REXAM

injecting new ideas

Implanting new ideas
into next generation depot syringes

Controlled release mechanisms for drug delivery have been the focus of continuous improvement over the past 20 years. Subcutaneous implants present the advantages of reducing side effects and allowing continuous drug release over weeks - or even months - in contrast to the rapid decline in medication blood levels which follows injections or pill intake.

However fragile implants require new transfer technologies under the skin which should not be fully dependent on expertise of the medical staff to prevent improper use. Drug-delivery devices need to be simpler, safer, and, in a context of increased homecare treatment and self-administration, more intuitive and convenient.

Implants of long acting parenteral drug formulation are known as depot systems. They are designed for the storage of active substances in the body ideally to provide slow and constant sustained release of the drug resulting in prolonged action. Implants are injected subcutaneously into the fatty tissue and serve as medication depots for the controlled dissolution of active ingredients. Then the drugs either act locally or diffuse into the bloodstream and have a systemic action. Typical depot treatments are hormone replacement therapy, palliative prostate cancer treatment or pain relief medication. The active substance diffuses over a period of several weeks, and the depot formulation either dissolves completely (biodegradable polymers) or the carrier need to be surgically removed.
To reduce patient discomfort, implants are becoming smaller but also more fragile. Biodegradable polymers bases avoid additional medical act of surgery to remove the implant once the active ingredients have been fully released.

Implanter for cancer treatment manufactured by Rexam Pharma

Examples of depot medications currently on the market include local depot such as ocular delivery for glaucoma treatment, sub-coetaneous contraceptive implant – for instance made of etonogestrel, pain relief treatments and hormone therapy, either to replace a hormone deficiency or to mimic its function. Depot treatment based on hormone therapy are also used for oncology.
For example leuprolide depot is typically given for prostate cancer treatment once a month to stop the production of a certain hormone needed for cell growth on the surface of some tumour cells. Different types of hormone therapies are categorized by their function and/or the type of hormone that is affected.

Depot implants have prolonged-release formulations

Prolonged delivery of a drug at controlled rate results in smoother plasma concentration. This induces reduced side effects and also a better therapy efficiency: many drugs have a narrow therapeutic index (difference between toxic level and therapeutic level) and the sustained release allows a better targeting of the appropriate delivery level. The patient body is benefiting overall from less drug injection with a depot system acting like a small portative infusion pump which does not require the patient to be maintained on a hospital bed. Patient comfort and healthcare budget are benefiting from the implant delivery technology. Disease management is improved, side effects are better controlled and, when possible, the cure accelerated.
New therapeutic opportunities are also emerging with depot syringe injections: the possibility of localized delivery and direct treatment of the site opens up new therapeutic horizons.

Innovative depot benefits the patient

For the patient, the convenience of treatment with depot drug delivery solution and the increased therapy comfort due to the reduced frequency of injections are key benefits. This results in improved patient compliance. In addition, new biodegradable polymers improve patient comfort by eliminating the need for surgical removal of the drug vehicle and also the risk of body rejection of the implant.

What is a depot syringe?

Parenteral implants are injected with a specific device through a needle, the implanter, also commonly called depot syringe. Depot formulations can either be completely liquid, semi-liquid or injected under a semi-rigid shape, small rods alike, typically one to five in a row. The injected liquid formulations will typically turn into gels inside the body for sustained release; the small "depot rods" will also transform into a gel solution when under the patient skin and then release the drug substances they have been impregnated with.

The changing environment, from more fragile or softer depot formulation to increased homecare injections, brings new challenges to the pharmaceutical industry including medical device manufacturers. The devices need to be designed and developed in the best way to ensure reliability and safety. The integration of safety feature on the depot injection device to prevent accidental needle sharp exposure is also a new requirement.

Reliability of depot syringes

Zero defect reliability is the quality standard that devices have to integrate from their conception up to the industrialisation process.

The pharmaceutical industry integrates important mutations to respond to this required level of quality. Each company involved in the device, including the mould maker, assembly machine manufacturer, device manufacturer and the pharmaceutical company is changing to become part of a network model.
The mutation from a "FIPco – Fully Integrated Pharmaceutical Company" to a "FIPnet – Fully integrated Pharmaceutical Network" allows targeting new challenges in complex delivery devices development:

- know-how's and innovative technologies are rapidly implemented for the patient benefit
- risk mitigation
- reduction of associated costs
- development of "universal" medications and drug delivery devices

The pharmaceutical network of trustworthy partners, each one specialist of its segment but understanding the other's quality requirements, is today the best solution to innovate into a pharmaceutical industry in mutation. "Patient first" is key to keep in mind for the development of a complex device such as a depot syringe implanter:

- easy to use devices that are reliable in all circumstances
- involvement of all the development partners of the network turned towards the patient safety is the guaranty for overcoming the challenges

Integrating quality from the conception of a injection device development ("Quality by Design") is a fundamental step for the success of the innovative development and it requires a structured approach:

- quality and performance through robust design conception
- DFM and DFA (design for manufacture and assembly) methods are used for mass production reliability of the depot syringe device
- overview of the impact of process capability on the final product performances
- reliability and risk mitigation are monitored trough FMEA process (failure mode and effects analysis) that allow to focus on critical factors through the probability of any given failure with the severity of the risk created by that failure mode
- procedures and controls implemented including full traceability, GMP (Good Manufacturing Process), manufacturing clean room environments
- continuous and real time quality insurance
- a strict "change control process" to maintain the same validation level on manufacturing site after change have been implemented.

