



# Preparation of nanoparticulate drug carriers

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4th Joint Symposium on Nanotechnology  
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# Current State & Future Directions

The global market for nanotechnology products;

✓ \$62.9 billion in 2020 and increased to about \$86 billion in 2021.

✓ The Global Nanotechnology Market Outlook 2025 is poised to grow at a CAGR of around 18.1% to reach approximately \$173.95 billion by 2025.



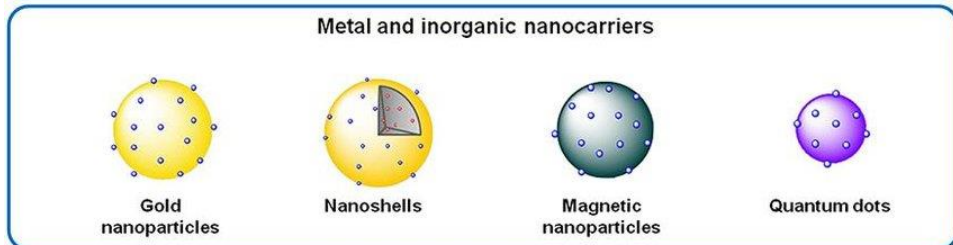
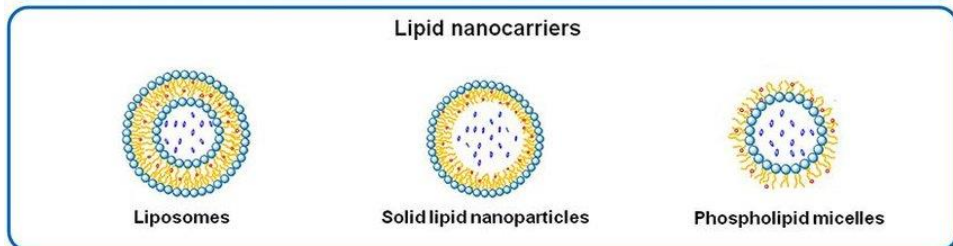
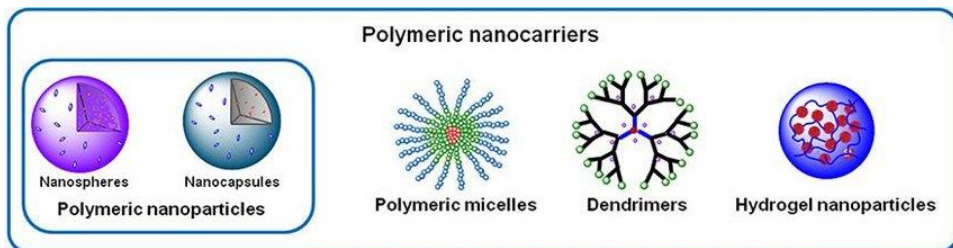
A **worldwide pharmaceutical market analyzing report** has been published by BCC Research.

✓ Industry market values was US\$214.2 billion in 2013 and US\$248.3 billion in 2014.



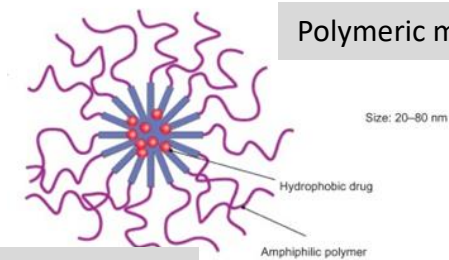
# Nanocarriers and nanotherapeutics

Nanoemulsions

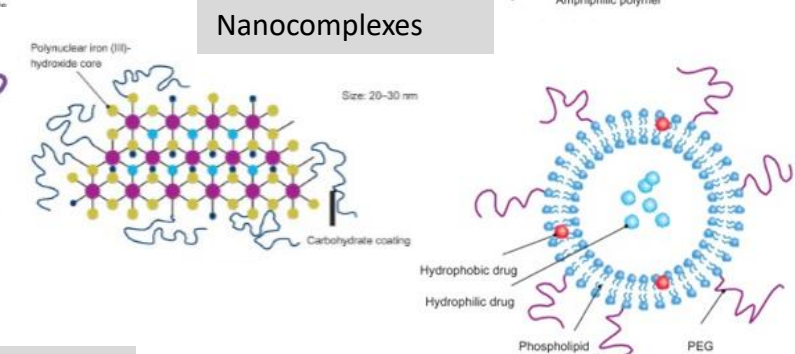


Dhanda, Rahul & Patel, Arpita & Thakkar, Hetal. (2015). *Nanopharmaceuticals: A Boon or Bane.*

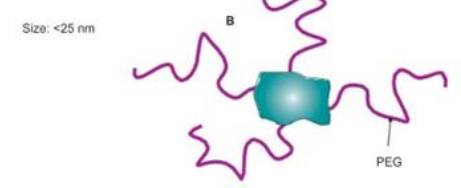
Polymeric micelles



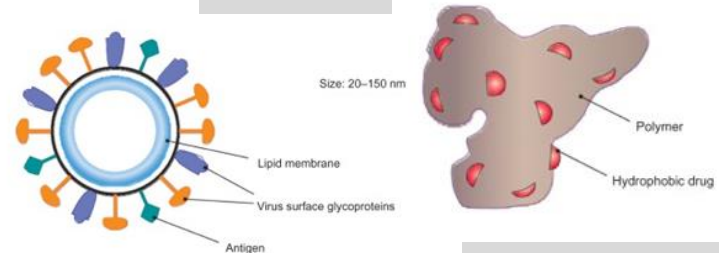
Nanocomplexes



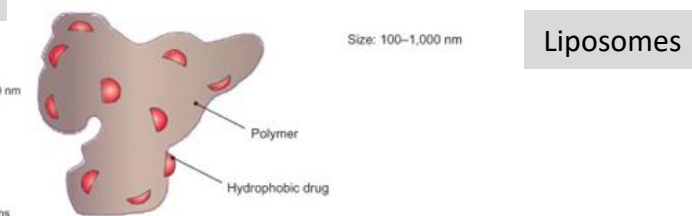
Polymeric Therapeutics



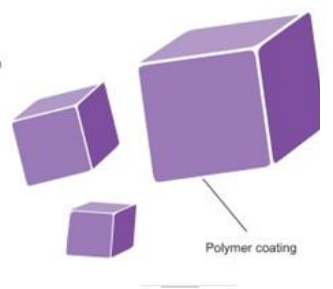
Virosomes



Liposomes



Nanocrystals

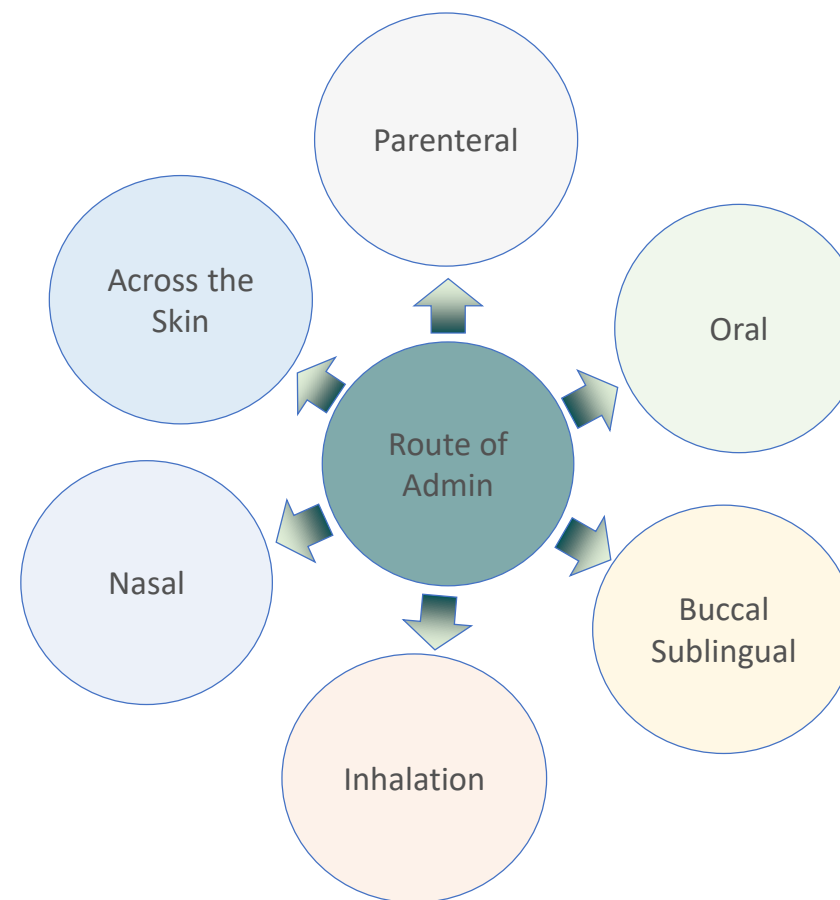


Polymeric Nanoparticles



# Type of Products

New Chemical Entities	New Biologicals	Approved Drugs New Formulations
Approved Drugs New Indications	Generics+	Biosimilars
Devices	Drugs&Devices Combinations	Gene Therapies Theranostics Cell Therapies



