CHAPTER

11

Upscaling and GMP production of pharmaceutical drug delivery systems

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"Nanomanufacturing" is a growing economy [1,2]. The nanomedicine industry in Europe is comprised of startups, small and medium-sized enterprises (SMEs), and large pharmaceutical or medical device companies, and most of the nanomedicine companies have products related to drug delivery systems (DDSs) and therapy. In nanomedicine applications, nanosized tools are used for the diagnosis, prevention, and treatment of disease by combining a number of fields such as drug delivery, in vivo imaging, biomaterials, and active implants [3]. Many nano-DDSs are approved and are in clinical use, and many more are being investigated in clinical trials (Table 11.1) [4,5]. Researchers focus their work more on novel DDS production methods which can fast and efficient. However, there are a declining number of clinically approved nanopharmaceutical DDSs in comparison to the last decade. This can be attributed mainly to difficulties in the industrial-scale manufacturing of quantities of quality products required for clinical trials using existing technologies or implementing such innovative methods in existing manufacturing plants. Establishment of good manufacturing practice (GMP)-compliant nanopharmaceutical DDS manufacturing at a large scale is the prerequisite of successful transfer from bench to bedside as shown in Fig. 11.1. GMP regulates not only the manufacturing processes but also all other areas of the processing chain of departments and facilities, including equipment and cleaning validations, training, hygiene, purchase, supply, warehousing, regulatory affairs, IT and personnel, as well as contracted manufacturers and suppliers. GMP is designed to minimize the risks involved in any step of pharmaceutical production that cannot be identified through testing the final product [6]. GMP is accepted EU- and US-wide and ensures quality and its sustainability throughout the whole supply chain.

Some known difficulties arising during translation from lab to larger scales, thus indirectly bench to bedside, can be listed as control deficiency, separation from undesired nanostructures or formulation components, scale-up issues, increase in production rate, reproducibility of critical quality attributes (CQAs) from

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TABLE 11.1 Examples of EU- and US-approved nano- and micropharmaceutical drug delivery systems.

Product name	Dosage form	Indication	Active substance	Approval year
Abelcet	Suspension (IV)	Fungal infections	Amphotericin B	FDA (1995)
Abraxane	Powder for infusion	Metastatic breast cancer	Paclitaxel	FDA (2005) and EMA (2008)
Ambisome	Powder for infusion	Fungal infections	Amphotericin B	FDA (1997) and EMA (1990)
Amphotec	Lyophilized powder for reconstitution (IV)	Fungal infections	Amphotericin B	FDA (1996)
Arestin	Topical microparticle	Dental antibiotic	Minocycline HCl	FDA (2001)
Atridox	Topical solution	Dental antibiotic	Doxycycline hyclate	FDA (1998)
Bydureon	Subcutaneous microparticle	Diabetes	Exenatide	FDA (2012)
Daunoxome	Powder and solvent for infusion	Antineoplastic	Daunorubicin citrate	FDA (1996)
Depodur	Extended release liposome injection	Chronic pain	Morphine	FDA (2004)
Diprivan	Emulsion for injection or infusion	Anesthetic	Propofol	FDA (1989)
Doxil	Liposomal injection	Ovarian cancer, Kaposi's sarcoma, multiple myeloma	Doxorubicin HCl	FDA (1995) and EMA (1996)
Elestrin	Topical gel	Hot flashes during menopause	Estradiol	FDA (2006)
Eligard	Powder and solvent for injection	Prostate cancer	Leuprolide acetate	FDA (2002)
Emend	Hard capsule	Antiemetic	Aprepitant	FDA (2003) and EMA (2003)
Estrasorb	Topical emulsion	Vasomotor symptoms associated with menopause	Estradiol hemihydrate	FDA (2003)
Feraheme	Injection	Treatment of iron deficiency anemia in patients with kidney disease (chronic kidney disease)	Ferumoxytol	FDA (2009)
Gastromark	Oral suspension	Imaging of abdominal structures	Poly [*N*-(2-aminoethyl)-3-aminopropyl] siloxane-coated nonstoichiometric magnetite	FDA (1996)
Lupron Depot	Suspension (SC)	Prostate cancer	Leuprolide acetate	FDA (1998)
Ozurdex	IV implant	Ocular	Dexamethasone	
Naprelan	Tablet	Rheumatoid arthritis and osteoarthritis, gout	Naproxen sodium	FDA (1996)

