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ROADMAP AND CONSENSUS PROTOCOLS FOR GMP PRODUCTION OF CHEMICAL ENTITIES AND NANOMEDICINES

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1. Bench to bed-side: Overcoming obstacles of large-scale manufacturing

In recent years, nanotechnologies applied to Nanomedicine offered engineered, tunable nanoparticles as an intriguing tool able to solve unmet problems in healthcare potentially. Economic expectations on nanotechnology predict a strategic and highly competitive market of about 1-3 thousand billion dollars by 2020. However, only a small number of the developments could make it to the world market in comparison the published work. The challenges of bridging the translational gap between lab and practice in the industrial context should be considered at early stages of the development. [1] Therefore, several efforts are required to fill the gap between labs and market, and sustain translational research aimed to the development of nanotechnology products, which can have a realistic application in clinical practice.

Recent developments on nano and microparticle formulations moved beyond simple particle types. More complex systems and set-up are required to cover the different aspects of the drug delivery ideas. Current top down nanoparticle manufacturing equipment such as milling techniques are limited with single type of nanoparticles and are not applicable to all substances. [2,3] Particle size can only be moderately controlled using these methods whereas the importance of the particle size and the homogeneity of the particle size is long being discussed for their effect on physiological processes. Polymeric nanoparticles such as enteric coated nanoparticles or extended release nanoparticles for parenteral applications, on the other hand, gaining importance for drug delivery systems. The production of these nanoparticle types in small scale is realised by many researchers but transfer to a commercial scale under current Good Manufacturing Practices (cGMP) conditions is one of the biggest challenges which remains to be solved. [4]

We need strategies, equipment and facilities that can reduce time-to-market for innovative formulations, reduce manufacturing and disposal costs, reduce energy consumption and finally can produce nano/microparticles, emulsions and encapsulations. Additionally, early establishment of strategies for ensuring the safety and quality of medications via Quality-by-Design (QbD) and Safe-by-Design (SbD) approaches ensure fulfilling regulatory requirements at the later stages. [5]

An up-to-date-technology has to show the following target profile:

- *Suitable for GMP-Production*
- *Identical hardware for small- and large-scale batch production or easy scale-up procedures*
- *Low cost*
- *Short production time*
- *Batch-to-batch reproducibility*

2. Prerequisites

cGMP does not only regulate the processes directly related to the manufacturing process in a pharmaceutical company but also all the related areas, premises and other processes, including equipment validations, hygiene, training and staff. cGMP aims reducing the risks that might be

encountered during pharmaceutical production and might have a direct effect on the critical quality attributes (CQA) of final product by identifying those critical process parameters (CPP) through testing the final product. GMP is an integrated part of pharmaceutical Quality Management (QM) System which ensures quality by verification, qualification and standardization of premises, equipment and processes. [1]

The requirements of GMP guidelines are complemented by ICH Guideline Q10 (Pharmaceutical Quality System)[1]. The Guideline ICH Q10, which has since been included in Part III of the EU GMP Guide, has three main quality objectives:

- *Product realization: The aim of the pharmaceutical QM system is to enable products to be manufactured in such a way that their CQA meet the needs of patients, doctors and authorities.*
- *Control and monitoring: The manufacturer should establish suitable monitoring and control processes in order to ensure the suitability and process capability of its processes.*
- *Continuous improvement: The manufacturer is obliged to identify and implement improvement possibilities with regard to its products, processes and systems. In doing so, he should base his knowledge on the current state of knowledge.*

2.1. DISTINGUISHING THE REQUIREMENTS FOR NANOSOLUTION AND NANOSUSPENSIONS AND NANOPARTICULATE MATTER CONTAINING FORMULATIONS

The European Commission defines a nanomaterial as “a natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm”[2].

Over the last decades, a wide range of nanocompounds for medical use have been developed with increasing sophistication levels. Engineered nanoparticles intentionally produced and designed with very specific properties in relation to their shape, size, surface properties and chemistry have provided a significant resource for nanomedicine. However, the physico-chemical properties of nanoparticle-based delivery platforms introduce complexity. Such complexity increases particle heterogeneity, thus delays clinical translation. Therefore, several efforts are required to fill the gap between research labs and market to sustain translational research aimed at the development of nanomedicines which have a realistic application potential in the clinic.

There is an immediate need for establishment of relevant methods, equipments and processes for nanoparticle characterization under GMP. The current regulatory barriers to commercialization are recognized by both industry and regulators. However, to date, no guideline or pharmacopeia chapter

[1] https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q10/Step4/Q10_Guideline.pdf

[2] European Commission (2013), Communication from the Commission to the European Parliament, the Council and the EESC. Second regulatory review on nanomaterials. Brussels, 3.10.2012, COM(2012) 572 final

has been dedicated to minimum requirements for characterization of nanotechnology products. EMA is developing guidance on the use of nanomaterials.