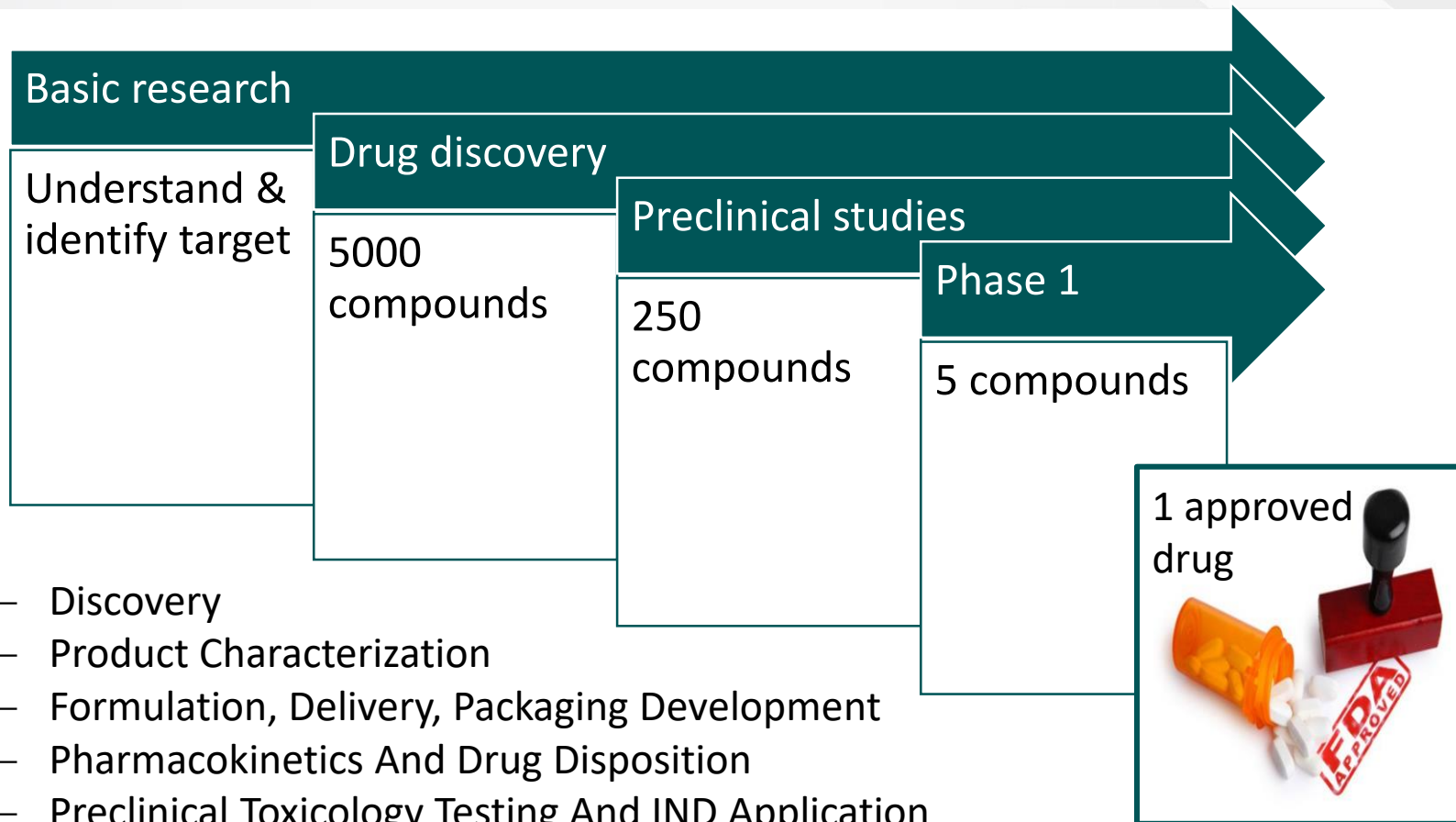


# Factors Driving the Development

- Market need for a product
  - Real -> Cure for pancreatic cancer
  - Perceived -> Nutritional supplements
- Potential
  - Compounds with activity against target receptor
  - Nascent technology
  - New insights through basic research
- Defined target market characteristics enable
  - Product to be promoted, distributed & sold
  - Good return on investment



# Timeline for Development NCE



- Discovery
- Product Characterization
- Formulation, Delivery, Packaging Development
- Pharmacokinetics And Drug Disposition
- Preclinical Toxicology Testing And IND Application
- Bioanalytical Testing
- Clinical Trials

# Nanotherapeutic Research and Development

Europe holds a leader position for scientific research but has failed to turn power into commercially available products

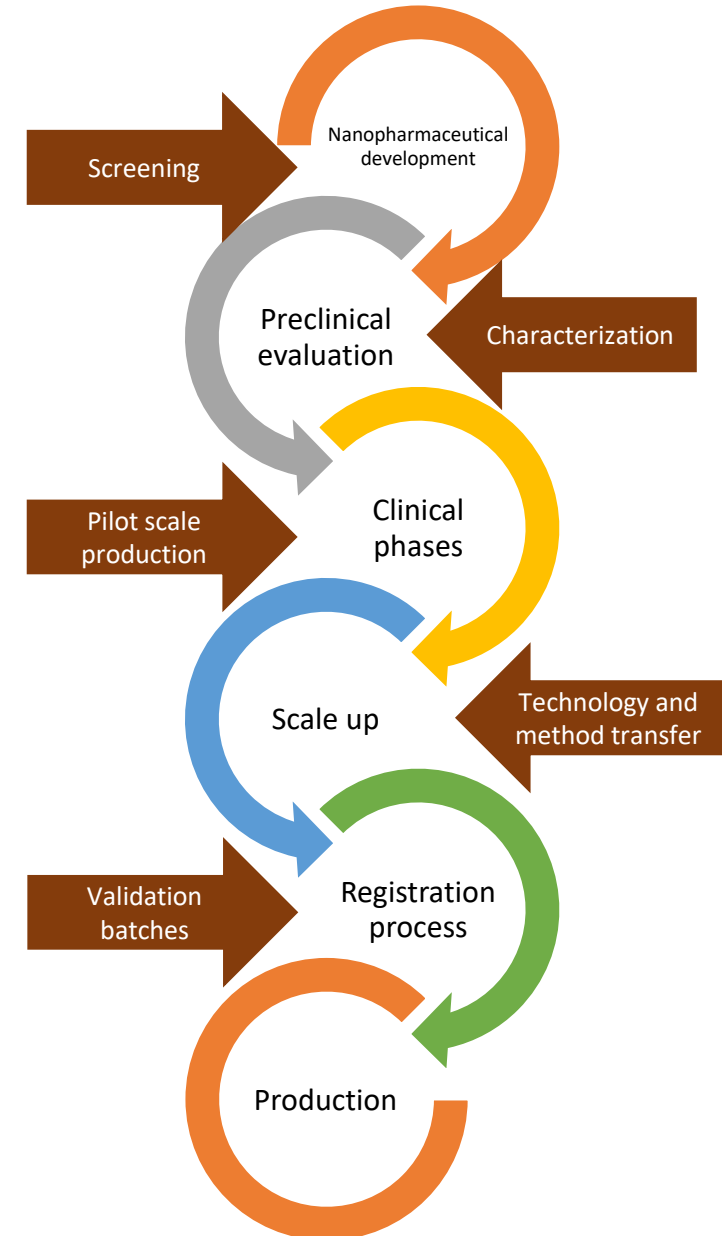
The final aim of R&D activities in the field of the nanotherapeutics is successful **translatable** trends. In this direction some difficulties rises;

- **Control** deficiency;
- Separation from undesired nanostructures;
- **Scale-up** issues;
- Increasing the production rate;
- **Reproducibility** from batch to batch according to particle size distribution, charge, porosity, and mass;
- **High costs of fabrication**;
- **Lack of nanosystem and living cell knowledge** like biocompatibility and toxicity;
- Lack of funds;
- **Unwillingness pharmaceutical industries to nanotherapeutics**



