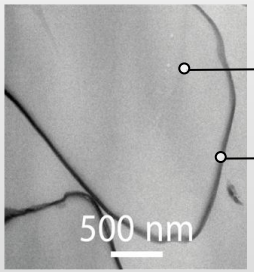
CONTROLLED RELEASE, SMARTER CARE

Terminal sterilization of controlled release coated azacitidine using gamma irradiation

2022-07-14

PharmaShell® – The high drug load delivery system enabling the next generation long-acting injectables through atomic layer precision



TEM image of PharmaShell coated API particle

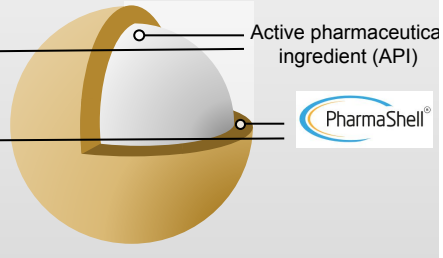
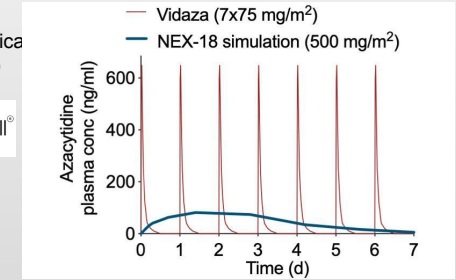


Illustration of PharmaShell's nanometer thick coatings



Concept data illustrating the avoidance of high and low plasma concentrations by using PharmaShell

- Drug delivery system encasing active substance microparticles with thin coatings (10—50 nm) of slow-dissolving inorganic oxides
- System based on Atomic Layer Deposition (ALD) technology, enabling Nanexa to control the thickness of the drug's shell with high precision and determine the rate of release of the drug in advance

- Immediate release formulations are converted into long-acting injectables with enhanced properties
- Drug concentrations are kept within the therapeutic window to achieve the maximum benefit

PharmaShell® – key benefits

1

Customised depot length

- Once weekly, once monthly or even less frequently

2

Control of initial drug release – minimises side effects and enables:

- Depot products of potent drugs
- Increased drug dose in the depot

3

High drug loads (up to 80%), enabling:

- Minimised injection volumes
- Use of less potent active substances
- Longer depot formulations

4

Versatility - applicable on a wide range of API characteristics

- Small molecules
- Biologics, peptides and proteins, etc.

5

In-situ stability

- Protects the active from degradation during depot time

6

Flexibility in respect of administration site

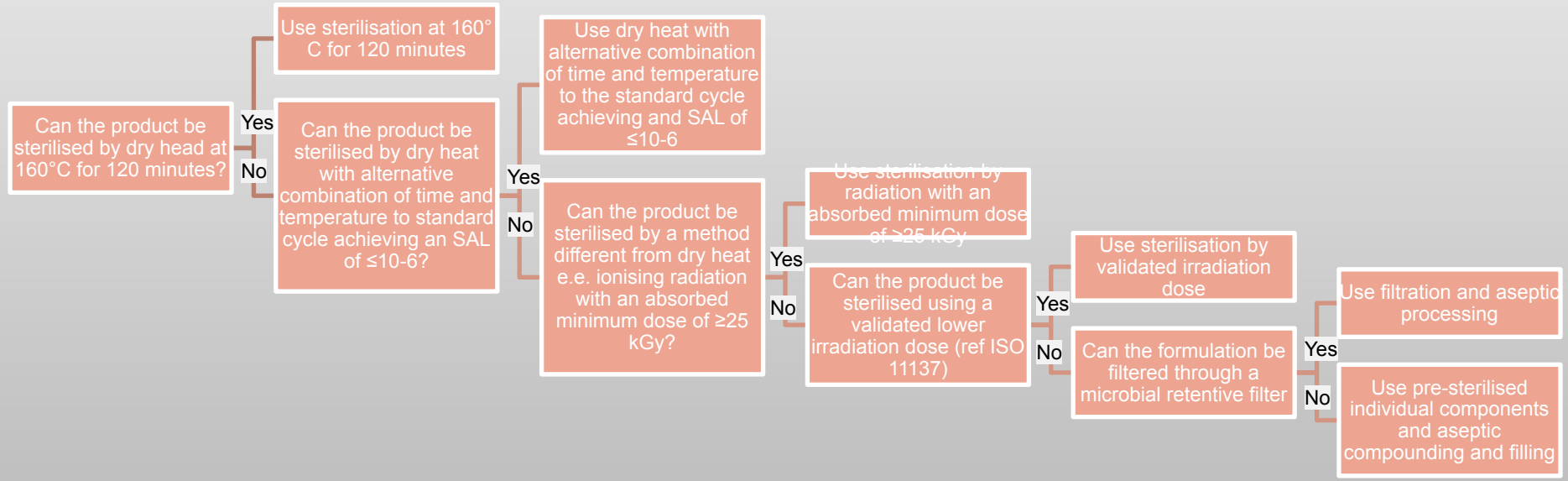
- Subcutaneous or intramuscular administration for systemic exposure
- Local administration e.g. intratumorally for local effect

Sterile products

- **Sterilization is defined as the process by which all living cells, viable spores, viri, and viroids are either destroyed or removed from an object or habitat**
- **Sterile products are totally free of viable microorganisms, spores, and other infectious agents**
- **All injectable products require sterility**
- **Can be achieved by:**
  - Passive process, that is, aseptic filtration and manufacturing process (nonterminal process)
  - Aggressive process (terminal sterilization) such as autoclaving, dry heat sterilization, or irradiation