Scale-up and optimization of the manufacturing processes for particles must be performed and all necessary documentation must be elaborated. The leap from the lab to the market is possible only by complying with EC regulation policy and applicability to industrial scales. The clinical translation of nanoparticles is an expensive and time-consuming process.

2.2. PHARMA GRADE AND CERTIFIED STARTING MATERIALS

Nanomedicine production under GMP requires certified and compliant active substances as starting materials. Even active substance aspect is considered during the lab scale, research period inactive raw materials (excipients) are often neglected. However, some physicochemical properties of those inactive formulation components might be critical material attributes (CMA) for the performance of the nanomedicine in-vivo. Successful scale-up and GMP compliant manufacturing would rely on careful selection and screening of starting materials and their suppliers as an integrated part of QbD. [6]

Thus, starting immediately at very early phases, a special attention should be given to selection of active and inactive components among already approved raw materials (compendial materials), if possible. If not, selection should be made among the substances that have Generally Accepted as Safe (GRAS) status. Failure to do so would delay market entry, since adequate toxicity data is prerequisite of clearance for clinical trials.

Current trends in the development includes chemical modification of (bio)materials for better performance. In case of modification of already approved (in)active substances, scale-up and GMP compliance aspect must be also taken into consideration. Those materials must be shown to comply with compendial rules and guidelines. And the most important of all, they must be produced with methods that enables availability at industrial scales.

2.3. GOOD DOCUMENTATION PRACTICES (GDP) AT EARLY STAGES

Good Documentation Practices (GDP) collectively and individually ensure documentation, whether paper or electronic, is attributable, legible, traceable, permanent, contemporaneously recorded, original and accurate. It is to be ensured that all researchers follow a uniform documentation status and that the implementation can be traced completely at any time and by every other researcher.

According to EU-GMP-Guidelines Capital 4 Part 1, a document should, by definition, provide evidence, record an event or fact, possibly also make arrangements for the future. All documents summarize a certain number and form of information, which, taken in isolation, form a unity that can no longer be separated without loss of information or meaning. In this sense, all instructions, protocols, laboratory journals, equipment books, etc. may be referred to as documents.

Some examples of GMP relevant document at research and development is provided below but not limited to:

- *maintenance, repair and cleaning of equipment and equipment (logbooks)*

- *calibration / qualification of laboratory equipment*
- *measures in case of deviations*
- *labelling and packaging of containers*
- *records of controls*
- *documentation of storage including Incoming goods*
- *analytical method validation*
- *handling standards and reagents*

2.3.1. General quality characteristics of GDP

All documents should follow below listed requirements:

- Handwritten entries must be easy to read and undeletable (usually with qualified blue pencil, not a pencil)
- The documentation should be correct. The verification of critical data is done according to the four-eyes principle, e.g. by means of cross-checking by a second person or by means of validated electronic procedures. (for example, when documenting pH values in case of printer failure)
- All instructions and records must be made and kept in a complete format. The completeness of a document should be easily recognizable and verifiable, e.g. by giving the complete page number and a table of contents
- Document content must be accurate enough to ensure the desired use. Unclear documentations should therefore be avoided. Terms like "generally", "mostly", "usually" are indicators of inaccuracy in the documentation.

2.3.2. Revision and correction of documents

In both instructions (e.g. SOPs) and records, no changes should be made that do not indicate whether they were made at the original entry or later. If changes are made to records, it should subsequently be possible to identify what the original content of the entry was. Therefore, the use of Tipp-Ex to correct overwriting, pasting over or just individual letters / numbers is inadmissible. If entries need to be corrected, the original entry should be crossed out so that it remains readable. The correction should be written so that a connection with the original entry remains recognizable. In addition, a signature / abbreviation of the person who made the correction and the date of correction and justification for the correction are required.

If a change of an already approved document (e.g. SOP) is necessary, a new version of the document should be released depending on the content of the change. The new document gets the next consecutive number (version number).

2.4. DETERMINATION OF CQA AND CONTROL STRATEGY AT EARLY STAGES

CQAs have relevance for clinical success and industrial sustainability of a developed product, as they are direct measures to safety and efficacy. Information from pharmaceutical development studies can be a basis for quality risk management. ICH Q8 Pharmaceutical Development [3] provides following definitions;

Quality Target Product Profile (QTPP): A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.