# Nanotherapeutic Translation

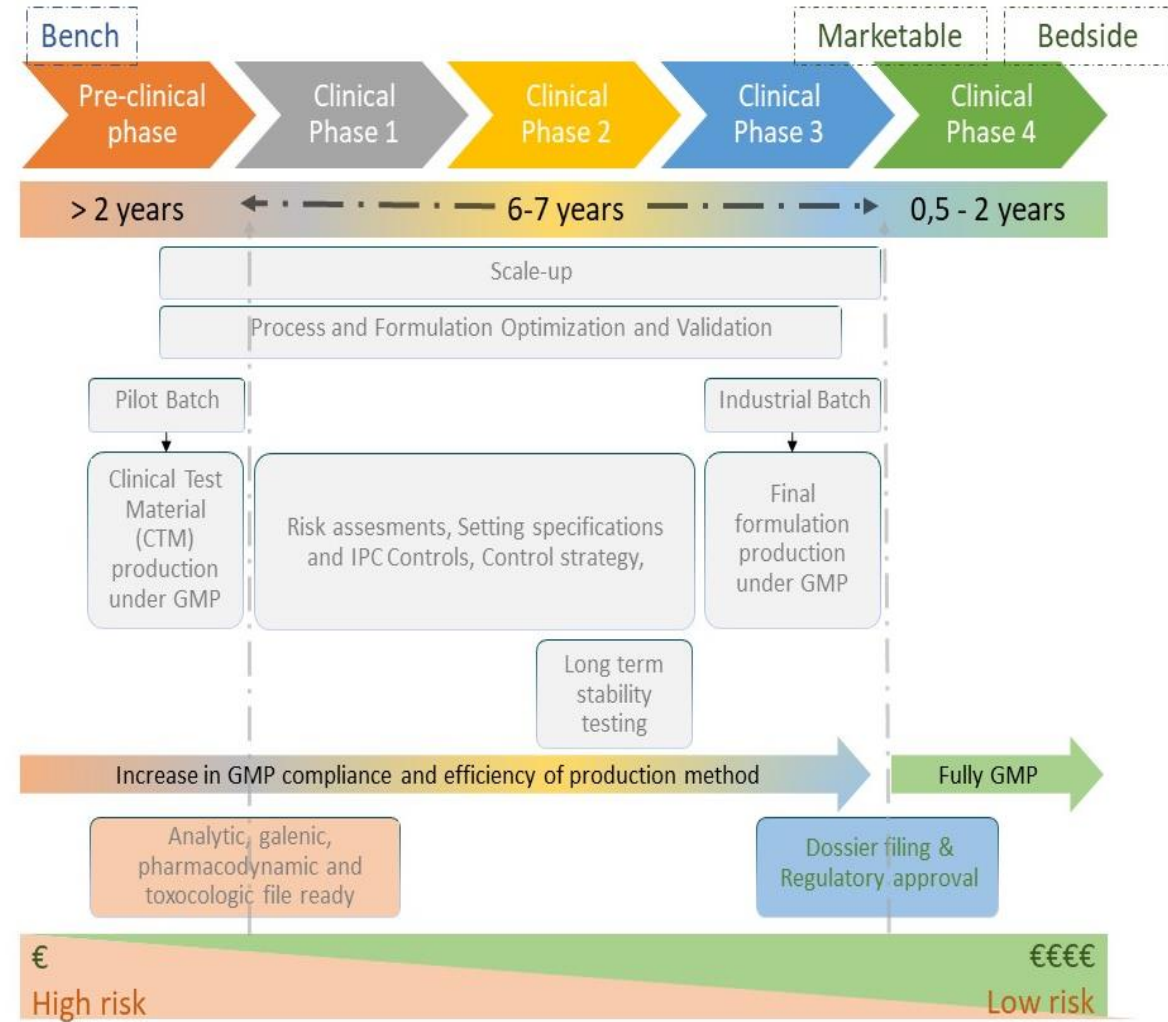
- Many novel promising lab PoC nano-pharmaceuticals across Europe and the world.
  - strong potential for providing more effective and safer therapies and diagnostic procedures for a wide range of diseases.





# Specific Challenges

- Main prerequisites for successful implementation: Affordable and advanced testing, manufacturing facilities and services for novel nano-pharmaceuticals
- Major challenge to produce the novel nano-pharmaceuticals to GMP quality in sufficient quantity for late pre-clinical and clinical testing



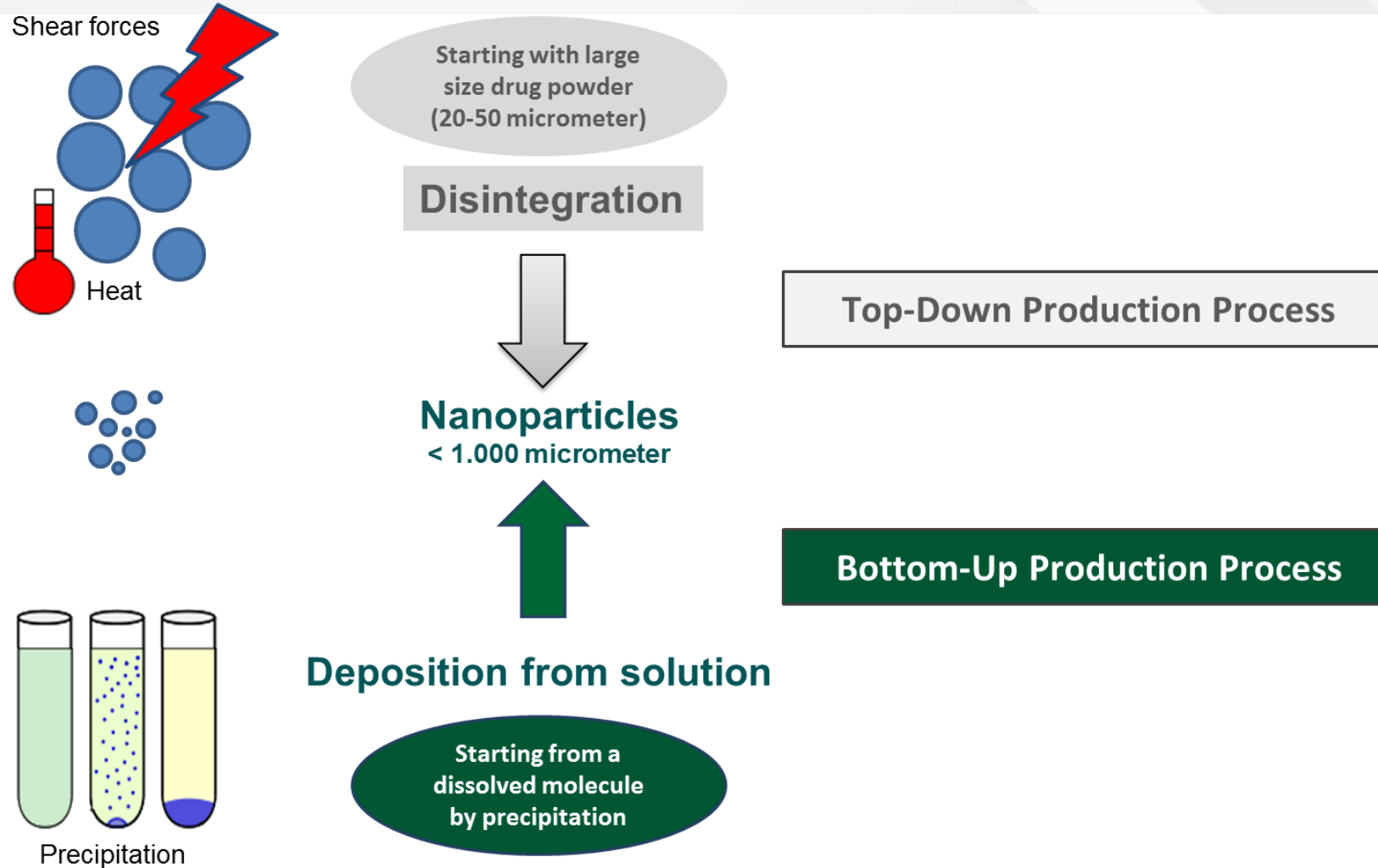
Nazende Günday-Türeli, Akif Emre Türeli, "Upscaling and GMP Production of Nanopharmaceuticals Drug Delivery Systems" in *Drug Delivery Trends: Volume 3: Expectations and Realities of Multifunctional Drug Delivery Systems*, edited by Ranjita Shegokar, Elsevier, 2020, p215-23



# Principles of Manufacturing of Nanotherapeutics

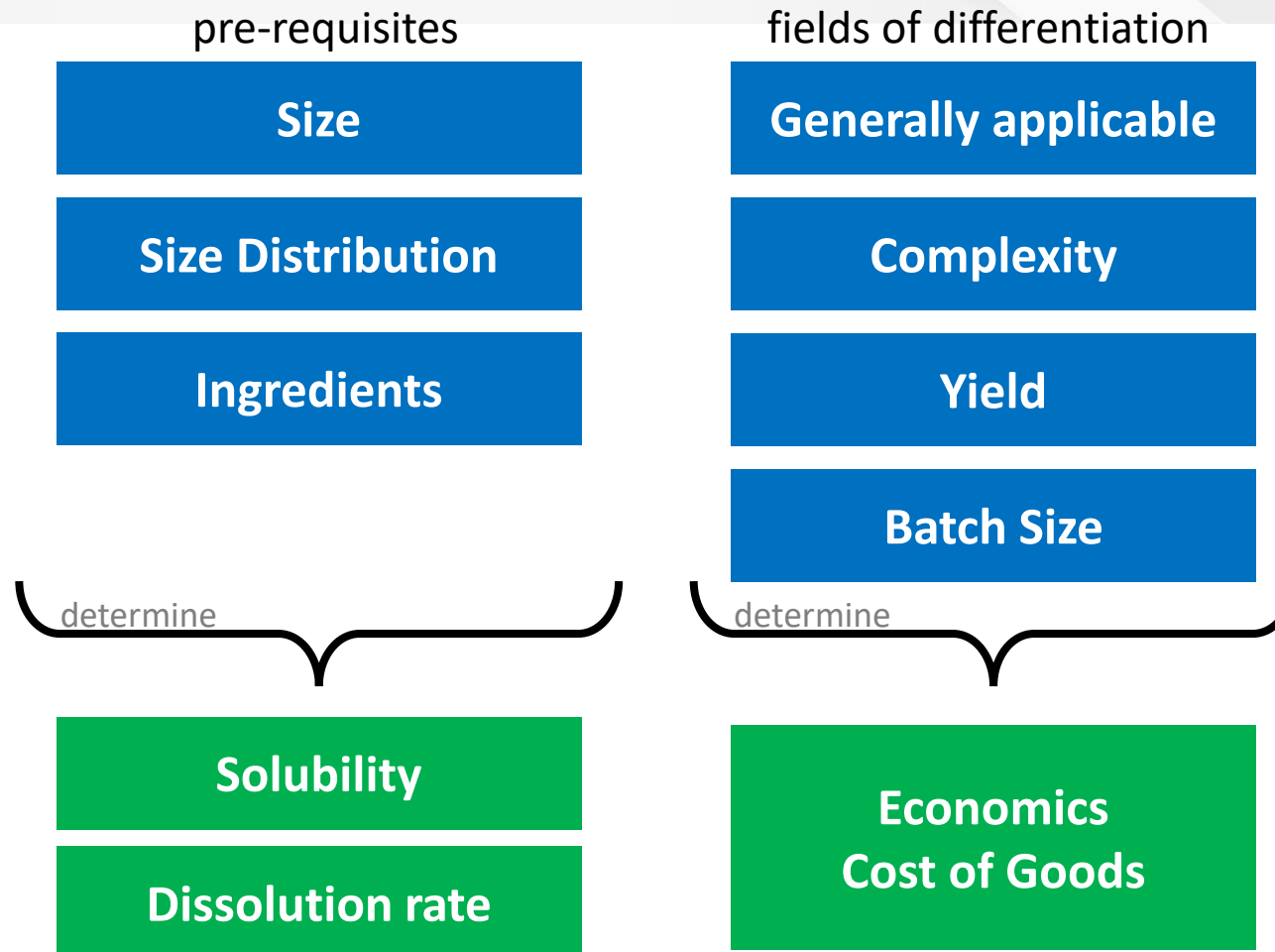


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# Manufacturing of Nanotherapeutics