TABLE 11.1 Examples of EU- and US-approved nano- and micropharmaceutical drug delivery systems.—cont'd

Product name	Dosage form	Indication	Active substance	Approval year
Rapamune	Tablet	Immunosuppressant; the prophylaxis of organ rejection in patients receiving renal transplants	Sirolimus	FDA (2002) and EMA (2001)
Risperdal Consta	IV microparticle	Antipsychotic	Risperidone	FDA (1998)
Sandostatin LAR Depot	SC microparticle	Long-term treatment of severe diarrhea and flushing	Octreotide acetate	FDA (1998)
Somatuline Depot	Suspension (SC)	Acromegaly	Lanreotide	FDA (2007)
Suprefact Depot	SC implant	Prostate cancer	Buserelin acetate	
Taxotere	Powder and solvent for infusion	Antineoplastic	Docetaxel	FDA (2004)
Trelstar Depot	IM microparticle suspension	Prostate cancer	Triptorelin acetate	FDA (2001)
Tricor	Tablet	Hypercholesterolemia and hypertriglyceridemia	Fenofibrate	FDA (2004)
Triglide	Tablet	Hypercholesterolemia and hypertriglyceridemia	Fenofibrate	FDA (2005)
Visudyne	Powder for infusion	Photodynamic therapy for age-related macular degeneration	Verteporfin	FDA (2000)
Zoladex	Implant (SC)	Prostate and breast cancer	Goserelin acetate	FDA (1997)
Zyprexa	Tablet	Schizophrenia	Olanzapine	FDA (2009)

EMA, European Medicines Agency; *FDA*, US Food and Drug Administration; *IM*, Intramuscular; *IV*, intravenous; *SC*, subcutaneous.

batch to batch, and high costs of manufacturing. Still, upscaling and production of innovative nanopharmaceutical DDSs is challenging for startups and SMEs, due to lack of resources to implemention GMP manufacturing at on/off site. Contract manufacturing organizations (CMOs) can satisfy this need but there are a very limited number of CMOs in the market that can support diverse portfolios and that have sophisticated equipment facilities, e.g., polymeric nanoparticle to dendrimer, therefore different CMOs are needed for different type of DDS.

Top-down technologies use physical or chemical methods to produce nanosize particles by breaking down larger materials, while bottom-up technologies assemble molecular or atomic components into complex features [7]. Most current pharmaceutical DDSs are produced by the top-down approach, which

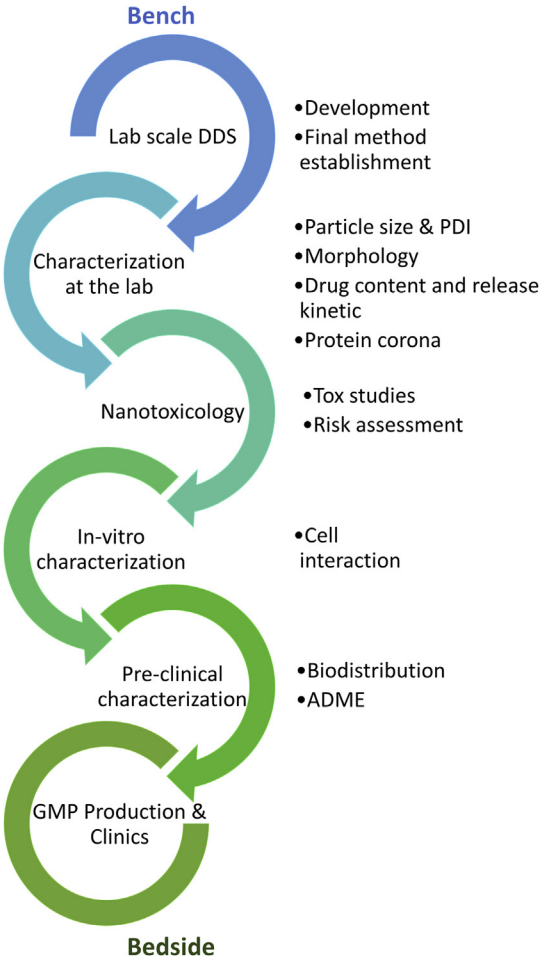

FIGURE 11.1 Main steps in the bench-to-bedside translation of nanopharmaceutical drug delivery systems (DDSs). *ADME*, Adsorption, distribution, metabolism, and excretion; *GMP*, good manufacturing practice.

requires large facilities and manufacturing areas for large-scale production and a considerable amount of equipment cost. Such methods have a huge environmental impact as well. On the other hand, we must acknowledge that over the last few decades, top-down methods have successfully served for production of many blockbuster drugs. Bottom-up methods, preferably via continuous manufacturing, can be mostly realized by existing equipment, which enables the control of CQAs with adjustment of production parameters via in-process controls (IPCs). Such manufacturing technologies usually offer ease in GMP implementation.