Critical Quality Attribute (CQA): A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Critical Process Parameter (CPP): A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

And overall of those aspects to be considered during the pharmaceutical development, a control strategy which deals collectively and individually with the above listed points, is required. Again, by ICH Q8 definition, **Control Strategy** is a planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

Control Strategy includes following elements (but not limited to):

- *Input material attributes (e.g. drug substance, excipients, container closure)*
- *Equipment operating conditions (process parameters)*
- *In-process controls*
- *Finished product specifications*
- *Controls for each unit operations*
- *Methods and frequency of monitoring and control*

Depending on the target product profile, CQAs might differ. However, particle size might be one of the most common quality attributes which determines the physiological faith of the particles in human body. Thus, manufacturing methods which can easily adjust the particle size to desired limits without sacrificing the homogeneity of the particle distribution is necessary to meet the market needs. Particle size is a batch size dependent parameter especially for the batch reactors and milling processes. In such processes, it is very difficult to stabilize the particle size to desired values with the increase in batch size. Manufacturing of particles within predefined size specification according

[3] https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf

to GMP regulations requires an efficiently controlled setup to be able to meet the quality standards in such complex particle systems.

In addition to particle size, shape, surface properties, crystallinity, stability or solubility can be CQAs. Identification and analysis of those CQAs are more complicated than the traditional bulk materials used in pharma-industry. Therefore, definition of CQAs and accordingly the control strategy to ensure quality and safety, a deep understanding of requirements both at GMP and nanotechnological development is required. An early integration of those aspects in the development is a key factor for reducing the time to market.

2.5. UNDERSTANDING THE GMP REQUIREMENTS DURING THE DEVELOPMENT PHASE AND INTEGRATION OF THOSE GUIDELINES ALREADY AT THE DEVELOPMENT LEVEL

GMP defines a set of regulations for the pharmaceutical industry that is EU- and U.S.-wide accepted, in order to ensure that quality is guaranteed and sustained throughout the whole supply chain. ICH Q8 Pharmaceutical Development guideline describes the principles of quality by design (QbD) and shows how concepts and tools (e.g., design space) could be put into practice for all dosage forms. QbD is defined as a systematic approach to development that begins with predefined objectives and emphasizes product and `process understanding and process control. Here design spaces serve as multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality. Finally, control strategies which are planned set of controls, derived from current product and process understanding, ensures process performance and product quality.

Application of quality by design and quality risk management according to guideline ICH Q9: Quality Risk Management, linked to an appropriate pharmaceutical quality system according to ICH Q10, provides opportunities to enhance science- and risk-based regulatory approaches.[4]

2.5.1. SOP generation at early stages both for analytical methods (characterization) and manufacturing

When we read the GMP and ICH guidelines, the demands of pharmaceutical QM system is perceived as abstract and many fail to properly address those requirements. Therefore, it is important to implement standard operating procedures (SOPs) clearly describing tasks, processes and responsibilities within a certain company, institution or facility. SOPs contain instructions of a foundation defines all tasks and at the same time specifies which employee is responsible for what. It is therefore important to proclaim the active involvement of QM in the individual SOPs. By this way, it does not remain optional or abstract and requires the implementation of the pharmaceutical QM according to the workflows described in the individual SOPs.

[4] https://www.ich.org/products/guidelines/quality/article/quality-guidelines.html

2.5.2. Early establishment of QC and IPC

Process analytical technology (PAT) guidance from US Food and Drug Administration (FDA)[5] and QbD approach by the International Conference on Harmonization (ICH) are the tools suggested by authorities as an integrated part of control strategy. The control strategy must be GMP compliant both for manufacturing process and physicochemical characterization methods to ensure efficacy and safety of final product. The control strategy should include following characterizations but is not limited to:

- *Particle size, size distribution, shape and morphology using orthogonal techniques such as electron microscopy and light scattering techniques,*
- *Zeta potential for defining the surface charge,*
- *Surface area*
- *Crystallinity (e.g. with XRD)*
- *Release kinetics*
- *Composition analysis for organic content and inorganic elemental analysis*
- *Purity and impurities*
- *Chemical information (e.g. FTIR, NMR, spectroscopy)*

Critical in-process controls (and their monitoring), including the control time points and in-process control methods, should be stated in writing (e.g. in form of SOPs). These procedures should describe the sampling methods and conducted using procedures designed to prevent contamination.

Critical process parameters (CPP) have to be identified and monitored for optimized manufacturing process. A parameter range has to be defined by using a specific experimental design exploring the limitations of a preparation process with regards to process stability (robustness) and batch-to-batch reproducibility. Depending on the complexity of the preparation process a Design of Experiments (DoE) approach can be undertaken to evaluate a key parameter range and its influence on product specifications. Experimental design can be used effectively for selecting the key factors affecting a response or optimizing responses.