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# Industrial manufacturing of nanotherapeutics

Despite tremendous efforts to **standardize** nanopharmaceutical DDS development and approvals made by governmental and private agencies, translation from lab to market remains a challenge to all key players of the pharmaceutical industry.

**Multidisciplinary scientific understanding and regulatory definition of nanomedicines** are still not satisfactory.

**Knowledge and guidance gap** are leaving the pharmaceutical industry behind in its attempt to find the best match for different stages of development, and thus clinical tests.

# TECHNOLOGY TRANSFER

## Road to GMP Compliance



### Technology transfer services for particle formulations

- Production method optimization to increase the GMP compliance and efficiency
- Scale up of production methods for particulate systems from particle production to end formulation
- Establishment of GMP compliant production method for particulate systems
- Optimization of existing formulations for a smooth GMP transfer
- GMP compliant method establishment for production of nanoparticles and microparticles
- Innovative GMP compliant technologies to meet required product specifications

Understanding your needs through experience.

MyBiotech provides technology transfer services for your established nanoparticle and microparticle formulations to increase the GMP compliance and efficiency.



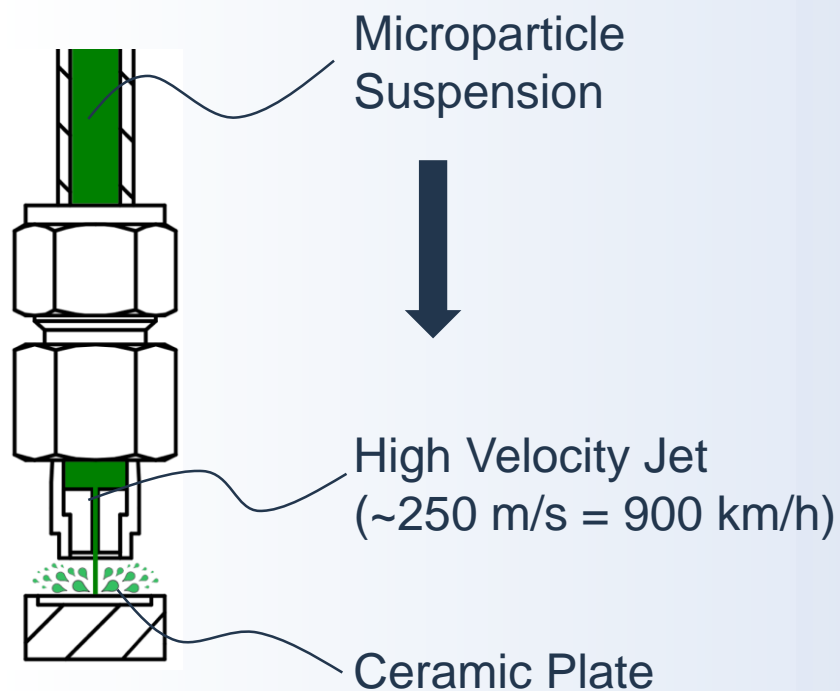
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# Manufacturing of Nanotherapeutics

## Continuous Particle Manufacturing CPM



## Patented scale up technology for **BOTTOM-UP** and **TOP-DOWN**

### TOP-DOWN

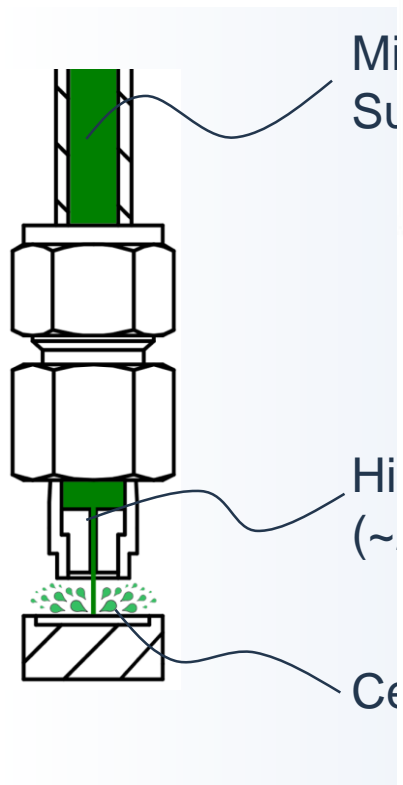
- High concentration of API
- Precise adjustment of particle size
- Homogenous particle size distribution
- Continuous production
- Production rate 600L/h



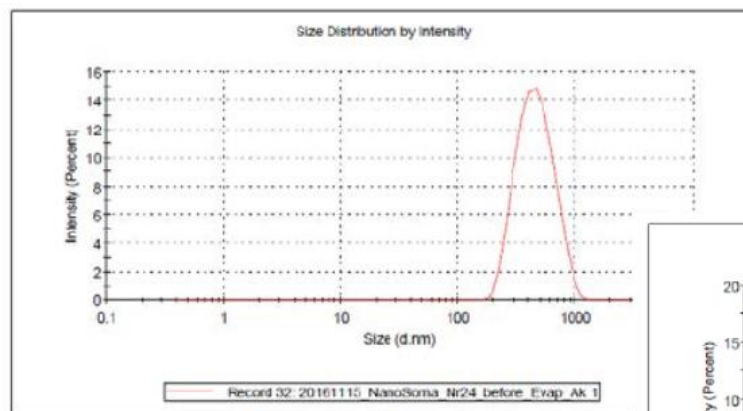


# Manufacturing of Nanotherapeutics

## Continuous Particle CPM

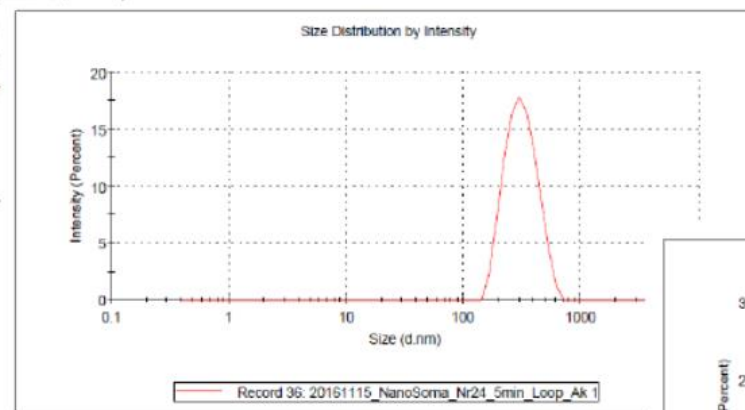


➤ Liposome preparation with CPM



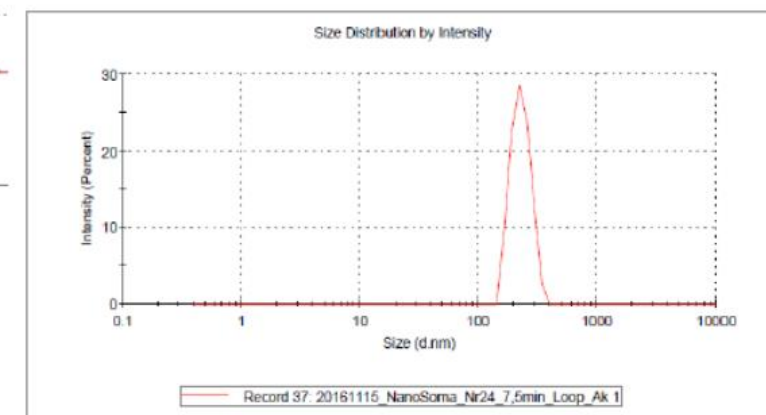
421.0 nm PDI:0.281

After preparation



289.3 nm PDI:0.088

5 min looping



225.5 nm PDI:0.072

10 min looping

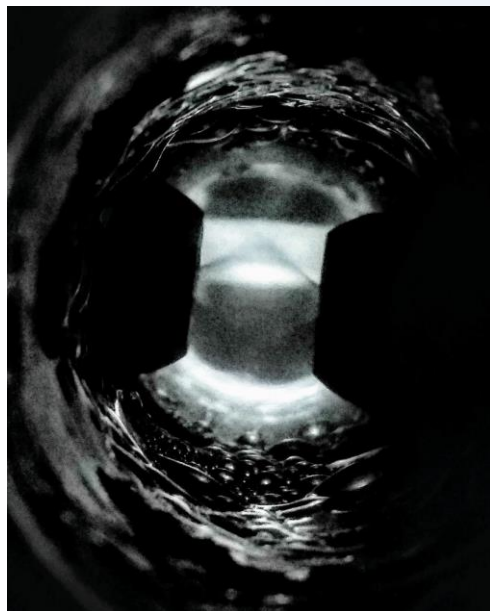


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# Manufacturing of Nanotherapeutics

