Characterization of novel formulations

Continuation of the introduction

Issues that you can get

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on behalf of the EBF

EBF Focus Workshop

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Disclaimer

This presentation summarises a recent literature survey and was prepared for this Focus Workshop. As such, it has not yet been discussed/shared in the EBF community.

CONTENTS

- Restriction
- Novel formulations (NF)
- FDA and Nanomaterials (NM)
- Nanomaterial formulations
  - Dendrimer formulations
  - Liposomal formulations
- Conclusion

RESTRICTION

- Important but outside the scope:

  Characterization during development and preparation of novel formulations;

- In this contribution:
- Characterization of a final formulation to verify concentration and other relevant properties prior to dosing;
- Nanomaterials; Dendrimers and Liposomes
- Restricted mainly to bioanalytical applications

NOVEL FORMULATIONS

- Nanoparticles
  - Carbon
  - Silica based
  - Metal
- Dendrimer
- Exosomes
- Liposomes
- Pro-drug
- ….

FDA AND NM‘s

- 3 FDA guidance's related to **N**ano**M**aterials:
  1. FDA’s nanotechnology considerations guidance June 2014
  2. Drug Products Including Biological Products, that contain Nanomaterials. Draft Guidance Dec 2017
  3. Liposome Drug Products. Guidance April 2018

What are nanomaterials according to the FDA? (EMA)

No hard definition (yet) but material should have: (1) at least one external dimension, or an internal or surface structure, in the nanoscale range (1 to 100 nm): (2) in practice up to 1000 nm. (From 1.)

Essential: unique properties, based upon its dimension, which differ from the corresponding macromaterials

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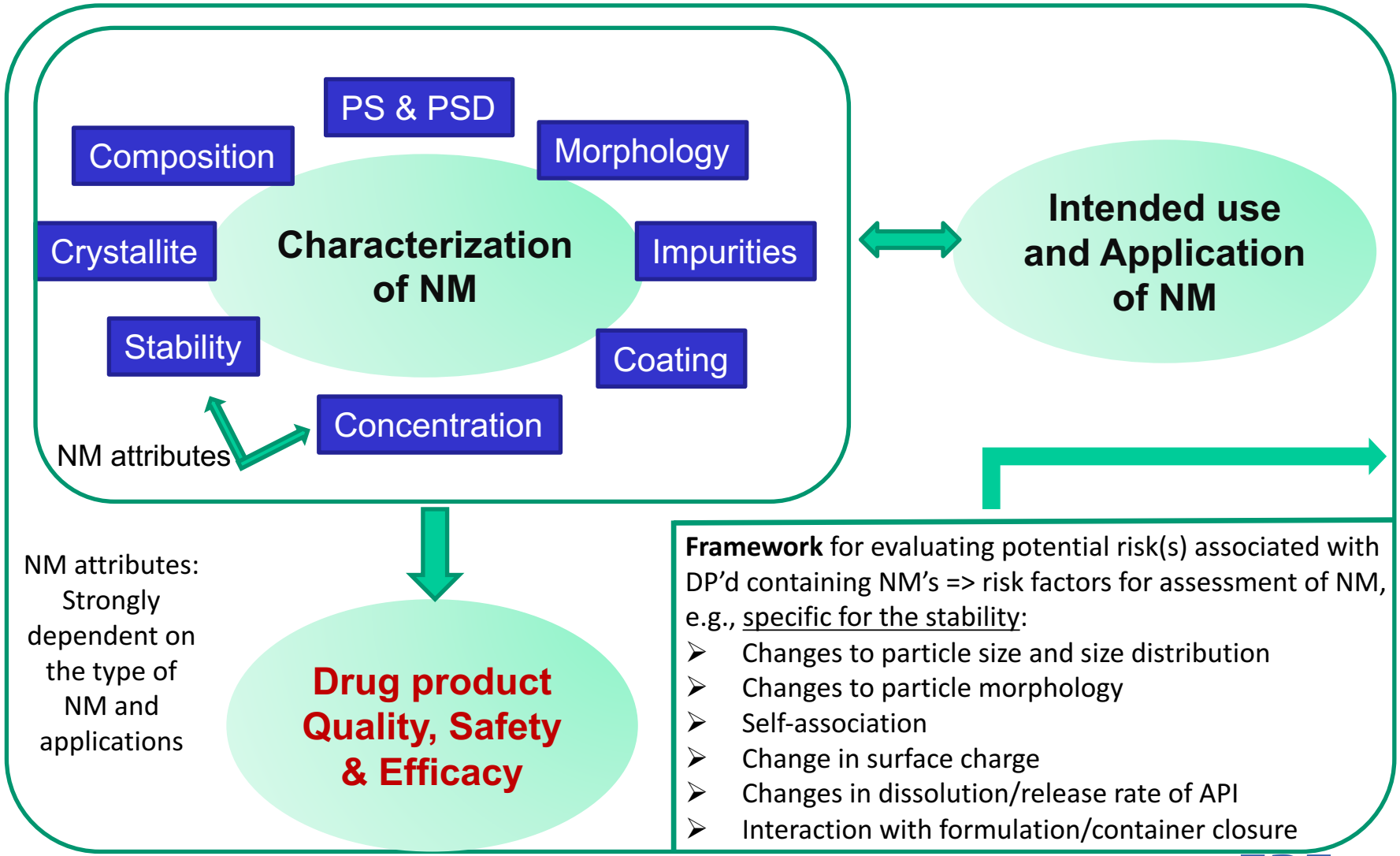
FDA AND NM's
basis of the quidance