New manufacturing methods, and eventually equipment, are required to enable larger production volumes with less energy and less material consumption but with higher control of product quality and safety. Such manufacturing methods and processes should be easily applicable or adaptable to a broad spectrum of complex DDSs and should fulfill the requirements for larger scale to control the CQAs of particles such as particle size and distribution, morphology, and nanomaterial-associated drug amount to accelerate the penetration of DDSs to market. Indeed, there has been growing interest in increasing the safety and quality of medications via Quality-by-Design (QbD) and Safe-by-Design (SbD) approaches while reducing the manufacturing costs by implementing more structured pharmaceutical development and production approaches [8]. These issues would not only enable market penetration but also ensure compliance with regulatory requirements at the later stages.

If one is seeking a universal solution to the three success-determining criteria of DDS manufacturing (namely scalability, sustainability, and GMP compliance), then one must address the reproducibility and methods to achieve thereof, IPCs, if applicable sterilization, nanotoxicology, storage stability, thus retaining characteristics dictating in vivo success and finally acceptance of all the foregoing listed at a regulatory level.

The European Medicines Agency (EMA) is a regulatory agency responsible for evaluating and supervising medicines for use in Europe to protect public and animal health. This agency controls the safety of medicines and looks at the safety concerns and changes in the benefit/risk balance of products. In addition, EMA

encourages innovations and research and provides scientific recommendations and protocol support in the development of new pharmaceutical products with the aim of developing high-quality, effective, and safe nanotherapeutics when expert evaluation is needed to confirm product regulations. Moreover, EMA has a large role in the development and authorization of orphan medicines like nanotherapeutics used in the treatment of rare diseases.

1. Scalability

Nanopharmaceutical DDS preparations are complex (the nature of starting materials, amounts, and numbers of components) and consist of multiple steps requiring different equipment for each stage until the final formulation is achieved. Additionally, complexity at the particulate level, in most cases, is in vivo fate determining [9–19]. Such methods are difficult to control even at the lab scale and most risks faced during scale-up arise from complexities of both nanopharmaceutical DDS and manufacturing method. However, clinical success can be only achieved if physicochemical properties (complexity at a particulate level) are sustained at large scale.

Given the complexity and limited yield in most cases, (i) achievable batch sizes, (ii) applicability of the employed manufacturing method to the existing resources and/or manufacturing lines, (iii) the costs of goods and economics might be the three critical points at the early stages of the supply chain determining if a nanopharmaceutical DDS will be taken to the next steps, regardless of the quality and success of the product.

During the development phase, the efficacies of the DDSs are defined by their size and size distribution, surface charge, and chemistry [20,21]. Thus those CQAs should be maintained after scale-up. However, most of the current lab-scale manufacturing methods require tremendous effort to implement them in existing, conventional manufacturing equipment. Industrial sustainability can only be achieved if translation aspects are considered at the early phases of the pharmaceutical development chain. SbD and QbD are to be considered at the very early phases of development. During the late development and scale-up phases, if possible, data processing and statistical methods should be employed to improve the understanding of the process.

For this purpose, design of experiments (DoE) offers an ideal solution for defining CQAs, deriving critical process parameters, and finding their effect on CQAs with a minimum number of experiments [22–24]. DoE offers experimental data-based mathematical model constructions of factors (i.e., independent factors) and targets (i.e., dependent variables) to accurately determine their relation. DoE means reduced costs in the short term due to relatively low experimental effort, and in the long term because of early determination of critical steps and attributes, which reduces risk.

The information gained by DoE analysis serves to set the IPC of the manufacturing process [23–27]. In addition to the IPCs, the knowledge gained during this stage provides a basis for the establishment of control strategies. Control strategies depend on the product specifications and its manufacturing method to ensure product quality with sustainable manufacturing methods. This knowledge not only serves design controls but also continuous improvement of the product, as shown in Fig. 11.2.