## Micro Spray Reactor MSR

Patented scale up technology for  
**BOTTOM-UP** and **TOP-DOWN**



[Spray pattern]



[Spray distribution]

## BOTTOM-UP

- Complex nanoparticles
- Layer by layer nanoparticle coating
- Precise adjustment of particle size
- Homogenous particle size distribution
- Continuous production
- Production rate 600L/h





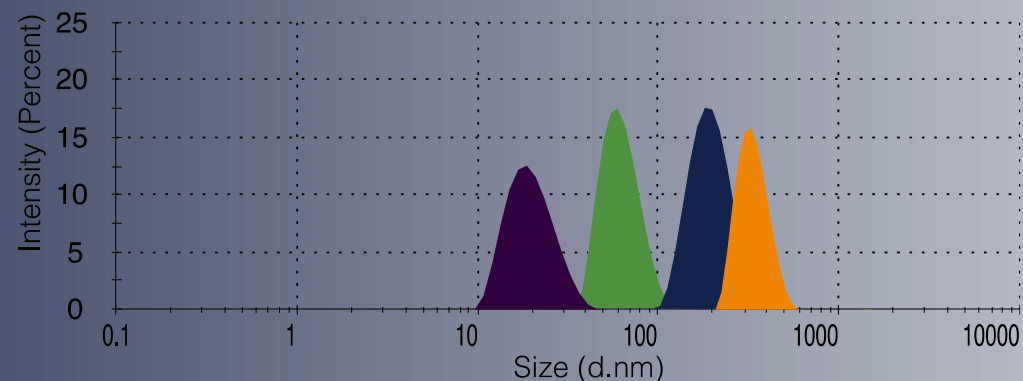


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# Manufacturing of Nanotherapeutics

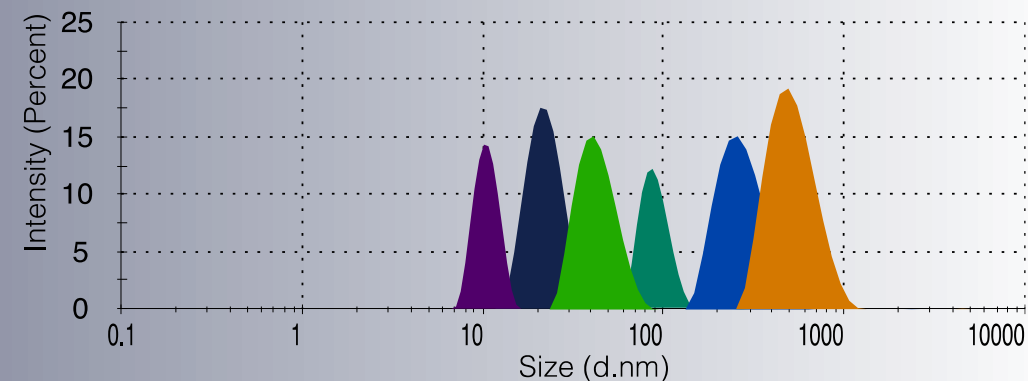
## Excellent Control

- Particle size can be adjusted both for bottom up or top down methods
- Formulation parameters and process parameters are used for the particle size adjustment
- Homogenous particle size distribution for all particle sizes



Based on formulation parameters

Based on process parameters



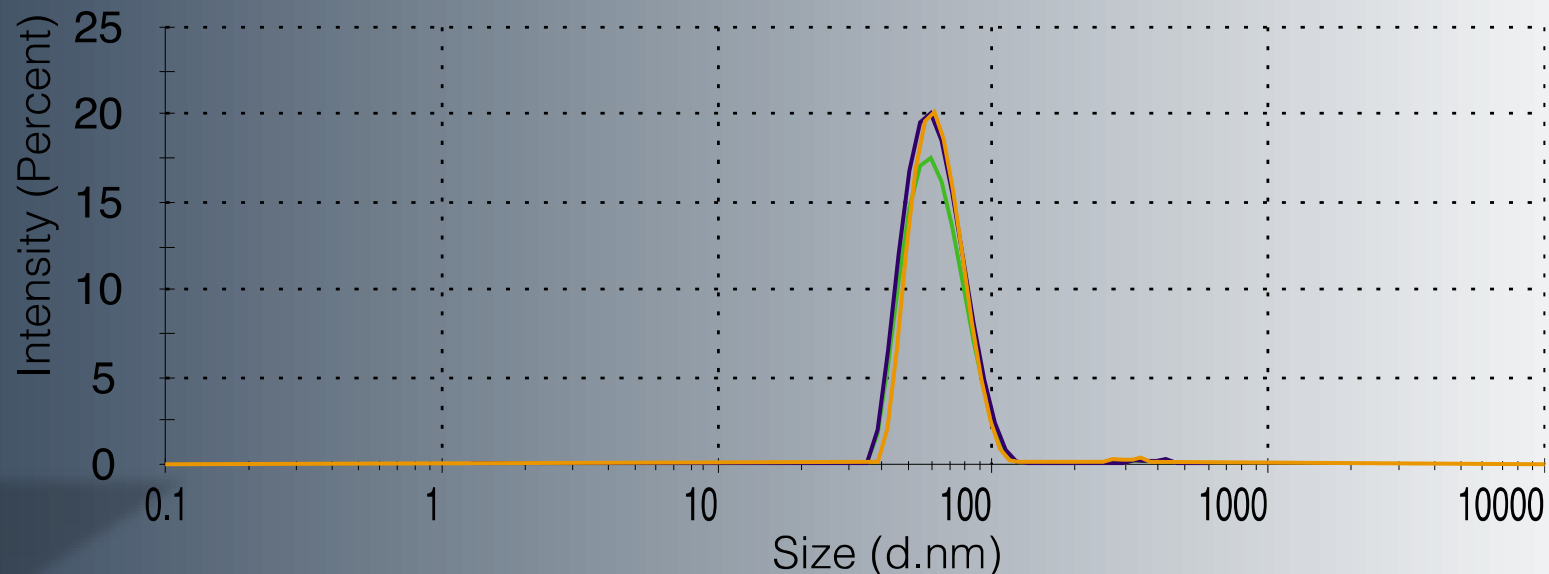


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# Manufacturing of Nanotherapeutics

## Excellent Repeatability

- ▀ Particle size and particle size distribution
- ▀ Low batch to batch variation
- ▀ Efficiently controlled process parameters





# GMP Downstreaming for Nanotherapeutics

## Purification

Removal of any organic solvent, free drug, or free formulation components, such as surfactants.

- **Crossflow filtration (CFF)** - enables continuous sterile manufacturing, easy transfer of method developments to GMP environment- requires extensive method development to maintain the physicochemical properties: selection of membrane including compatibility, exchange media, volume.

## Sterilization

- **Moist heat sterilization**: saturated steam under pressure – may jeopardize physicochemical properties, thus CQAs of nanopharmaceutical DDS (e.g. size, encapsulation thickness),

- **Sterile filtration** – cannot be employed to particles >220 nm
- **Gamma irradiation**

## Lyophilization

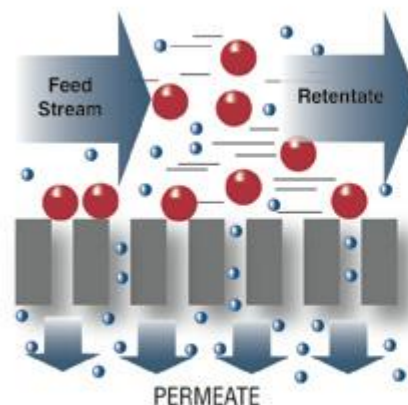
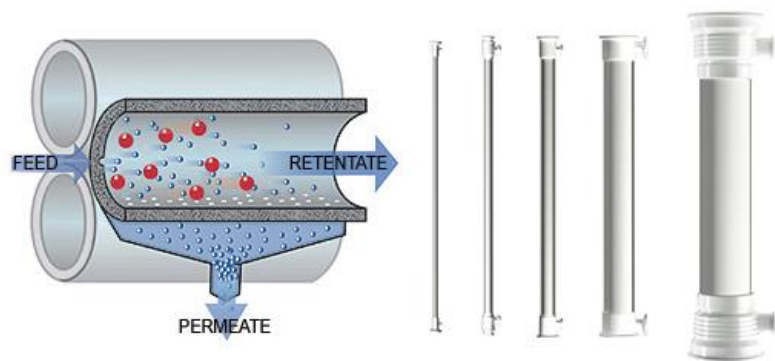
Freeze drying by sublimation from a frozen sample and desorption under vacuum.