2.5.3. Training of the personnel already at the lab scale

ICH guideline Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients require that there should be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the manufacture of intermediates and APIs.[6] Trainings should be periodically assessed. These trainings should include but not limited to:

- *GDP,*

[5] FDA guidance for industry: Process Validation: General Principles and Practices (2011), FDA guidance for industry: PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance (2004)

[6] https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q7/Step4/Q7_Guideline.pdf

- *Safety,*
- *Handling nanomaterials,*
- *Hygiene,*
- *Equipment operation,*
- *Equipment qualifications,*
- *Etc.*

Training is recognized in the preamble to the cGMP regulations as a dynamic process ensuring skilled workforce, improved productivity, and higher levels of product and service quality[7]. The training program should depend on the criticality of the operation performed. Training should be given by a qualified person.

SOPs need to be effectively applied into practical activities executed in manufacturing. Trainings minimize possible mistakes that can be related to false interpretation of SOPs or lack of knowledge on the processes in case of lack of SOPs. By this way, alterations and deviations can be avoided.

2.5.4. Validations

Regardless of the application, the objective of validation of a procedure is to demonstrate that it is suitable for its intended purpose.

2.5.4.1. METHOD VALIDATION

Analytic method development and validation are key elements of any pharmaceutical development program. Often considered routine, too little attention is paid to them with regards for their potential to contribute to overall developmental time and cost efficiency. These method related activities are interrelated. They are iterative, particularly during early drug development phases. Parts of each process may occur concurrently or be refined at various phases of drug development. Changes encountered during drug development may require modifications to existing analytic methods. Additionally, owing to their unique size-dependent properties, nanomedicine characterization requires specific analytical methods for characterization of CQAs.

ICH defines following procedures as the most common types ones:

- *Identification tests*
- *Quantitative assays*
- *Qualitative and quantitative tests for impurities*
- *Dissolution testing (release testing)*

Additionally, FDA suggests use of different strategies to ensure that the developed methods are stability indicating[8]. In its very short terms, this means that the method should be capable of

[7] A WHO guide to good manufacturing practice (GMP) requirements – Part 3: Training, accessed on September 2019
[8] https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf

accurately measures the active ingredients, without interference from degradation products, process impurities, excipients, or other potential impurities, and can detect the changes of properties of the drug substance and drug product over time.

Both ICH and FDA agree on the (bio)analytical parameters to ensure method validation suitability:

- *Selectivity and specificity*
- *Sensitivity*
- *Linearity (Calibration curve)*
- *Accuracy*
- *Precision*
- *Recovery*
- *Stability of the analyte (eventually in the matrix for bioanalytical samples)*
- *QC samples*
- *Reference standards*

2.5.4.2. PROCESS VALIDATION

One of the most common pitfalls for innovative nanomedicine is the suitability of the manufacturing method and equipment used and the need for process validation and equipment qualification concepts. ICH guidelines require that the data and know-how generated during development studies should provide the basis for process improvement, validation (or verification), and any IPC to be integrated.

Minor changes in manufacturing of nanomedicines or a small mistake in their characterization might affect their quality and safety. For this reason, precise control of the manufacturing process is required. [4]

2.5.4.3. CLEANING VALIDATION AND CROSS CONTAMINATION PREVENTION

The cleaning process must be validated by pharmaceutical manufacturers with cGMP regulations. Formally, “Cleaning validation is documented evidence that an approved cleaning procedure will reproducibly remove the previous product or cleaning agents used in the equipment below the scientifically set maximum allowable carryover level”. The efficiency of cleaning process must be determined by a quality control process for a specific cleaning event[9].

Cross contamination is the contamination of start material or intermediate product, or end-product with another material or product during production, sampling, packing, storage or transport. Cross contamination in pharmaceuticals has become a huge concern and avoiding the contamination is very critical and the appropriate technical or organizational precautions must be followed to avoid it. Among them, separation of production areas especially required for products like penicillin, live vaccines; or separation in time followed by appropriate cleaning; providing appropriate air lock and air extraction systems; minimizing the re-circulation of insufficiently treated air; avoiding the risk of

[9] PIC/S Guide to GMP for Medicinal Products; Annex 15 Qualification & Validation, accessed on September 2019

contamination by protective cloths by keeping them inside, following the cleaning procedures for effective cleaning of equipment which is the common reason of cross-contamination; production by using "closed systems"[10].