Considering the vast number of nanopharmaceutical DDS preparation methods and the variety of nanopharmaceutical DDSs of different materials, it is almost impossible to offer a “one-size-fits-all” kind of upscaling platform. However, since the challenges listed earlier are valid for all nanopharmaceutical DDSs and their preparation methods, one can employ a similar strategy for reducing risk during upscaling. Top-down methods for larger

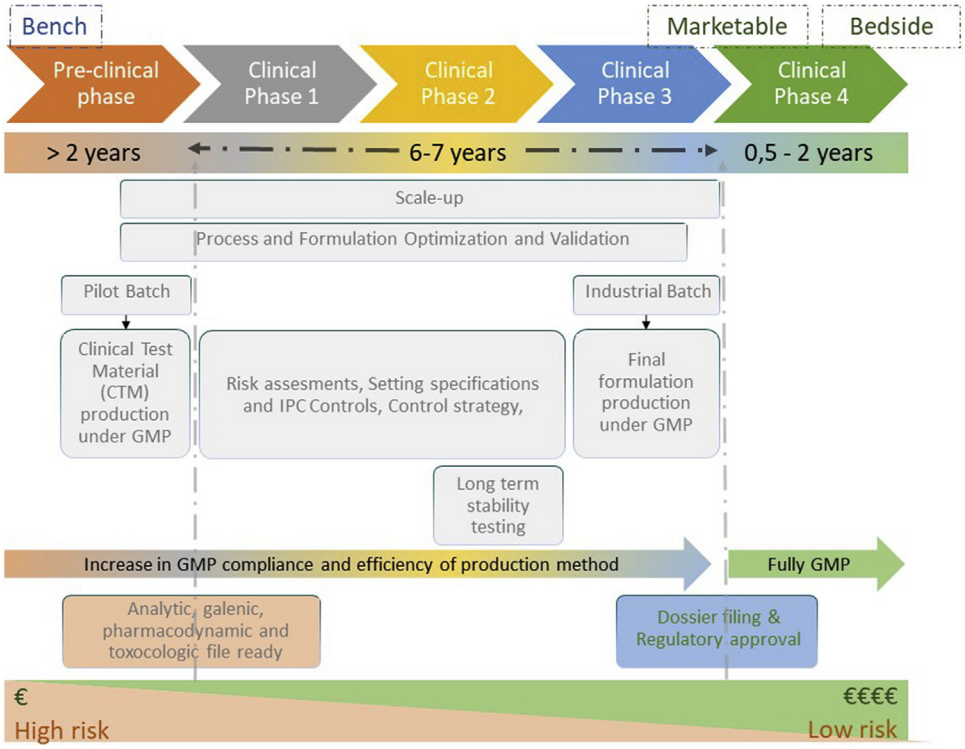

FIGURE 11.2 Continuous improvement of nanopharmaceutical drug delivery system and good manufacturing practice (GMP) compliance through different stages of development. *IPC*, In-process controls.

scales (e.g., milling) have already been used for many products in the market. However, bottom-up methods are not yet as prominent in the marketed products [28].

1.1 Top-down methods

1.1.1 Milling

Milling is an already well-established commercial technology that has been used for top-down nanoparticle production for many years [29–32]. The method is based on transforming larger, bulk particles into smaller-sized particles by energy transfer and mechanical grinding [29]. There are different set-ups available in the market for different batch sizes, and also for industrial batch sizes. Unfortunately, the system already offers scale-up via suitable set-ups [33], and the need for large rooms and equipment investment are the main drawbacks of the system. It is also worth mentioning that nanoparticles prepared by such techniques show polydispersity, and often an additional surfactant and solvent are required to prevent agglomeration and extreme increase in temperature because of high energy input [34]. Longer milling times required for the preparation of fine particles (10–100 nm) resulting in impurities that are difficult to separate from the product can be noted as another limiting aspect of the technique.

1.1.2 High-pressure homogenization

Since emulsification is a thermodynamic process, homogenization that takes place at room temperature results in larger particles and a

broader size distribution, whereas processes with applied high temperature are not suitable for thermolabile active substances [35]. High-pressure homogenization is an energy-intensive process and long homogenization cycles are required for smaller and narrower particle size distributions. On the other hand, this technique does not require use of organic solvent, and scale-up is generally accepted as feasible [35,36] since there are already commercially available high-pressure homogenizers suitable for large batch sizes [37].