Key technical innovations for next generation depot syringes

New generation depot syringe developed by Rexam

The next generation of depot syringes need to be patient-friendly, designed for ergonomic and simple operational mode. The device has to adapt from an injection technology which was in the hands of a medical specialist to an intuitive, easy to use new device concept compatible with a foolproof administration. For instance the depth of implants deposition under the skin is a key parameter for depot drug delivery. With the "old generation" of depot, protocols of injections were relying on medical expertise for the success of transfer of the "depot rods". The doctor or the nurse had to insert the needle to a certain depth under the skin of the patient to perform a pre-cavity into which the depot rods would be deposit, one after the other, while the syringe was slowly moved back from the deeper injection point. This complex operational mode needs today to be replaced by new implanter technology.

A new retro-injection technology

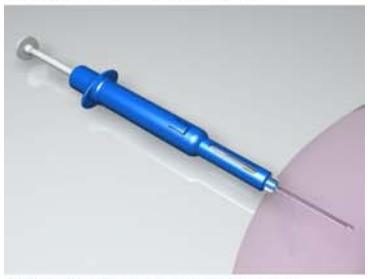
Owner example is the depot-syringe technology developed by Rexam. The retro-injection technology has been designed to answer this requirement.

Maintaining the device in contact with the skin surface, the user keeps simply pushing the pluner rod and the needle automatically retracts while depositing the several rods under the skin, at a fixed depth and well separated one from the other.

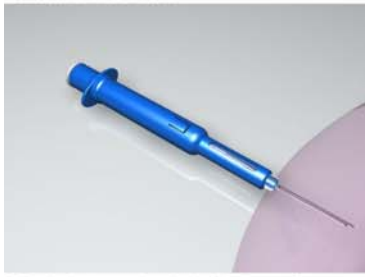
1. Retroinjection device ready for implants transfer: cap protecting the plunger rod and the needle are removed

2. The visualisation window allows implants cheking

3. The needle is inserted under the skin



4. At the end of injection implants start to be transferred under the skin



5. The implants are deposited while the needle retracts. Automatic activation of the safety system in parrallel.

6. The depot syringe can be safely discarded. The safety sleeve remains protective to prevent needle stick injuy.

This device also presents the particularity to maximize the implant rods protection before and during deposition under the skin. Fragile, often soft, smaller implants are becoming the market rule. New generation depot syringe need to carefully transfer the rods under the skin while applying as little effort and pressure as possible on the rods to preserve their integrity and defined shape. These latter parameters are keys for kinematics measures of drug sustained release. Any constraint applied to the rods during injection under the skin would jeopardize the pharmacokinetics of drug diffusion.

Rod sizes, lengths and number greatly differ from one depot therapy to the other. Therefore design flexibility of the implant device is a technological parameter to consider from device conception.

The visualization window of the device is also an essential parameter to be able to check before injection, integrity of implants and also to follow implants transfer under the skin, while injecting. This double visualization step ensures the right transfer of the treatment and is part of the de-risking process.

The ideal device should also be capable of high speed production once industrialized. The device manufacturer, being part of the "FIP-net" industrial network integrates from the early stage of design conception the pharmaceutical industry concerns. For example the ease of depot rods loading is key for an efficient industrial process.

Developing on the other hand a partnership network with needle specialists, allows the new depot syringe concept manufacturer to integrate for the patients comfort the newest perforating injection needle with minimum diameter into the new generation retro-injection (or "back injection") depot syringe. This needle type is designed to avoid coring, is siliconized and presents a triple bevel.

Automated safety device for the needle shielding

Legislations and Healthcare authorities are encouraging in several countries (including USA, Canada, Europe…) a higher degree of protection of nurses and homecare patients by the use of needle sharp safety devices. Rexam has implemented into its standard depot syringe its patented safety device technology for user protection. The safety system is fully passive and does not require any extra gesture from the user end-point. A protection sleeve automatically covers the needle at the end of the injection while removing the needle from the patient skin. Having no needle exposure greatly reduces the risks of accidental injuries and contaminations.

The development of a successful new generation depot syringe needs to combine the experience from design conception of implanter and injection technologies based on patient requirements and integrate the valuable learning of industrialization of depot syringe, to meet today's new implants requirements.

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