

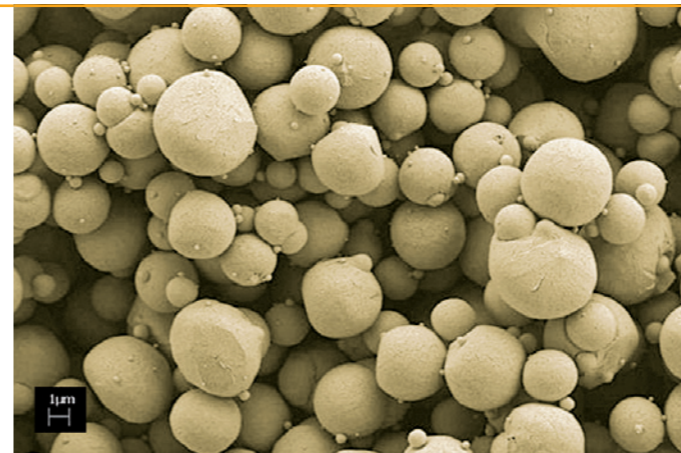
Value through Innovation

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Drug Product Development of Biopharmaceuticals



Assembly of autosampler (left),
Development laboratory (right)



SEM image of a spray-dried powder (left),
Preparation of filling line (right)



State-of-the-art technologies

As part of its one-stop shop concept, Boehringer Ingelheim offers pharmaceutical development of biopharmaceutical actives, applying state-of-the-art technologies. The dosage form portfolio ranges from liquids (including highly concentrated liquid formulations), lyophilized and spray-dried powders to inhalable presentations. The services on offer include selection and optimization of appropriate primary packaging such as vials, pre-filled syringes and cartridges as well as development of application systems. We provide a comprehensive set of flexible options to meet the specific needs of your biopharmaceutical molecule on its way to becoming a drug product.

Formulation development

Standardized approaches are in place to speed up the development of a formulation for use in toxicological or first-in-men studies (programmes: “time-to-tox”, “time-to-clinic”). The protein is adapted to the individual formulation on the basis of data collected during biophysical and physico-chemical characterization studies. Typical techniques applied

are, e.g. calorimetry and fluorescence spectroscopic methods to investigate the thermal and biophysical stability of proteins under various conditions. The best composition in respect of, e.g. pH, buffer salts, ionic strengths and stability will finally be selected to suit your therapeutic protein. The development and use of automated and miniaturized equipment enable us to achieve explicit conclusions in early stages of drug product development. Stress stability testing of selected formulations, a service supported by our Department of Analytical Sciences, rounds off formulation development.

Expertise is available in the development of many different finished product categories, e.g.:

- ▶ **Liquids:** low concentration – high concentration liquid formulation for injection or inhalation
- ▶ **Lyophilizates:** vials or dual-chamber cartridges for injection
- ▶ **Powders:** in vials or devices for inhalation or injection after reconstitution
- ▶ **Protein-coated microcrystals:** for inhalation or injection after dissolving

Our formulation scientists will provide their knowledge and skills in the devel-

opment of proteins, peptides, gene therapeutics and second-wave biopharmaceuticals to make your product a success.

Packaging and application devices

Packaging components are selected specifically to fulfil the needs of the formulated protein and to provide for user convenience as well as meet medical and marketing needs. Our packaging experts focus on optimizing existing components or on developing new packaging in close collaboration with our suppliers.

The standard packaging options available are as follows:

- ▶ **Vials:** 2 mL–100 mL
- ▶ **Syringes:** 0.5 mL–10 mL (plastic or glass)
- ▶ **Cartridges:** single-chamber (1.5 mL and 3 mL), dual-chamber (2 x 1 mL, 2 x 2 mL)

Application and transfer devices as well as pens, auto-injectors, inhalation devices (e.g. Handihaler® or Respimat®) or other application devices are selected and optimized according to the specific requirements of our customers.

A broad range of packaging related methods and tests have been established:

- ▶ Container closure integrity (e.g. frequency-modulated spectroscopy)
- ▶ Functionality (e.g. break-loose & gliding forces)
- ▶ Surface characterization (e.g. atomic force microscopy)
- ▶ Seat of crimping cap and related stopper compression (e.g. residual seal force)

Testing the compatibility and stability of formulations and packaging is another service on offer.

Process development

A conclusive physico-chemical characterization of formulation behaviour and the use of custom-made down-scale and simulation models constitute the fundamentals for process development prior to transfer to pilot scale. In addition to a chemical assessment, the physical properties of formulations are frequently investigated, e.g. clarity, density, surface tension, viscosity, and foaming behaviour.

Shear-stress simulation and droplet characterization as well as down-scale

models for filtration, filling or capping of vials are examples of state-of-the-art process development. Based on the data collected, an initial statement can be made on potentially critical process parameters. A product-specific risk assessment for the transfer from laboratory to pilot scale is performed.

Pilot facility - aseptic filling

The first transfer of a process from laboratory scale to pilot scale is typically intended to prove the robustness of the process. As soon as process robustness has been proved, clinical supplies can be manufactured.

Lot sizes for clinical supplies in the pilot facility:

- ▶ **Liquid products** (vial sizes 2 mL–100 mL): ca. 1,200–40,000 units
- ▶ **Freeze-dried products** (vial sizes 2 mL–100 mL): ca. 1,000–10,000 units
- ▶ **Syringes** (1 mL, 2.5 mL, 10 mL): ca. 2,000–10,000 units
- ▶ **Single-chamber cartridges** (1.5 mL or 3 mL): ca. 2,000–15,000 units
- ▶ **Dual-chamber cartridges** (2 x 1 mL or 2 x 2 mL): ca. 2,000–10,000 units

In addition to standard in-process controls, state-of-the-art technologies are developed and implemented to assure product quality, e.g. the online monitoring of stopper setting.

Our pilot facility meets cGMP requirements and has been successfully inspected and audited by authorities and many clients.

Pharmaceutical development

Part of our concept is to offer the complete drug product documentation for IND or IMPD applications. Our major goal in pharmaceutical development is to design and generate cost-effective robust formulations and processes that ensure the ultimate stability and reproducibility of your drug product.

Take advantage of our know-how, resources and capacity in the development of your drug product – from mind to market.