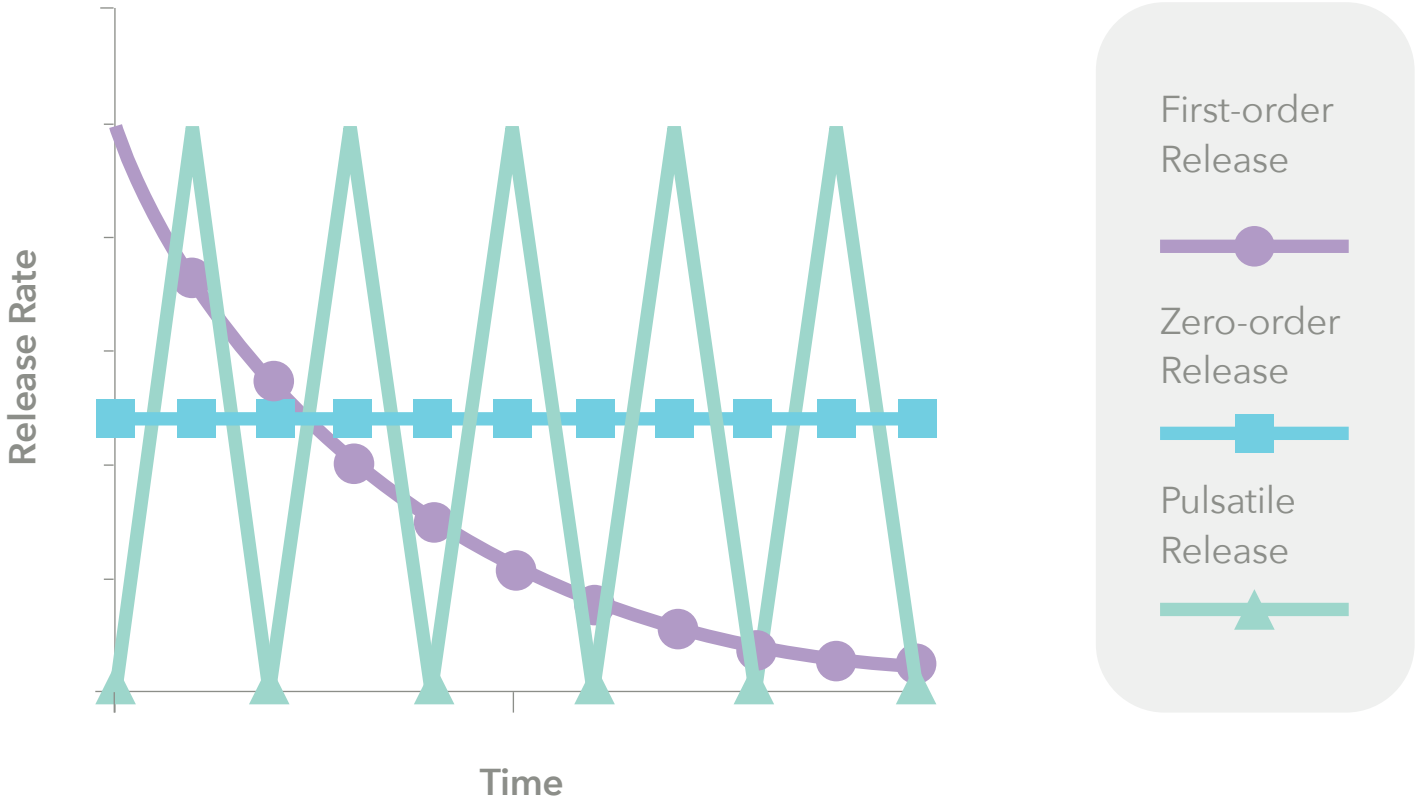


Figure 3: Comparing drug release profiles

Long-Acting Injectables (LAIs)

The benefits

Like implantables, LAIs are also designed to provide sustained or controlled localized or systemic drug release. However, rather than implanting a device in the body, LAIs are parenteral drug formulations designed to be injected once every few months. There are multiple different forms:

- Microsphere Depot Injections
- Gel/Suspension-Based Depot Injections
- Nanosuspensions