Terminal sterilization

- **Production performed in environment for low bioburden**
- **Sterilization in final package – no further processing of product**
- **Regulatory guidance: Decision tree for sterilization choices for non-aqueous liquid, semi-solid or dry powder products**



Dry heat sterilization feasibility

- **Firsthand option for sterilization of dry products**
- **Dry heat sterilization is mainly used for glassware and other utensils**
- **Feasibility on PharmaShell coated azacitidine**
- Exposure to 160°C for 2 h

Dry heat sterilization feasibility

- Function tests according to specification:

	Untreated	Heat treated
Visual appearance		
Total impurities	0.5%	2.6%
Coating integrity test	18%	35%

- **Dry heat sterilization was rejected as terminal sterilization of PharmaShell coated azacitidine**

Gamma irradiation feasibility: product

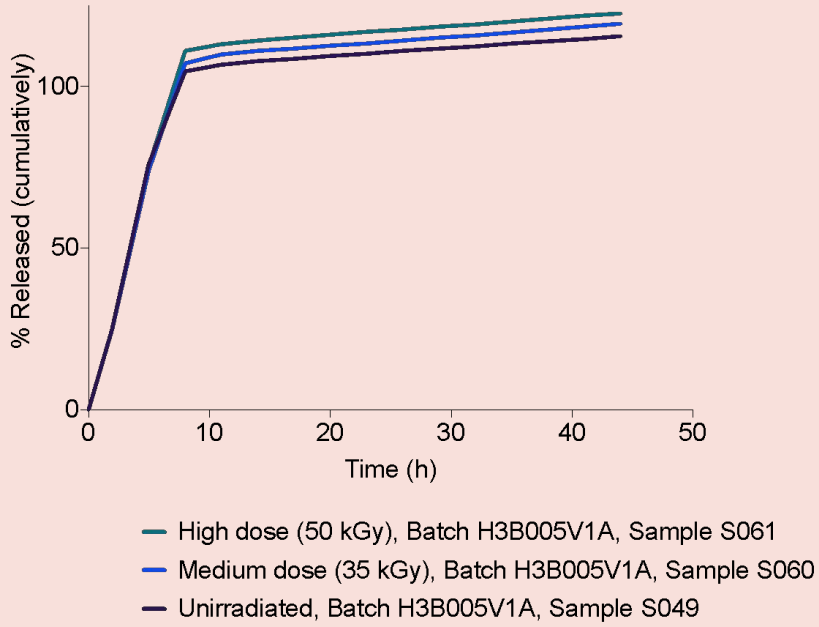
- **Irradiation is second option for sterilization of dry products**
- **Gamma irradiation most common irradiation technique**
- **Used for decades mainly for medical device and food industries**
- **Gamma particles causes ionization of chemical bonds which leads to breakdown of nucleic acid**
- **Feasibility on PharmaShell coated azacitidine**
- Exposure to medium (35 kGy) and high (50 kGy) dose

Gamma irradiation feasibility: product

- No changes during in product properties was found when testing functions according to specification

	Untreated	35 kGy	50 kGy
Visual appearance			
Assay	84.8%	85.0%	84.8%
Total impurities	1.0%	0.8%	1.0%
Particle size (Dv50)	6.1 µm	5.6 µm	5.6 µm

Gamma irradiation feasibility: product

Dissolution	

- **Gamma irradiation was found suitable as a sterilization of NEX-18 powder product at doses up to at least 50 kGy**

Gamma irradiation validation

- **Low dose verification using a single batch concept**
- Step 1: Sample was produced, and 10 units were withdrawn.
- Step 2: Bioburden was determined in 10 units.
- Step 3: Dose based on average bioburden results and ISO11137-2:2015 (Table 9) was determined. In our case average bioburden was 7.0 and therefore, the VDmax25 dose was 6.7 kGy
- Step 4: Dose verification experiment were performed by irradiated the 10 units using the VDmax25 dose. Then, the units were tested for sterility.
- Step 5: Interpretation of results: since no unit demonstrated positive test of sterility, 25 kGy was verified as suitable irradiation dose. (Two positive units would have required a new verification, three or more positive units would have required a corrective action)

Key takeaways

- PharmaShell® is a high drug load delivery system for Long-Acting Injectables
- Gamma irradiation does not change the properties of PharmaShell® coated azacitidine
- A single batch concept was used to validate the terminal sterilization of the product.
- Gamma irradiated PharmaShell® coated azacitidine was released for clinical trials.

Well-positioned for growth with a strong project pipeline, collaboration with Big Pharma, extensive patent protection and solid financial position

Nanexa in brief

Founded in Uppsala in 2007, Nanexa is a drug delivery company focused on the development of the company's nano-based technology system PharmaShell®

Multiple feasibility studies with global leaders such as AstraZeneca and strategic partnership with Applied Materials in place

Nanexa's solution

Nanexa's drug delivery system, PharmaShell®, encapsulates drug particles in a shell with controlled solubility, substantially delaying the release of the drug

Two-streamed business model based on developing products in-house as well as licensing to external parties

PharmaShell®

Product licensing

Internal development of "super-generics" (improved versions of existing drugs)

Technology licensing

Broad portfolio of external collaborations

Nanexa highlights

- PharmaShell® patents secured on major markets, with several more pending approval
- Nanexa has started its first clinical study with a phase I first-in-human (FIH) study during Q2'21
- GMP-certified facility ensuring supply throughout clinical development
- Listed on Nasdaq First North

1) Transparency Market Research, Drug Delivery Systems Market, 2018