3. BOTTLENECKS

3.1. DIFFICULTIES IN STANDARDIZATION WITHIN LAB AND INTER-LAB

As already stated in the Nano2Clinic proposal, because nanotechnology is such a new field, there are few standards and few reference physical and biological characterization data that researchers can use to choose which nanodevices might be most suitable for a given clinical or research application. A lack of standard assay and characterization methods also makes it difficult to compare results from different laboratories.

In order to overcome this problem, integrating the GMP requirements at early stages plays a crucial role. Use of SOPs, person dedicated lab journals following GDP, method validations and training of the personnel can be listed as key elements for preventing analyst-, lab- and chemicals charge-dependent inter- and intra-lab differences. Reproducibility can be achieved.

3.2. ACQUIRING PHARMA GRADE STARTING MATERIALS

Any material used in the pharmaceutical (nano)drug product should to be manufactured under appropriate manufacturing practices and supplied under good distribution practices. The exact definition of "appropriate" manufacturing and distribution depends on the starting material by its role in the formulation as active or inactive ingredients.

The European Pharmacopoeia (Ph.Eur.), the United States Pharmacopeia – National Formulary (USP-NF), and the British Pharmacopoeia (BP) describe the quality requirement of substances to be used in (nano)formulations, their test methods and the limit of critical properties in a dedicated monograph to assure the safety and quality of the excipient. Monographs also provide the analytical methods and specifications.

Although excipient (inactive ingredients) qualification does not directly require regulatory certification, such substances must be capable of satisfying the requirements for being used in a (nano)medicine formulation. This can be achieved by working with excipients that have a certificate of specifications (CoS) and a certificate of analysis (CoA) accordingly. Another strategy might be first running a screening for confirming approved use of selected excipient. The FDA database for inactive ingredients can be employed as a useful and trustworthy source[11]. Once the excipient comes with a hit in the database, it is listed by name, dosage form, and the maximum amount of excipient contained in an approved drug of that listed dosage form. Special attention should also be given to the dosage form and amount in that dosage form, since allowed ranges might differ depending on the dosage form. In EU, to our best knowledge there isn't a comparable databank that offers the list of approved excipients. However, scientist are encouraged to search drug catalogues such as the

[10] https://www.hpra.ie/docs/default-source/default-document-library/5-2-cleaning-validation.pdf?sfvrsn=0 , **accessed on September 2019**
[11] https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm

"Die Rote Liste" (Germany), "Dictionnaire Vidal" (France), or "The Electronic Medicines Compendium" (UK).

When a previously in any dosage form not approved excipient is intended for use in a (nano)formulation, a series of test and analysis must be performed to demonstrate their quality and safety and submitted to European and US regulatory authorities.

3.3. DIFFICULTIES IN TRANSLATING LAB METHOD TO INDUSTRIAL METHODS

In the scale-up process, the physicochemical properties of nanoparticle need to be maintained. These include particle size distribution, drug loading and drug release profiles. To achieve these, the relationship between manufacturing processes and physicochemical properties of the nanoparticles should be understood. As well as these in the scale-up process, the regulatory requirements should be met. This is to ensure reproducibility, efficacy and safety of GMP grade products.

Most of the researchers employ repeated centrifugation as washing step of their manufacturing process for purification purposes. However, centrifugation at larger scale comes along with costs associated with the investment on a suitable equipment, its maintenance and also qualification. Additionally, purification based on centrifugation might be time intensive. Another common approach is dialysis of the samples, where the sample is inserted in an exchange medium of an extremely large volume in comparison to suspension to be purified. Dialysis might take days till the specifications are reached. At industrial scales, these methods are ought to be replaced by cost-friendly and GMP compliant methods. Tangential flow filtration (TFF) offers a solution to above listed bottlenecks. TFF is continuous separation method and it can be easily transferred to GMP environment without any batch size limitations. CFF set-up can be easily qualified for GMP compliance and process validation can be easily performed. On the other hand, use of CFF comes along with an extra method development step for using the right system components (e.g. membrane type and size) and parameters (flow rates, washing times etc.).

3.4. COST VS. CHOICE OF INDICATION

Many nano based formulations, either passively or actively target a tumor site, are being developed for cancer treatment [7,8]. Efficiency of passive targeting on tumor accumulation enhancement, decreased normal tissue exposure has been already shown with many preclinical and clinical studies[9]. However, proving efficacy of active targeting is much more complicated and not easy to achieve [8,10,11]. In most of the approved nano-enabled formulations, an already approved active pharmaceutical ingredient is nanoformulated. One cannot neglect that working with already approved active pharmaceutical ingredients reduce the costs dramatically since all the efficacy and safety is shown. Thus, financial risk is much less in comparison to a novel substance. Manufacturing new substance based nanoformulations come along also with extra financial burden, also due to the Chemistry, Manufacturing, and Controls (CMC) requirements of cGMP. If the innovative nano-enabled substance or formulation requires use of a specific equipment that is not commercially available yet (thus lacking all the qualification info/data), thus burden is dramatically increased.