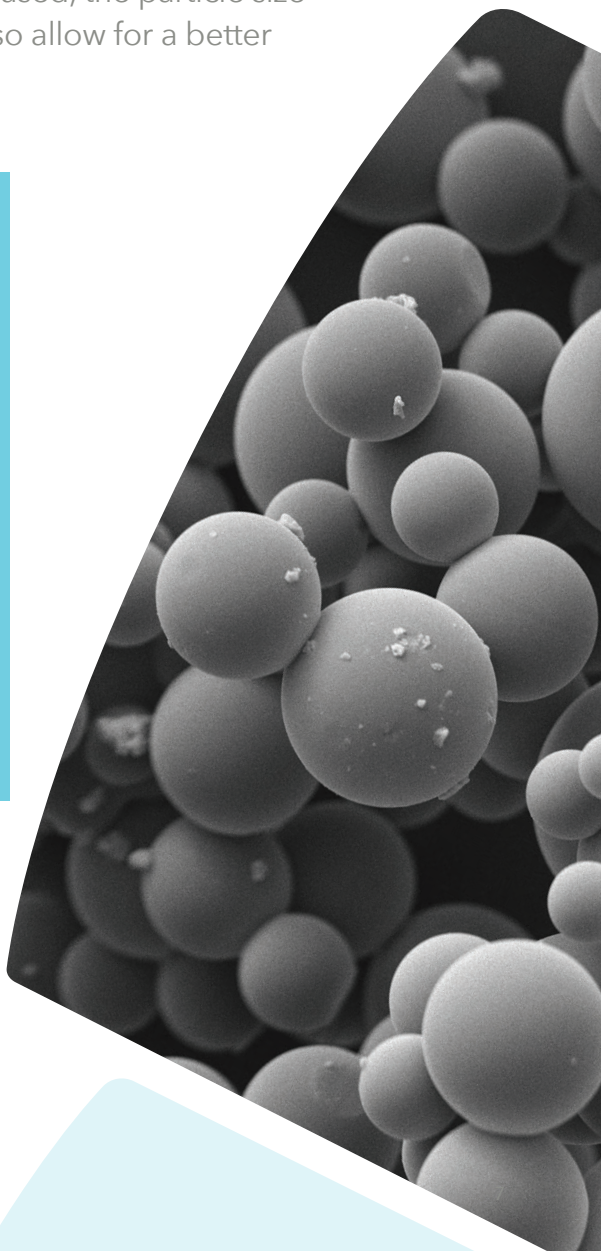
Compared with other dosage forms, LAIs offer a range of benefits. Like implantables, they provide prolonged and constant therapeutic effect – replacing daily or weekly injections, infusions, or pills. This is especially useful for the treatment of chronic diseases.

As with implantables, LAIs require less API to achieve the same therapeutic effect as a traditional alternative, reducing side effects and decreasing wasted API. They also allow IP protection for novel dosage forms and a proven mechanism for developing 505(b)(2) products, helping to differentiate from products on the market.

The release profile of a LAI can be adjusted based on the polymer used, the particle size (of microspheres or nanomilled API), and the drug loading. LAIs also allow for a better therapeutic effect for drugs with a short half-life.

LAIs in action

- **Lupron Depot®** is a 1, 3, and 6-month PLGA microsphere depot injection used to deliver leuprolide acetate for the treatment of prostate cancer, endometriosis, fibroids, and central precocious puberty.
- **Aristada®** is a 2-month nanosuspension injection used to deliver aripiprazole lauroxil for the treatment of schizophrenia.
- **Atridox®** is a 1-week PLGA suspension depot injection used to deliver doxycycline for the treatment of oral gum disease.



Developing successful long-acting products

To ensure the successful development of a LAI or an implantable drug product, it is important to take a number of factors into account.

In the following sections, we explore the key challenges and considerations that must be considered by manufacturers.

Section 2: Formulation Challenges

Both LAIs and implantables provide similar extended-release benefits for patients. Nevertheless, each one has its own unique features, and one may be preferable over the other for certain treatments or sites of action.

Drug developers may want to evaluate both approaches early in a project to decide which is the best option for the needs of their product.

Deciding between LAIs and implantables

There are several considerations that need to be considered when choosing between LAIs and implantables:

- **API compatibility:** most implantable dosage forms are produced via thermal processes, such as hot melt extrusion or injection molding. Some APIs cannot be exposed to high temperatures or shear without degradation, meaning these processes are not an option. It is possible to lower processing temperatures via formulation techniques, but for some APIs, it will be necessary to opt for injectables to circumvent the need for such processes entirely. Conversely, the microsphere method commonly used in LAIs utilizes solvents during manufacturing that may denature large-molecule APIs and make the process difficult to scale. In such cases, implantables may be the more viable approach.
- **Market landscape:** the choice of LAI or implantable will also depend on which option provides a valuable alternative to existing marketed products, including other long-acting dosage forms. For example, if an LAI already exists, it may be preferable to develop an implantable with a longer duration of action.
- **Route of administration:** implantables are especially useful for certain routes of administration. For example, intravaginal rings offer a convenient means of delivering drugs to women. However, for products designed to treat a broader patient population, injectables are preferred.
- **Patient preference:** some dosage forms are favored over others due to perceived comfort issues. Because long-acting products are often developed to overcome poor patient compliance and treat chronic conditions, it's important to keep the end user in mind. Many drug developers perform acceptability studies to determine the preferred dosage form for their target patient population.