To protect thermophysical properties,

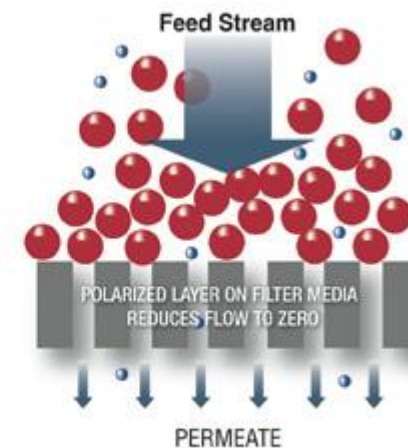
- nanoparticle/cryoprotectant ratio,
- investigation of cryoprotectant interaction,
- zeta potential measurements to study the particle surface changes

should be extensively studied in development.

# Cross flow filtration



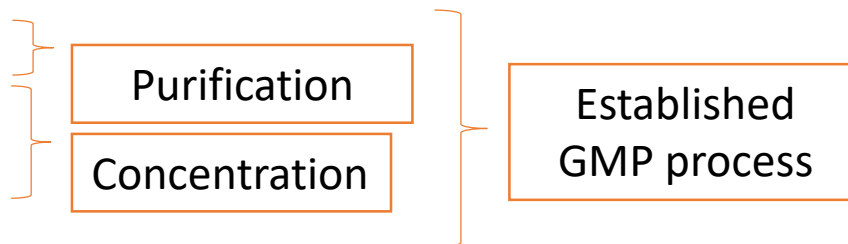
**Tangential (Cross) Flow Filtration**  
(high permeate rate)



**Dead-End Filtration**  
(low permeate rate)

<http://spectrumlabs.com/filtration/Edge.html>

- Removal of organic solvent
- Removal of dissolved API
- Concentrating of nanoparticles



# CFF Modules



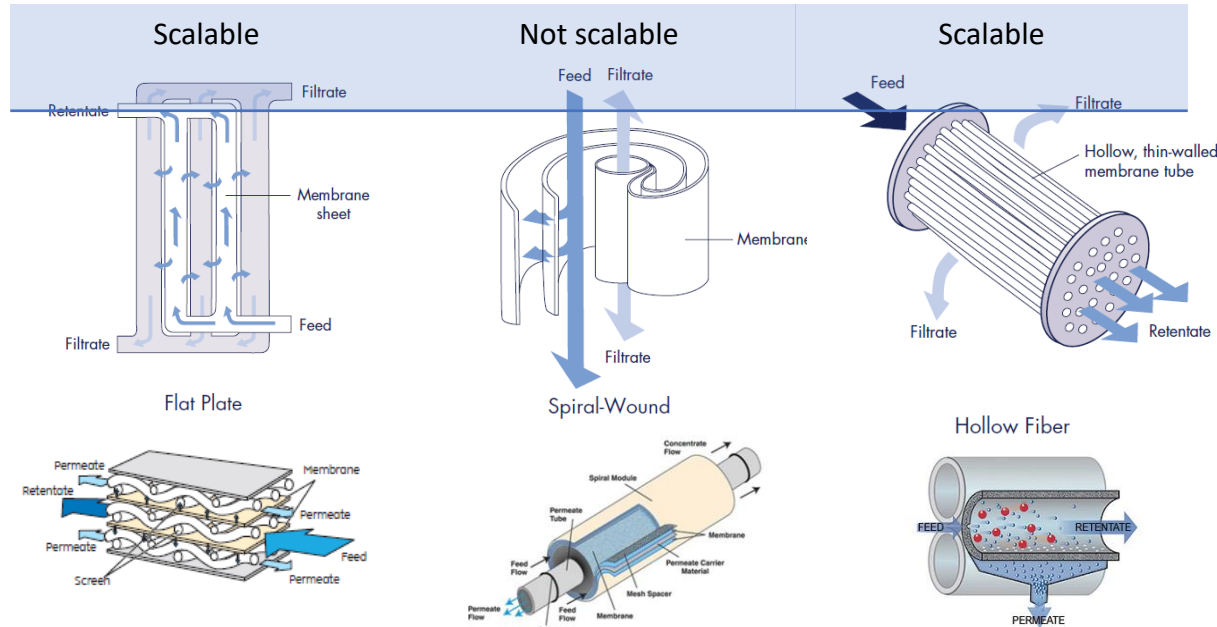
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Flat Plate	Spiral-Wound	Hollow Fiber
Non-uniform flow path High packing densities	Hollow central core, filtrate passes through the membrane and spiral to the core.	Easy to set-up  Faster processing times

Membrane corners

The separator screens  
increase the turbulence in  
flowpath leading to higher  
efficiency

No build up and loss of  
product



# CFF: Membrane Types

## *Modified Polyethersulfone (mPES)*

- Hydrophilic membrane
- Low protein binding for higher product yield
- Higher flux rate and faster processing time

## *Mixed Cellulose Ester (ME)*

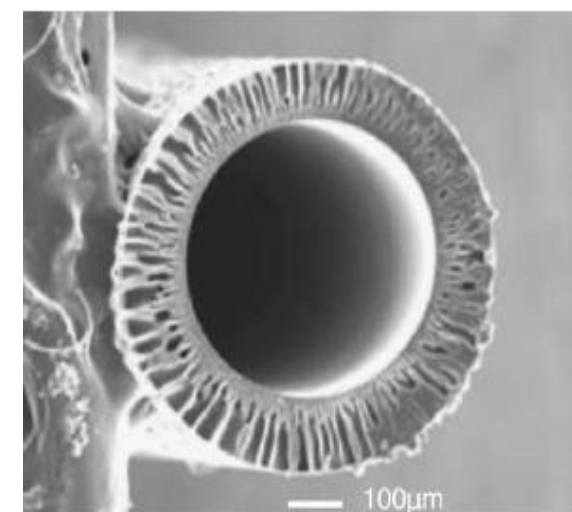
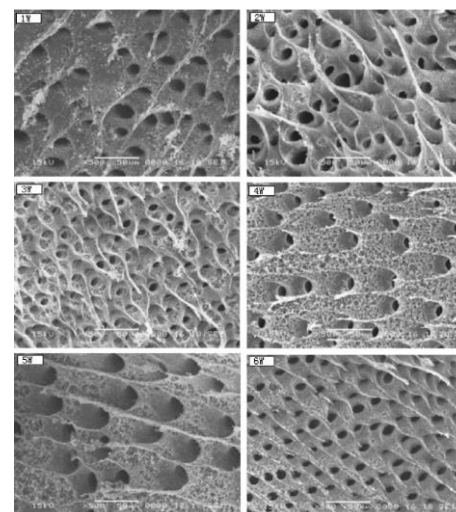
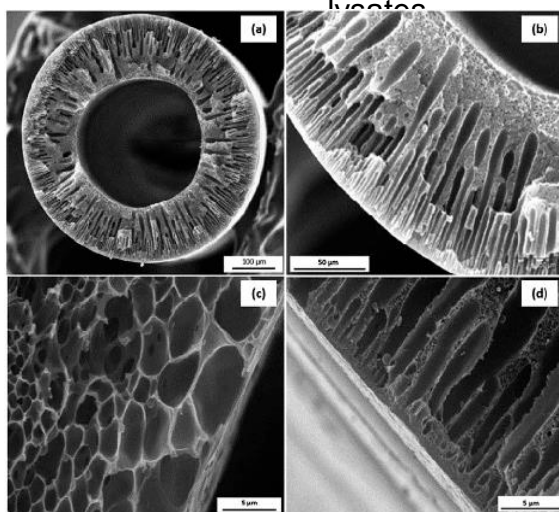
- Hydrophilic membrane
- Low protein binding
- Higher flux rate and faster processing time
- Highly biocompatible for filtration applications with cells, cell and virus

## *Polysulfone (PS)*

- Hydrophilic membrane
- Low protein binding
- More resistant to acid and bases, and surfactants
- Nanoparticle processing and diafiltration

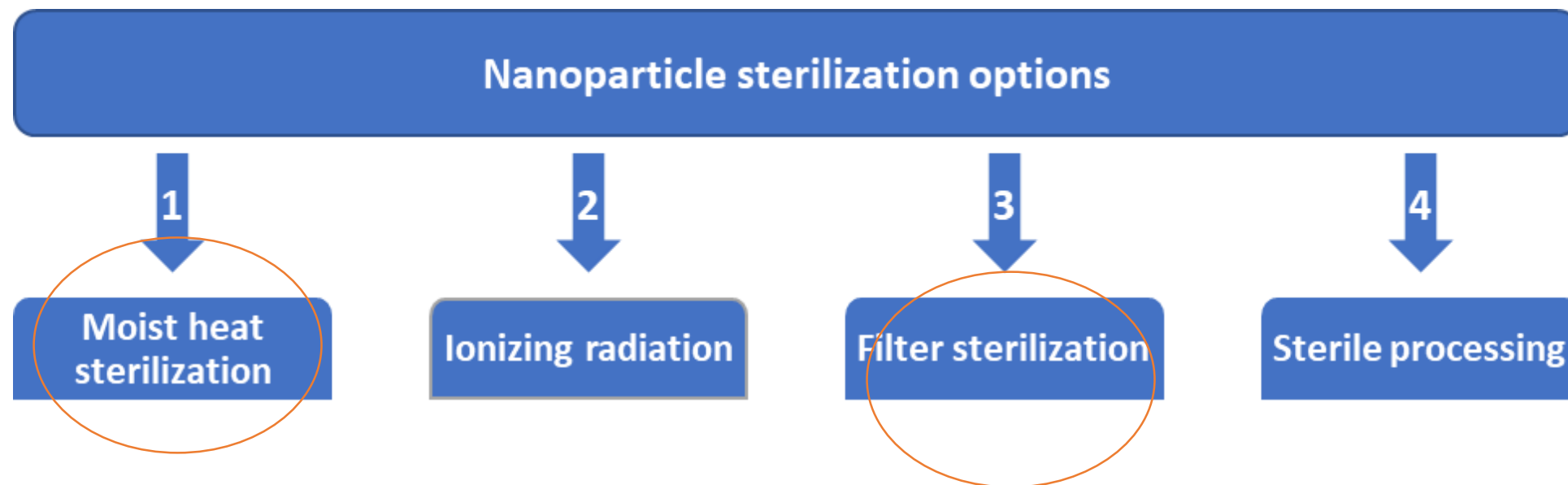
## *Polyethersulfone (PES)*

- Hydrophilic membrane
- Low protein binding
- More resistant to acid and bases, and surfactants