As a consequence, people tend to go for cheap clinicals and sacrifice the versality, even a better performance can be achieved by more complex systems. Literature shows that in comparison to the large amount of investment required till the clinical phase is reached, the number of nano-enabled formulation that have been approved is relatively small [7,8].

3.5. INTERDEPENDENT COMPANIES AND LACK OF CENTRES WITH COMBINED KNOW-HOW AND INFRASTRUCTURE

Many promising results are obtained across Europe and US for high quality, safe nanoformulations. However, there are many challenges on the way from bench-to-bedside development of nanomedicines. These include but not limited to regulatory gap, industrial applicability and quality control aspects, GMP quality production, stability and in sufficient quantity (pilot-scale) for late pre-clinical and clinical testing. Accordingly, as already stated in the Nano2Clinics COST-Action description, there is unmet need for developing and strengthening industry-academia relations for fostering the clinical translation of nanomedicine from bench to bedside. Considering the multidisciplinary aspects involved in a nano-pharmaceutical product development, a single entry point for the development, testing and upscaling of nanoformulations is urgently needed.

4. CURRENT STATE-OF-THE-ART FOR UPSCALING

4.1. DARWIN MICROFLUIDIC CHIPS

Micro-channels form the microfluidic chip by etching or molding into materials like glass, silicon or polymer commonly Polydimethylsiloxane (PDMS). The desired features like mixing, pumping, sorting or controlling the biochemical environment are achieved by the connected micro-channels. The microfluidic chip is connected to the outside by inlet and outlet openings. The injection and removal of the liquids or gases from the microfluidic chip is through these openings. On this purpose, external active systems are added such as pressure controller, peristaltic pump; or passive ways are used such as hydrostatic pressure. A wide variety of solutions for flow control can be found on Darwin Microfluidics[12].

4.2. ADVANCE MATERIAL TECHNOLOGY (COFLORE)

The high performance, versatility and scalability of dynamic flow reactors overcome the critical difficulties for process development and scale-up. Coflore dynamic mixing generates efficient mixing without mechanical seals or rotating shafts. The reactors provide excellent mixing, low axial distribution for good plug flow, low pressure drop from simple geometry, easy handling without blocking, they are suitable and easy to clean for also GMP application. The Coflore Agitated Cell Reactor (ACR) is a low throughput dynamic flow reactor with a channel divided into ten discrete stages which maintain the flow from 10 seconds to 10 hours of reaction time. The other features are integral heating and cooling, temperature monitoring, operating up to 10 bar, multistage addition and sampling. ACR system is developed for laboratory use with capacities of 10 mL to 100mL. The

[12] https://www.elveflow.com/microfluidic-tutorials/microfluidic-reviews-and-tutorials/microfluidics-and-microfluidic-device-a-review/ , accessed on September 2019

independency of the parameters like reaction time, tube length or tube diameter from flow and mixing, simplify the scale-up. The system can be scaled up to pilot or production plant via Coflore Agitated Tube Reactor (ATR) and Coflore RTR, 10L and 100L respectively [13].

4.3. MICROJET REACTOR TECHNOLOGY

MicroJet Reactor (MJR) is a GMP compliant bottom up platform for the continuous production of micro and nanoparticles. MJR is designed to enable production of different particles types including nanoemulsions, nanocrystals, polymer encapsulated particles, amorphous particles, extended release particle systems under cGMP.

MJR with confined impinging jet principle, enables very high-quality, homogeneous distributed particle production. Combined with quality by design, efficient production of highly specialized, customized particles with narrow particle size distribution is succeeded. Particle size is efficiently controlled to the desired values through production parameters such flow rate, temperature and pressure. [12] Furthermore, MJR technology can be utilized for the manufacturing of multilayer particles where particles are coated with additional polymer layers to modulate the particle characteristics. In addition to increased efficiency in preparation owing to manufacturing under controlled conditions, utilising MJR eliminates the disadvantages and bottlenecks of the traditional preparation techniques, such as high cost equipment, limited batch sizes, long production times and applicability to only single particle types.

MJR is designed to meet the batch requirements of pharmaceutical industry even for high volume products. Production volumes up to 600L/hour using a single reactor can be realized with MJR technology. Due to continuous art of manufacturing under controlled conditions, the quality and the homogeneity of the particles stay constant throughout the manufacturing process. Continuous manufacturing of the particles is strongly controlled by simple process parameters stabilizing the particle size throughout the entire batch.