1.2 Bottom-up methods

1.2.1 Nanoprecipitation

Nanoprecipitation is based on spontaneous formation of nanoparticles upon mixing water-miscible organic solvent into the aqueous phase. Nanoparticle formation takes place spontaneously once the organic solvent containing the substance diffuses into the aqueous medium in which it is insoluble [23,38]. The nanoprecipitation method offers high efficiency at lab scale, does not require energy input, sonification, or very high temperatures, and the most common organic solvents employed are nontoxic [22,25,39]. However, control over particle size and polydispersity index is dramatically decreased during scale-up [38]. Additionally, purification to remove organic solvent and free active substance requires long down-processing times. It has been reported that high-pressure homogenization and wet milling processes have been combined with nanoprecipitation steps to achieve smaller particles of narrow size distribution [40].

1.2.2 Salting out

This method is particularly suitable for (bio) polymeric DDSs. The polymer dissolved in a water miscible organic solvent is mixed with an aqueous phase containing high salts concentrations or electrolytes. The presence of salts and/or electrolytes prevents solvent diffusion after mixing. Nucleation is observed once excess water is added to induce diffusion of the organic solvent. Purification, for example, via cross-flow filtration, is required to remove the organic solvent and salting-out agent. The salting-out method offers high efficiency and easy scale-up. However, extensive washing for purification purposes requires long down-processing times.

1.2.3 Supercritical fluid technology

Supercritical fluid technology is one of the most prominent methods for nanopharmaceutical DDS manufacturing. Use of mild temperature conditions and no necessity on organic solvent offer advantages and large scales can be achieved by commercially available set-ups. However, CO_2 being a poor solvent and the high costs of equipment and manufacturing can be listed as disadvantages of the technique.

2. Sustainability

Sustainability is a wide-open concept that is applicable and integrated at most cases to many different areas: economics, environment, and society. When pharmaceutical DDS manufacturing is considered, it requires the use of freely available (not batch size-limited), nontoxic materials to prepare DDS; use of the least number of formulation components and as few manufacturing steps as possible with minimized by-products and waste (energy saving, environmental friendly methods); use of water as a solvent if possible; and temperature conditions close to room temperature, etc.

GMP requires compliant raw materials with identification not only for active substances but also for inactive raw materials (excipients),

which might be critical for the performance of the DDS in vivo. To ensure sustainability, selection and screening of starting materials and their supplier should be an integrated part of QbD. Sustainability of a pharmaceutical DDS is directly related to its nanotoxicology. Components should be chosen among already approved raw materials (compendial materials) or should at least have the status of generally accepted as safe (GRAS). Enough data should be already available or collected prior to any clinical test. Even this is not much of a problem in the case of compendial or GRAS materials, and it can cause years of delay before clinical use if a raw material with no adequate toxicity data is being used for DDS preparation. Such a delay is usually expected when chemical modifications on the nanocarriers (lipids, (bio)polymers etc.), or even active substances for enhanced performance are done. Another bottleneck in use of such raw materials is the potential need for upscaling and GMP conformant manufacturing. Such modifications performed under lab conditions might lack control of the reaction, cause nonspecific by-products, require use of harsh solvents or use of catalyst(s), which must be removed from the system, and usually have low yields and long reaction times. Under such conditions, modification methods must be optimized to overcome the foregoing listed problems, and purification of the modified molecule must be performed to a pharmaceutically acceptable level in accordance with the current guidelines and pharmacopeia. Optimized modification must be capable of delivering quantities with enough substance for industrial scale at high pharmaceutical quality.

GMP compliance of active substances and inactive substances, as well as materials that come in direct contact with pharmaceutical DDSs (e.g., primary packages, tubings, applicators, etc.), are out of the scope of this chapter; however, readers are encouraged to refer to these aspects during development.

2.1 Downstreaming for parenteral formulations

2.1.1 Purification

Regardless of the employed components, purification of pharmaceutical DDS is an important step of the development phase to ensure removal of any organic solvent, free drug, or free formulation components, such as surfactants. Conventional methods that are applied for downstreaming of pharmaceuticals need adjustments before being used for nanopharmaceutical DDSs. The gold standard approach in research projects for purification is either dialysis or repeated centrifugation-washing steps. However, such methods might require extremely long processing times to reach the acceptable limits and eventually investment in equipment capable of processing industrial scales, which would directly impact the cost of the product in the case of successful applications. Such purification methods should be replaced by lower-cost, easy-to-perform, and standardized options, such as crossflow filtration (CFF).