Overcoming formulation challenges

Once a pharmaceutical company has selected either a LAI or an implantable dosage form for their drug product, they must then consider several other factors that need to be addressed for successful formulation. Each dosage form poses unique challenges that must be overcome in the formulation development stage.

Considerations for LAI formulations

First and foremost, when developing a LAI, it is important to consider which formulation approach to use to achieve effective controlled release of the API. There are several possible approaches that can be taken and each one has unique benefits that must be considered to achieve the Target Product Profile (TPP).

The most common approaches for developing an LAI include:

- **Microsphere formulation:** this approach incorporates solid, bioresorbable polymeric microspheres which encapsulate the API and break down over time to release the drug.
- **Gel depot formulation:** this approach employs a polymer, solvent, and API to form an injectable suspension within a syringe or vial. Once injected, the hydrophobic, bioresorbable polymer forms a tight depot and degrades over time to release the drug.
- **Nanoparticulate or microparticulate suspensions:** this approach employs nanomilling, a "top-down" approach to particle size reduction or particle engineering to provide the appropriate particle size distribution. The dissolution rate then controls the drug release to provide the desired duration of action.

However, all these approaches have challenges that need to be tackled during the formulation development stage.

For example, when developing **microsphere and gel depot formulations**, it's vital to ensure the API is compatible with the polymer being used as an excipient along with the solvent used in the manufacturing process and to monitor the stability of both components over time. The sterilization process – necessary for any injectable formulation – must not adversely impact the properties of the API or polymer. Attention must also be paid to particle size distribution to create a formulation capable of delivering drug at the desired release rate and duration.

For **nanosuspensions**, it is crucial to optimize the milling process in order to achieve the target particle size distribution (this is often determined via a combination of benchtop testing and early *in vivo* studies). Selecting the proper stabilizers is also key to prevent the agglomeration of particles within the primary container and maintain a consistent particle size over time.

Considerations for implantables

When thinking about developing an implantable formulation, it is important to consider which approach to use. Several approaches are possible and each one has unique features that will affect its compatibility with the API.

Possible approaches include:

- **Hot melt extrusion or injection molding:** this process involves applying heat and pressure to melt a polymer and force it though an orifice in a continuous process. The process can produce a range of release profiles for polymeric implanted devices depending on the type of die that is employed. For example, simple extrusion of a solid profile produces matrix-type systems, which follow first-order release kinetics (see Figure 3). Reservoir systems, on the other hand, may utilize a co-extrusion process that results in a drug-loaded core surrounded by a rate-controlling polymer membrane. Some reservoir systems also consist of a tube or molded component that is filled with a drug in solid or liquid form. These systems achieve near zero-order release kinetics where the drug-release rate does not vary significantly over time (see Figure 3).
- **Silicone molding:** these implants are manufactured via a curing process, which utilizes combination of heat and a catalyst, to produce a drug-loaded silicone device. Care must be taken to ensure the API is compatible with the selected catalyst.
- **Solvent-based processes:** in cases where an API is thermally sensitive, solvents can be used to impregnate a polymer with a drug or dissolve API and polymer in solution for casting. Solvent processing is also used to create drug-eluting coatings that are applied via spray- or dip-coating methods.

As with LAIs, the choice of formulation approach for an implantable device depends on API compatibility. For example, when considering solvent-based approaches, the chosen solvent must not contribute to the degradation of the API. Solvent compatibility studies should be conducted at the start of a project to narrow down the selection.

For hot melt extrusion and silicone molding, it is important to consider the thermal and shear sensitivity of the API. APIs that break down easily under heat may not be suitable for these processes without accommodations. Incorporating plasticizers, changing the screw design, or selecting polymers with lower melt temperatures are methods of minimizing degradation of an API.

While the examples above are the most common methods of manufacturing drug-eluting implants, there are also novel designs that incorporate several techniques, such as the example below.