# Sterilization of Nanotherapeutics

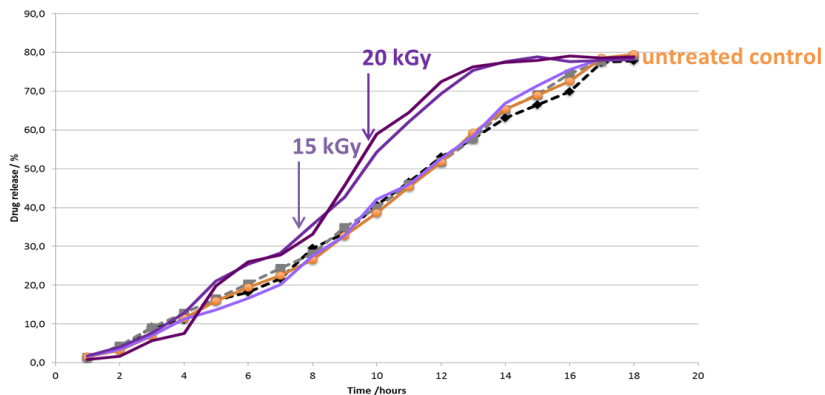
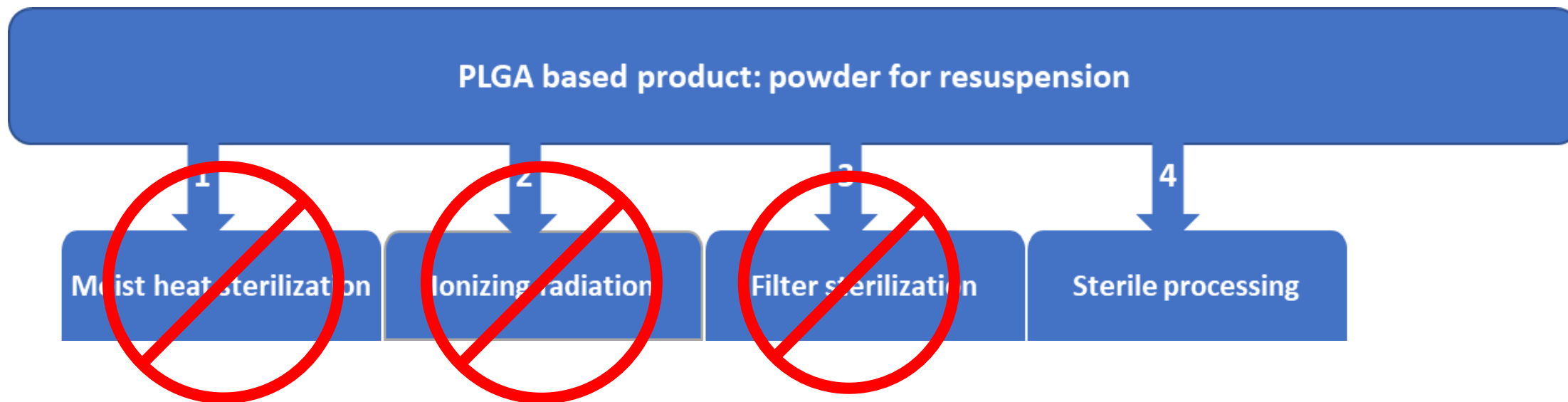


**The sterilization option for the nanoparticle formulations depends on:**

- Particle size of the formulations
- Type of formulation
- Structure of formulations
- API used in the formulations

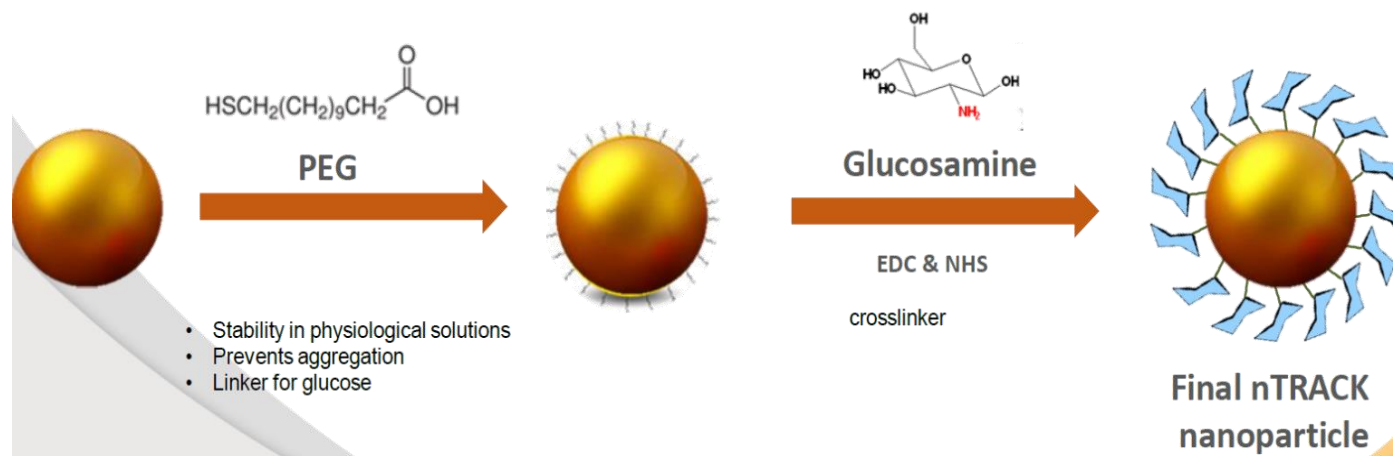


# Sterilization of Nanotherapeutics

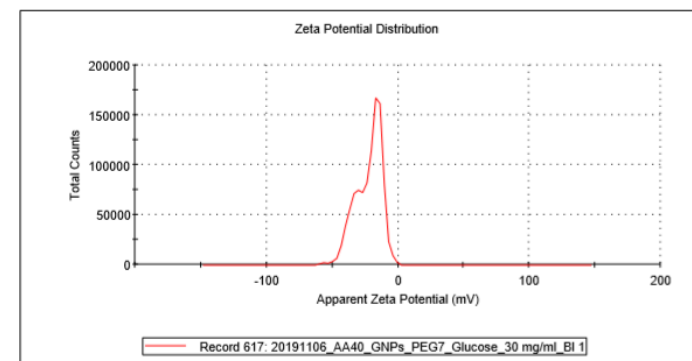
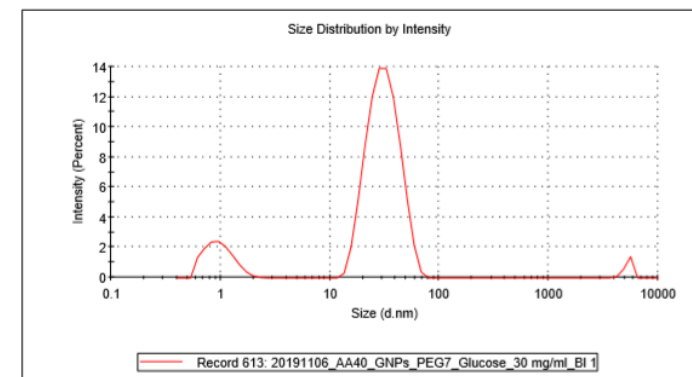