Unlike traditional dead-end filtration methods, the crossflow filtration (CFF) method employs a tangential flow of medium that enhances the filtration process without causing clogging. The CFF method is a continuous method that enables the scale-up of downstreaming processing cost and is time efficient. Sterile manufacturing, which is required for most of the nanopharmaceutical DDSs of interest, is also realizable with CFF enabling continuous sterile manufacturing. CFF requires extensive method development for process establishment, including selection of membrane, exchange media, and volume, to maintain the physicochemical properties of DDS after production and to prevent any change or agglomeration. Extra caution needs to be taken for the selection of the membrane, its compatibility, and the absence of nonspecific adsorption in

the membrane. Once the CFF method is established, it can be easily transferred to the GMP environment without any batch size limitations because of continuous processing. Additionally, most of the currently available GMP conformant CFF systems are coupled with integrated IPCs to ensure a robust and reproducible process, which runs automatically until the specifications are fulfilled. Such features also allow standardization and process validation, thus fulfilling the GMP requirements.

2.1.2 Sterilization

Many conventional processes are available for sterilization of parenteral formulations; however, they are not always applicable to nanopharmaceutical DDSs. In most cases, parenteral formulations are sterilized by exposure to saturated steam under pressure [40]. Under such conditions, nanopharmaceutical DDS might show change in physicochemical properties depending on the employed formulation components. If such changes are observed in CQAs of the nanopharmaceutical DDS (e.g., size, encapsulation thickness, etc.), in vivo performance might be dramatically affected. Sterile filtration or gamma irradiation, both generally accepted processes, might be alternatives to steam sterilization. However, sterile filtration cannot be employed in nanopharmaceutical DDSs <220 nm, since most commonly used membrane-enabling separations of any microbial component possess this pore sizes. Difficulties might also arise for particle sizes close to that cut-off value. Under such conditions, a preliminary proof-of-concept must be conducted to make sure that the particles do not cause clogging or are not retained by the membrane. Regardless of the size of the nanopharmaceutical DDS, a compatibility and process yield test must be performed to ensure that the particles are not interacting or being retained by the membrane.

2.1.3 Freeze drying

Freeze drying, also known as lyophilization, is based on removing water from a frozen sample by sublimation and desorption under vacuum. It has already been well established in many industrial sectors, including the pharmaceutical and food industries [41]. When freeze drying pharmaceutical DDSs (e.g., for ready-to-dilute final dosage form purposes), thermophysical properties of the nanoparticle suspensions must be taken into consideration. Additionally, sample particle concentrations and the nanoparticle/cryoprotectant ratio should be carefully adjusted, since highly concentrated nanopharmaceutical DDSs tend to agglomerate and even aggregate. To minimize the stress from freezing and desiccation, cryoprotectants are added to the sample to protect the nanoparticles. To ensure that the nanopharmaceutical DDSs remain unchanged, a freeze/thawing study should be realized to compare the CQAs before and after freeze drying. This study can be performed as an integrated part of the development stage for choosing the right cryoprotectant for formulation of particles intended to be freeze dried. Such characterizations mainly include optimization of reconstitution time, changes in release kinetics, thermal analysis (e.g., differential scanning calorimetry) to investigate the interaction with the cryoprotectant for early detection of potential incompatibilities, and zeta potential measurements to study the particle surface changes.

2.2 Downstreaming to solid dosage forms

2.2.1 Granulation

Wet granulation is a very well-established standard unit operation with a vast amount of available equipment configurations in the pharmaceutical industry, and most manufacturing

sites use this process for conventional processing. The effects of wet granulation on the properties of solid dispersions were recently reported with emphasis on physical stability and dissolution [42]. The powder properties after granulation, such as particle size and distribution in powder form and after redispersion, flow properties, bulk density, and hygroscopicity, determine the impact of granulation on dissolution and final dosage form performance. Nanoparticles should be in vivo dispersible and they should not change their physicochemical properties. Potential stability affecting conditions might be granulation liquid (high amounts of nanoparticles agglomerating over low amounts of granulate), and the drying temperature, which might significantly affect physical and chemical stability [42,43].