Novel HIV prevention treatment from Northwestern University

Researchers at Northwestern University sought to develop a long-acting subcutaneous implant for prevention of HIV transmission. The implant was required to be tunable, easily manufactured, and deliver the API with zero-order kinetics.[8]

As a result, the researchers developed a novel implant design wherein Pathway™ thermoplastic polyurethane (TPU) tubes were loaded with pellets of drug (tenofovir alafenamide hemifumarate, TAF). Different prototypes were produced varying polymer selection and device geometry to develop a predictive model of drug release. The design showed promise as a modular implant technology, and similar approaches can be used to formulate thermally sensitive APIs.

Section 3: Development And Commercialization Considerations

Once the choice between LAI or implantable has been made and the formulation approach has been chosen, it is important to think carefully about scaling up processes for manufacturing.

Addressing potential scaling challenges

Developers of LAI and implantables commonly experience pitfalls that can cause unnecessary delays. To maximize the chances of a successful scale-up, the points below should be considered:

Utilizing scalable solutions

Whenever possible, it is important to consider and use formulation processes, equipment, and materials that can be easily scaled up. Using widely available equipment and well-established processes can be an effective way of achieving this goal. When utilizing alternative approaches during R&D, such as a novel formulation technique or piece of equipment, there should be a clear path to scale-up for each step in the process. Looking ahead and developing robust processes upfront can save significant time and money down the line.

Another key consideration is the availability of the materials used in the LAI or implantable. For instance, the polymer chosen for the formulation should be readily available at pharmaceutical quality and at commercial scale. The excipients should also be manufactured under Good Manufacturing Practice (GMP) principles and come with supporting data, including Drug Master Files (DMFs) and excipient information packages. A good polymer supplier will have this information ready or be able to generate it to assist in your regulatory filings.

Processes and equipment should also be chosen according to their availability and viability at larger scale, as well as their suitability for aseptic processing (if the product is not amenable to terminal sterilization). This is particularly crucial for LAIs, which often have complex manufacturing processes.

Performing robust process development upfront

The path to scale-up should be considered from the start of a project, even if it is in early-stage development.

This can allow companies to plan for potential challenges that will need to be addressed when manufacturing at scale to minimize delays. For example, HPAPI handling requires specialized cleanrooms. Planning for scale-up as early as possible can ensure the right infrastructure is available, help conserve materials, avoid pitfalls downstream, and ensure compliance with regulatory requirements.

Understanding how Critical Process Parameters (CPPs) change from benchtop to large-scale

This is a particular issue in sterile processing. For example, benchtop processes for formulating a LAI use open beakers, while sterile product manufacturing may use a closed or fully-contained system. Open vessels allow for evaporation, but this is not possible in the closed manufacturing vessels. When transferring into an enclosed vessel, the polymer concentration might have to be changed to account for the lack of evaporation.

Likewise, milling or mixing processes may not scale in a linear fashion, which can impact the particle size distribution for a nanosuspension and other characteristics of microsphere formulations.

Meeting the processing requirements of LAI and implantable products

LAIs often rely on large equipment trains to accommodate steps, such as emulsification, solvent evaporation, filtration, drying, or high energy media milling. Implantables, meanwhile, rely on extrusion of molding techniques with large equipment lines and secondary polymer processing equipment, such as dryers, cryomills, and blenders.

With this in mind, it is crucial to plan for processing space and proper utilities to accommodate large-scale equipment, something not all pharmaceutical companies are equipped to achieve.

Safe solvent handling

Several LAI and implantable formulation processes require the use of solvents, including microsphere production.

The waste streams from these solvent processes are considered hazardous, meaning that they pose a health and safety risk to employees, local communities, and the local environment. Manufacturing large scale batches of microspheres can result in large volumes of solvent waste, so it is important to devise a strategy to collect and dispose of solvent waste safely. In the US, the Occupational Safety and Health Administration (OSHA) monitors the disposal of such waste to ensure compliance with legislation.

Specialized materials and processes

Finally, when scaling up, it is important to consider the specialized materials and technologies needed for efficient and effective large-volume manufacturing. The selection of materials or equipment will depend on the specifics of the formulation approach chosen.

For example, microsphere LAI formulations often involve the use of solvents and steam-in-place sterilization – these can affect standard gaskets, diaphragms, and other polymeric machine components. Such equipment may need to be replaced at a higher rate, or valves may need to be adjusted more frequently to maintain pressure during manufacture.