# Glucose coated gold nanoparticles



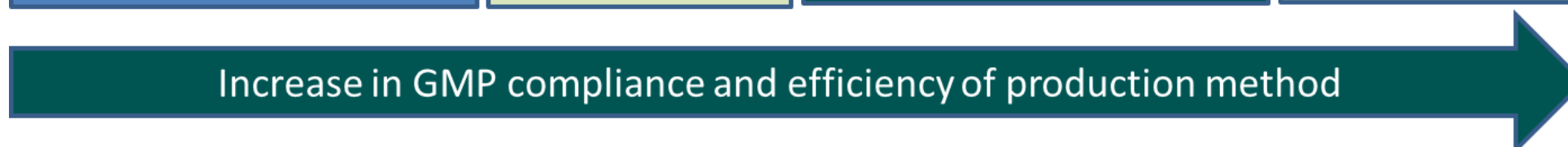
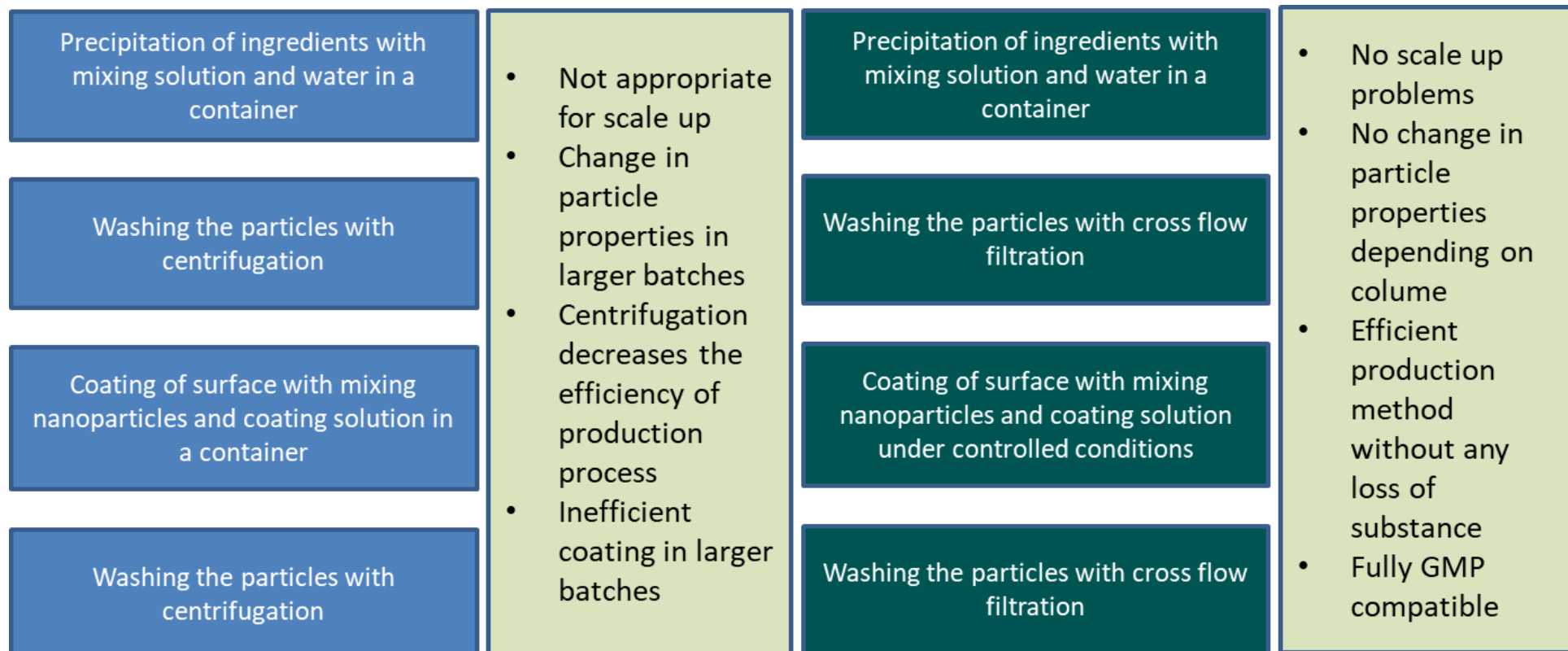
- Stability in physiological solutions
- Prevents aggregation
- Linker for glucose



AA-40	Particle size, nm	PDI	Zeta, mV
GNPs	21,67	0,551	-29,9
GNPs_Glucose	23,15	0,433	-22,5



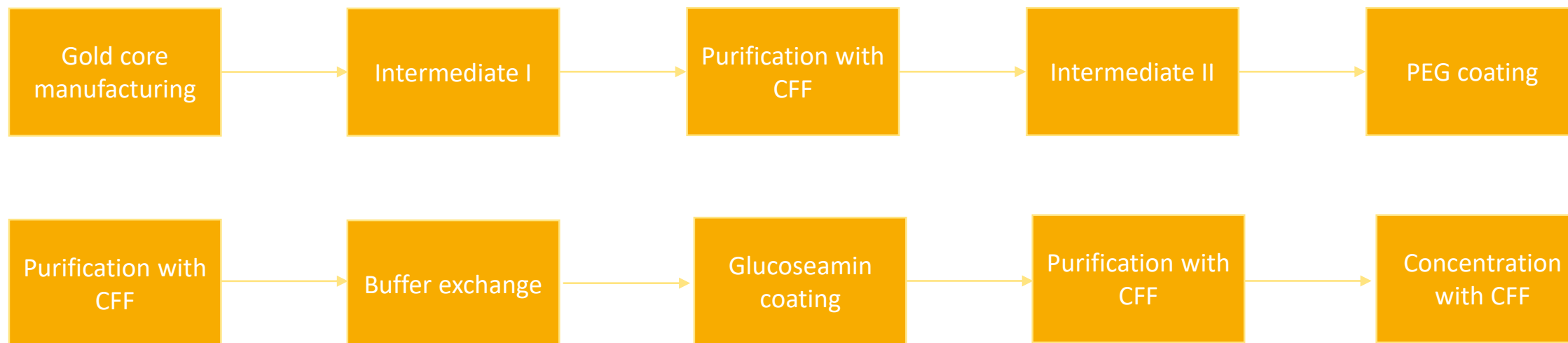
# Technology transfer concept





# Technology transfer to GMP compliant method

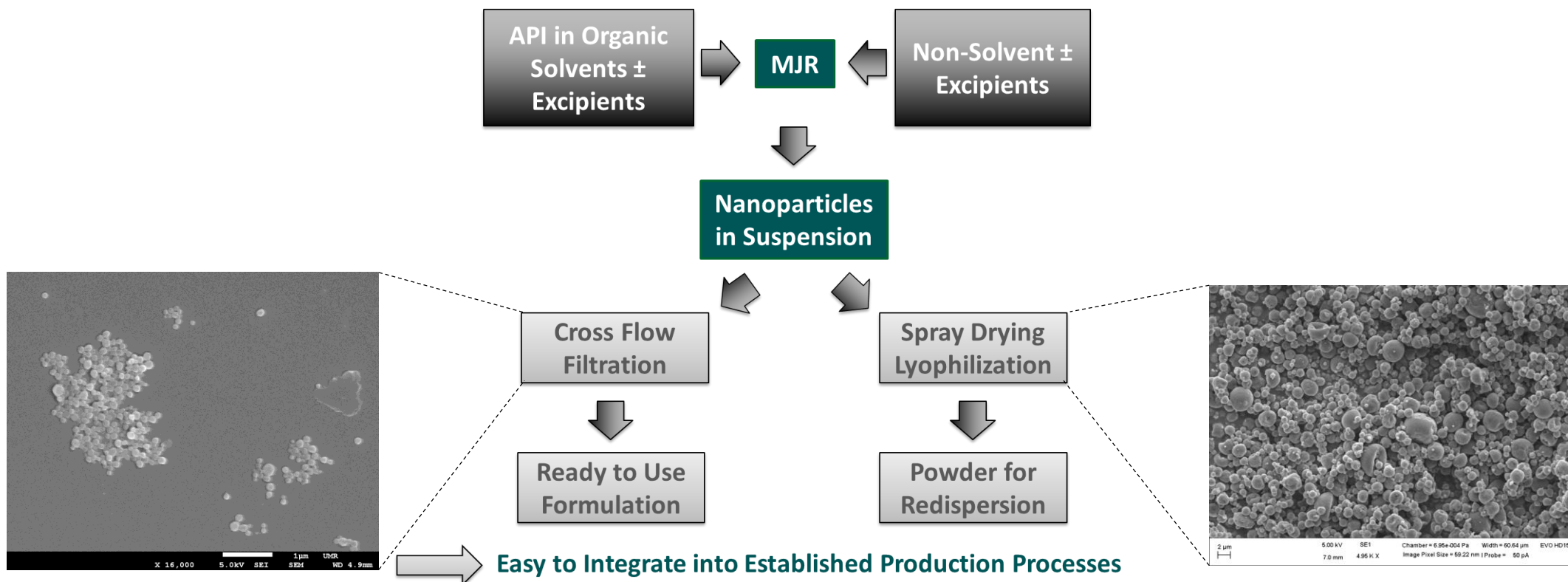
- Decreased gold concentration in one of the samples manufactured.
- Critical process parameters are identified which might lead to decreased gold concentration
- Specifications are set for the critical process parameters



# Biomolecule loaded polymeric NPs

## GMP compliant process concept

Process for Liquid Dosage Forms





**Phoenix**  
[www.phoenix-oitb.eu](http://www.phoenix-oitb.eu)

## Pharmaceutical Open Innovation Test Bed for Enabling Nano-pharmaceutical Innovative Products

**PHOENIX** bridging the innovation valley of death between science and nano-pharmaceutical product

...to enable the **seamless, timely and cost-friendly** transfer of **nano-pharmaceuticals** from **lab bench to clinical trials** by providing the necessary **advanced, affordable and easily accessible** PHOENIX-OITB.



This project received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 953110.



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# PHOENIX OITB: “SEP” for any end-user with all level of R&D&I activities from lab to market

## One stop shop

- A non-profit, self-sustained, independent legal entity
- smooth transfer from lab to GMP covering all necessary QES, regulatory, and upscaling aspects
- One-stop Shop
  - Access to R&D&I and manufacturing facilities and services across Europe at fair conditions through SEP
  - Reduced costs for production and regulatory compliance
  - Harmonized PQMS for testing, QES characterization, scale-up and GMP production
  - Paving the way for commercial and industrial implementation.



This project received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 953110.



# MyBiotech

## Contact



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