2.2.2 *Spray drying*

In conventional spray drying, a feed solution is atomized into a fine spray over a nozzle through which a dried hot air stream is codelivered. The contact between the hot inlet air stream and spray results in evaporation of solvent and dries the feed solution into solid product in a single-step process [44]. Just like in the case of wet granulation, the powder properties, such as particle size and distribution in powder form and after redispersion, flow properties, bulk density and hygroscopicity, determine the impact of process parameters on downstream processing and final dosage form acceptability [45]. It is very important that the downstreaming process does not change the CQAs of the nanopharmaceutical DDS. Thus the powder must be carefully characterized for its interdependency on the process parameters [22,44–46]. Feed solution concentration, inlet air temperature, and air flow rate can be counted as process parameters having a potential effect on yield, particle size, and distribution and drying efficiency as outputs.

3. GMP compliance

Quality assurance employs rules and regulations under standardized conditions to ensure that the "quality" is consistent by manufacturing and controlling the product with quality standards, specifications, and regulatory requirements, thus GMP. GMP is embedded in quality management systems (QMSs) to ensure quality by verification of facilities, utilities and departments, equipment, and processes.

The "Quality Measures Manual" is a master document describing the regulations that the pharmaceutical company follows, ensures that products and services meet the demands, defines the implementation of all elements of the QMs with applicable policies and responsibilities, and shows the processes and their interaction(s) [6]. Standard operating procedures are clear instructions written in sufficient detail for routine operations to ensure efficient, analyst/performer-independent, accurate and high-quality output and/or performance, without leaving any room for interpretations.

Qualification and validation should establish and provide written proof that the facilities, utilities and departments, the equipment, and the processes have been designed in accordance with the requirements of GMP (Design Qualification), have been built and installed in compliance with their design specifications (Installation Qualification), and are in accordance with their design specifications (Operational Qualification). To ensure that such facility, equipment, or process must meet predetermined specifications and quality attributes, further continuous-routine qualifications are performed in a timely manner (Process Validation or Performance Qualification). To ensure continued validated and qualified status of facilities, utilities and departments, equipment, and processes a change control should be performed. All validation and qualification activities are defined in the Validation Master Plan.

GMP ensures quality by verifying that the product meets the specifications derived from the CQAs. For this reason, one must assess the potential impact of changes or fluctuations on the CQAs during manufacturing. One possible solution is integration of continuous process monitoring, including IPCs, assessing the robustness of the method, and accordingly designing the control strategy to minimize the chances of a product failure. Process analytical technology guidance from the US Food and Drug Administration (FDA) and the QbD approach by the International Conference on Harmonization are the tools suggested by authorities as an integrated part of control strategy. Not only does the manufacturing process need to be complaint to GMP conditions but also the physicochemical characterization methods must ensure efficacy, consistency and safety of the final product. Thus the effect of manufacturing processes on physicochemical properties of the nanoparticles should be well understood and the regulatory requirements should be taken into consideration. This knowledge can be obtained by employing QbD during the development and scale-up phase, as already discussed in the previous sections.

When SbD is considered, the main aim is to realize "Safe Products" by design, thus developing less hazardous nanopharmaceutical DDSs based on chemical and other properties. The assessment and management of risks of nanopharmaceutical DDSs is shown in Fig. 11.3, identifying, characterizing, and testing via safety assessment tools that nanopharmaceutical DDSs can be developed as "safe" by gradual optimization. Later, at a suitable stage in project, researcher and public awareness must be raised by guidance and training. Industrial safety during manufacturing of nanopharmaceutical DDSs is not within the scope of this chapter; however, industrial safety assessment and enhancement cannot be neglected. Additionally, SbD applies not only to the products and their uses, but also to their production conditions, since chronic exposure is a critical problem.