MJR technology is a continuous manufacturing process which allows the production of different batch sizes from 1 kg up to 250 kg batches using the same equipment. In other words, production of small CTM batches and also full-scale commercial batches can be realized using the same equipment.

It is a manufacturing platform where no limitation on particle types or batch sizes apply. Particle size and batch size can be freely determined without effecting the quality of the particles.

4.4. BATCH REACTORS WITH CONTROLLABLE PROCESS UNITS AND VARIABLE STIRRERS

The optimization of batch reactors has many potential advantages, including better productivity and higher safety, good quality of product, and batch-to batch determinedness. Reaction temperature is used commonly as the controlled parameter in process control. It may affect the reaction rate, side reactions, distribution of side products, or polymer molecular weight and molecular weight

[13] http://pi-inc.co/assets/brochures/Coflore-brochure.pdf , , accessed on September 2019

distribution. As many reactions are exothermic in order to control reaction temperature, the released heat must be controlled by the system. Besides that, the reactor pressure is a function of batch temperature in a process where the reactor pressure is essentially the vapor pressure. In gas phase reactions, in oxidation and hydrogenation reactions, or in high-pressure polymerization, the reaction rate is also a function of pressure. In a controlled reactor system, some features should be provided such as the ability to maximize production and minimize shutdowns, the ability to minimize the variations in utility and raw material demand, the ability to provide constant conversion, yield, and product distribution, easy start-up and shutdown [13].

5. CURRENT REGULATORY STATE FOR GMP APPLIED TO NANOPARTICLES

Nanomedicinal products are mostly evaluated as dictated for the conventional formulations in a regulatory context. Many attempts have been made by publishing several scientific opinions, however, to our best knowledge, to-date there are no guidelines or pharmacopeia chapter has been dedicated to minimum requirements for manufacturing, characterization or release of nanotechnology based pharmaceutical products. In one of the latest communications, FDA announced that existing guidelines are expected to apply for nanotechnology products and they reflect the FDA`s current opinion on all the aspects of GMP manufacturing of nanopharmaceuticals. [1] Some of the existing guidance documents, originally intended for conventional formulations but expected to be applied for pharmaceutical nanotechnology products, whenever applicable, are listed in the following section. Please also note that some of the guideline are accepted and released by both regulatory authorities. To facilitate the reading, such guidelines are provided only once under one of the listed authorities. We also strongly encourage the reader to refer to The Nanotechnology Characterization Laboratory (NCL) SOPs. NCL has already developed a standardized analytical cascade that tests the preclinical toxicology, pharmacology, and efficacy of nanoparticles and devices[14].

5.1. EXISTING GUIDELINES

ICH Guidelines [15]

Quality:

Q1A - Q1F Stability

Q2 Analytical Validation

Q3A - Q3D Impurities

Q4 - Q4B Pharmacopoeias

Q5A - Q5E Quality of Biotechnological Products

Q6A- Q6B Specifications

Q7 Good Manufacturing Practice

[14] https://ncl.cancer.gov/resources/assay-cascade-protocols
[15] https://www.ich.org/products/guidelines.html

Q8 Pharmaceutical Development

Q9 Quality Risk Management

Q10 Pharmaceutical Quality System

Q11 Development and Manufacture of Drug Substances

Q12 Lifecycle Management

Q13 Continuous Manufacturing of Drug Substances and Drug Products

Q14 Analytical Procedure Development

Safety:

S1A - S1C Carcinogenicity Studies

S2 Genotoxicity Studies

S3A - S3B Toxicokinetics and Pharmacokinetics

S4 Toxicity Testing

S5 Reproductive Toxicology

S6 Biotechnological Products

S7A - S7B Pharmacology Studies

S8 Immunotoxicology Studies

S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

S10 Photosafety Evaluation

S11 Nonclinical Pediatric Safety

FDA guidance for industry [16]

Analytical Procedures and Method Validation: Chemistry, Manufacturing, and Controls Documentation

Comparability Protocols- Chemistry, Manufacturing, and Control Information

Current Good Manufacturing Practice for Combination Products

Residual Solvent in Drug Products Marketed in the United States

Guideline on General Principles of Process Validation

Good Laboratory Practice Regulations: Questions and Answers

Liposome Drug Products: Chemistry, Manufacturing, and Controls: Human Pharmokinetics and Bioavailability, and Labeling Documentation

Process Validation: General Principles and Practices

Developing Medical Imaging Drug and Biological Products Part I: Conducting Safety Assessment; Part II: Clinical Indications; Part III: Design, Analysis, and Interpretation of Clinical Studies