The extrusion processes for implantables, meanwhile, require significant capital investment in equipment, such as extruders, cutting equipment, and other tools for polymer processing. Specialized tips, dies, or molds may also be needed, such as crosshead dies for co-extrusion or film dies for extruding films. Early planning of the production line investment and upgrade process is key to ensure that the right equipment is sourced, qualified, and implemented in time for the smooth transition from benchtop to GMP manufacture.

Section 4: The Importance Of Expert Support

Developing a LAI or implantable drug product and successfully bringing it through clinical trials can be daunting, especially for companies that have never embarked on such a project before. These dosage forms require specialized expertise and facilities, and many pharma companies lack this capability in house. This is where the contract development and manufacturing organizations (CDMO) come into play.

Some CDMOs have years of experience in taking new LAI and implantable projects from early-stage development all the way to scale-up and GMP manufacturing. These CDMOs have invested in equipment, space, and personnel who understand the nuances of developing long-acting drug products.

Working with a single partner for development, scale-up, and GMP manufacturing can significantly streamline the process for LAIs and implantables by minimizing the number of technology transfers required and thus reduce development risk.

CDMOs can provide support in scaling up LAI and implantable clinical development and manufacturing by providing:

- **Expertise in process design and scale-up, including for sterile products**
- **Flexible cleanroom utilities and facilities staffed by experienced scientists**
- **Formulation and analytical expertise to measure critical product attributes and recommend changes as needed**

Working with such expert CDMO partners can help maximize the likelihood of successful LAI and implantable development. It can also help speed up development timeframes and ensure the new product reaches clinical trials as quickly as possible.

Section 5: How LLS Health Can Support

Lubrizol Life Science Health (LLS Health) is a CDMO partner with decades of specialized expertise in the development and manufacturing of LAIs and implantables.

Our expert team has successfully formulated and scaled-up a number of long-acting products for a wide range of clients—from start-ups and non-profits to large pharmaceutical organizations. Our experience has enabled many clients to make the transition from benchtop processing into GMP manufacturing. LLS Health, CDMO Division has even developed and co-patented an intravaginal ring now approved for sale in Europe.

In the past five years, LLS Health has worked on more than 50 long-acting products, including:

- **Implants**
- **Intravaginal rings**
- **Injectables**
- **Drug-eluting medical devices**

Breadth of specialist expertise

LLS Health's experience spans several routes of administration, including subcutaneous, vaginal, ophthalmic, intramuscular, and otic products.

We are capable of supporting most LAI and implantable projects from early-stage feasibility studies to formulation development, scale-up, and GMP manufacturing for clinical trials. Our team is highly experienced in technology transfers, and we partner with our clients, using our experience and knowledge to optimize and improve upon processes.

We have an experienced team and the proper facilities to accommodate aseptic processing. We have a DEA license for all Schedules and, for certain processes, we can incorporate highly potent APIs. This makes LLS Health the ideal partner for a wide range of challenging LAI and implantable projects.

Flexible and agile support

LLS Health has strong relationships all the leading polymeric excipient providers and a wide range of in-house Pathway™ TPU excipients suitable for implants and intravaginal rings. We are a technology and formulation agnostic CDMO that will advise on a range of different formulation approaches to find the right approach for your API.

Our highly flexible cleanroom space also allows us to transfer in fully developed processes and supply material for engineering batches or clinical trials.

At LLS Health, we offer support to projects in any stage, with the goal of helping pharma companies maximize their chances of success.

What LLS Health offers to drug formulators

- **Formulation expertise** – providing troubleshooting during early-stage and scale-up activities
- **Analytical method development and validation –** in-house analytical services provide efficient characterization and release testing to reduce project timelines
- **Tech transfer and scale-up support** – providing critical input to process development, assisting the transition to larger batch sizes
- **Quality support** – providing critical oversight for data management, environmental monitoring, and documentation
- **Stability testing** – offered for both standard and specialized conditions, supporting pharma companies to establish shelf life and storage conditions

Conclusion: Dosage Forms With Unique Potential

Both LAIs and implantables have already made a considerable impact on drug delivery, but there is still significant untapped potential. Not only do long-acting products provide enhanced therapeutic effect, but they also substantially improve the patient experience, delivering more patient-centric options for serious and chronic conditions.

As such, it is no surprise that new projects are entering the pre-clinical pipeline all the time, despite the unique challenges associated with their development. With proper planning and the right team, it is possible to predict and overcome these challenges to streamline the development process.

LLS Health's experienced, customer-centric is here to help clients translate their projects from development to production.

Speak with our Long-Acting Experts

To find out more about how we can support your LAI or implantable drug development project, visit our website.

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