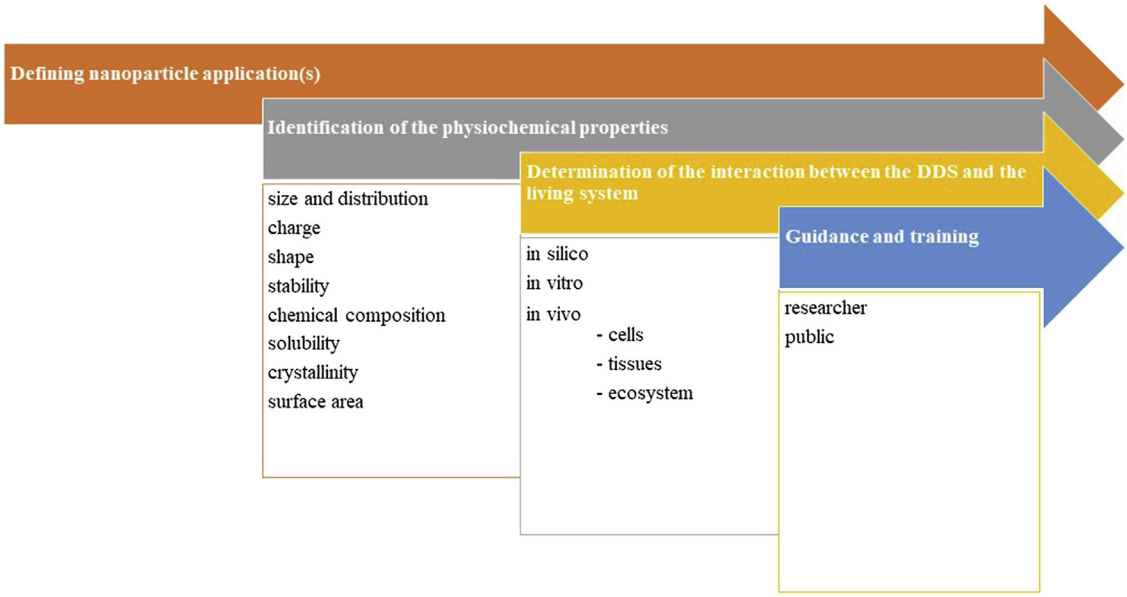

FIGURE 11.3 Risk analysis process. *DDS*, Drug delivery system.

As shown in Fig. 11.3, once the application of nanoparticles is defined, these particles must be characterized extensively for their physicochemical properties and CQAs must be defined. Such characterizations include but are not limited to physical characterization:

- Particle size, size distribution, shape, and morphology using electron microscopy
  - Particle size and size distribution determination using light scattering techniques (orthogonal measurement to electron microscopy)
- Zeta potential determination
- Viscosity
- Solubility
- Surface area
- Crystallinity
  - X-ray powder diffraction
- Release kinetics

chemical characterization:

- Composition analysis
  - Organic content with liquid chromatography-mass spectrometry, inorganic elemental analysis by inductively coupled plasma spectroscopy, or electron microscopy with energy-dispersive X-ray spectroscopy
- Chemical information
  - Fourier transform infrared, Raman, or nuclear magnetic resonance spectroscopy
- Purity and impurities
- Surface chemistry/surface analysis
  - Time-of-flight secondary ion mass spectrometry or X-ray photoelectron spectroscopy

The FDA has already made two guidelines available on topics relating to pharmaceutical products and DDSs: "Final Guidance for Industry—Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology"[1] and "Draft Guidance for Industry—Drug Products, Including Biological Products, That Contain Nanomaterials."[2] These guidelines make suggestions in detail for minimum requirements on nanopharmaceutical DDS characterizations.

CQAs must also be evaluated for their function and potential impact on product safety, in addition to product performance. The risk assessments should link the CQAs to product safety, and their effect on safety and performance must be assessed in case of changes or fluctuations.

A major uncertainty in risk assessment is the lack of understanding on how and to what extent biochemical interactions and eventually reactions occur at the molecular level of the nanoparticle surface with biological fluids, cells, tissues, and systems, e.g., receptor-specific interactions, overcoming biological barriers, corona effect, etc. Further information on such interactions would enable risk prediction of a specific pharmaceutical DDS (qualitatively and quantitatively). During recent years there has been tremendous effort to close this information gap via in vitro [12,47–49], in silico [8,22,50–53], and in vivo [16,31,35,54,55] assays and tests.

4. Conclusion

Since the mid-1990s, following the very first FDA-approved nanopharmaceutical DDS, nanotechnology has been very popular thanks to the innovative solutions it can offer to the

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considering-whether-fda-regulated-product-involves-application-nanotechnology

[2] https://www.fda.gov/media/109910/download

major challenges of the pharmaceutical industry. Nanotechnological strategies are attractive solutions to improve the bioavailability of poorly soluble drugs, and to improve therapies, in vivo imaging, and in vitro diagnostics, as well as the production of biomaterials and active implants [56]. However, multidisciplinary scientific understanding and regulatory definition of nanomedicines are still not satisfactory. This knowledge and guidance gap are leaving the pharmaceutical industry behind in its attempt to find the best match for different sections and stages of development, and thus clinical tests. Despite the tremendous efforts to standardize the development and approval of nanopharmaceutical DDSs made by governmental and private agencies, translation from lab to market remains a challenge to all key players of the pharmaceutical industry.

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