[16] https://www.fda.gov/animal-veterinary/guidance-regulations/guidance-industry

Content and Format of Investigational New Drug Applications (INDs) for Phase I Studies for Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products

Early Development Considerations for Innovative Combination Products

Guidance for Reviewers: Pharmacology/Toxicology Review Format

Guidelines for Submitting Documentation for Manufacture of and Control for Drug Products

Guidelines for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances

Drug Interaction Studies-Study Design, Data Analysis, and Implications for Dosing and Labelling

Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In-Vitro

Non-Clinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternative Route

Non-Clinical Studies for Safety Evaluation of Pharmaceutical Excipients

Safety Testing of Drug Metabolites

Single Dose Acute Toxicity Testing for Pharmaceuticals

Statistical Aspects of the Design, Analysis and Interpretation for Chronic Rodent Carcinogenicity Studies of Pharmaceutical

FDA Nanotechnology Guidance Documents[17]

Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology

Safety of Nanomaterials in Cosmetic Products

Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives

Use of Nanomaterials in Food for Animals

Drug Products, Including Biological Products, that Contain Nanomaterials (Draft guidance)

[17] https://www.fda.gov/science-research/nanotechnology-programs-fda/nanotechnology-guidance-documents

References

[1] N. Günday Türeli, A.E. Türeli, Good Manufacturing Practices (GMP) of Magnetic Nanoparticles, in: N.T.. K. Thanh (Ed.), Clin. Appl. Magn. Nanoparticles, CRC Press, Taylor and Francis, Boca Raton London New York, 2018: pp. 473–482.

[2] J.K. Patra, G. Das, L.F. Fraceto, E.V.R. Campos, M.D.P. Rodriguez-Torres, L.S. Acosta-Torres, L.A. Diaz-Torres, R. Grillo, M.K. Swamy, S. Sharma, S. Habtemariam, H.-S. Shin, Nano based drug delivery systems: recent developments and future prospects, J. Nanobiotechnology. 16 (2018) 71. doi:10.1186/s12951-018-0392-8.

[3] C.A. Charitidis, P. Georgiou, M.A. Koklioti, A.-F. Trompeta, V. Markakis, Manufacturing nanomaterials: from research to industry, Manuf. Rev. 1 (2014). https://doi.org/10.1051/mfreview/2014009.

[4] M. Wacker, Nanocarriers for intravenous injection--the long hard road to the market., Int. J. Pharm. 457 (2013) 50–62. doi:10.1016/j.ijpharm.2013.08.079.

[5] J. Rantanen, J. Khinast, The Future of Pharmaceutical Manufacturing Sciences, J. Pharm. Sci. 104 (2015) 3612–3638. doi:10.1002/jps.24594.

[6] D.P. Elder, M. Kuentz, R. Holm, Pharmaceutical excipients — quality, regulatory and biopharmaceutical considerations, Eur. J. Pharm. Sci. 87 (2016) 88–99. doi:https://doi.org/10.1016/j.ejps.2015.12.018.

[7] C.L. Ventola, Progress in Nanomedicine: Approved and Investigational Nanodrugs, P T. 42 (2017) 742–755. https://www.ncbi.nlm.nih.gov/pubmed/29234213.

[8] H. Havel, G. Finch, P. Strode, M. Wolfgang, S. Zale, I. Bobe, H. Youssoufian, M. Peterson, M. Liu, Nanomedicines: From Bench to Bedside and Beyond, AAPS J. 18 (2016) 1373–1378. doi:10.1208/s12248-016-9961-7.

[9] J.M. Caster, A.N. Patel, T. Zhang, A. Wang, Investigational nanomedicines in 2016: a review of nanotherapeutics currently undergoing clinical trials., Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol. 9 (2017). doi:10.1002/wnan.1416.

[10] S.M. Moghimi, A.C. Hunter, J.C. Murray, Long-circulating and target-specific nanoparticles: theory to practice., Pharmacol. Rev. 53 (2001) 283–318.

[11] M.L. Immordino, F. Dosio, L. Cattel, Stealth liposomes: review of the basic science, rationale, and clinical applications, existing and potential., Int. J. Nanomedicine. 1 (2006) 297–315.

[12] N. Günday Türeli, A.E. Türeli, M. Schneider, Optimization of ciprofloxacin complex loaded PLGA nanoparticles for pulmonary treatment of cystic fibrosis infections: Design of experiments approach, Int. J. Pharm. 515 (2016) 343–351. doi:https://doi.org/10.1016/j.ijpharm.2016.10.025.

[13] D.C. KENDALL et al., Process Control and Optimization, in: Process Control Optim., 2006: p. VOLUME II.