FDA AND NM‘s

Nanomaterial Physicochemical Characterization Methods

Method suitability: Sponsors should ask:

1. Is the method capable of detecting and characterizing the material in the size range of interest

   Issues: differences related to techniques; e.g., laser diffraction versus light scattering, or various forms of microscopy

2. Does the methodology require a sample preparation that may significantly alter the nanomaterial attribute being measured during analysis

   issues: dilution, drying (later slide), or sonication

3. Can the analytical equipment have unintended interactions with the nanomaterial

   issues: filter (next slide)

CHARACTERIZATION of NM‘s

NM issue examples

Frequent sample preparation issues

- Nanomaterials may interact with the filter medium, causing a loss of sample.
- Alternatively, in some methods a filtration step may lead to an erroneous conclusion that all material passing through the filter is in a dissolved state, because nanomaterials may pass through filters while remaining discrete entities (e.g., as nanocrystals instead of dissolved molecules).
- Various crystal forms of the same material may exist
- Differences in coating of NM’s results in new formulation

CHARACTERIZATION of NM‘s

NM issue examples

Frequent sample preparation issues

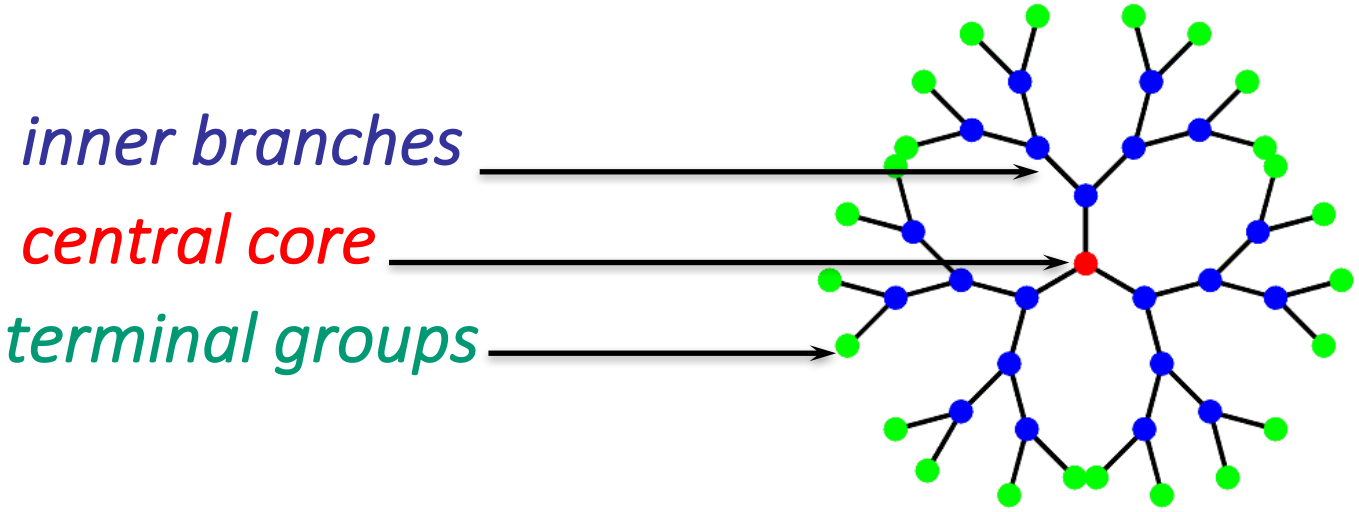
Diluting or drying out a formulation or sample for analysis may produce substantial changes in the nanomaterial

E.g., Avg PS of iron sucrose colloid particles measured by AFM decreases from 22 to 9 nm when the formulation was diluted with deionized water from 5 mg/ml to 2 mg/ml.

Conclusion: sample preparation can be critical for the NP formulation => standardization is important

Characterization of Dendrimers

- Definition: spherical polymers highly ordered 3D structure 1.1 – 9 nm:



- Characterization is important for predicting and elucidating their properties, morphology and interactions (transport, solubility)
- Characterization requires many techniques
- Choice depends on the functionality

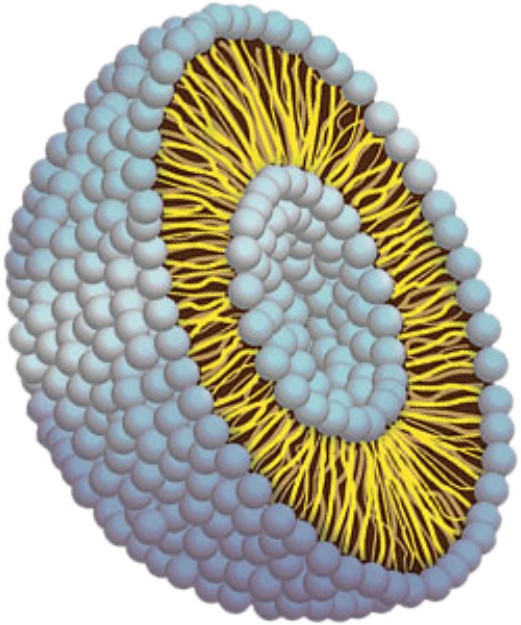
Characterization of Dendrimers (ctd)

- Most important methods:
  - NMR, MALDI TOF, ESI-MS; FT-IR, RAMAN;
  - UV-VIS, Fluorescence, Electrophoresis;
- Less important (support synthesis or in case of issues):
  - Rheology, TGA, DSC, Microscopy, Electrophoresis, X-ray
- **Issues:**
  - pH; any change in condition that affects the pH will much likely change the dendrimer properties
  - Same; salt concentration, temperature

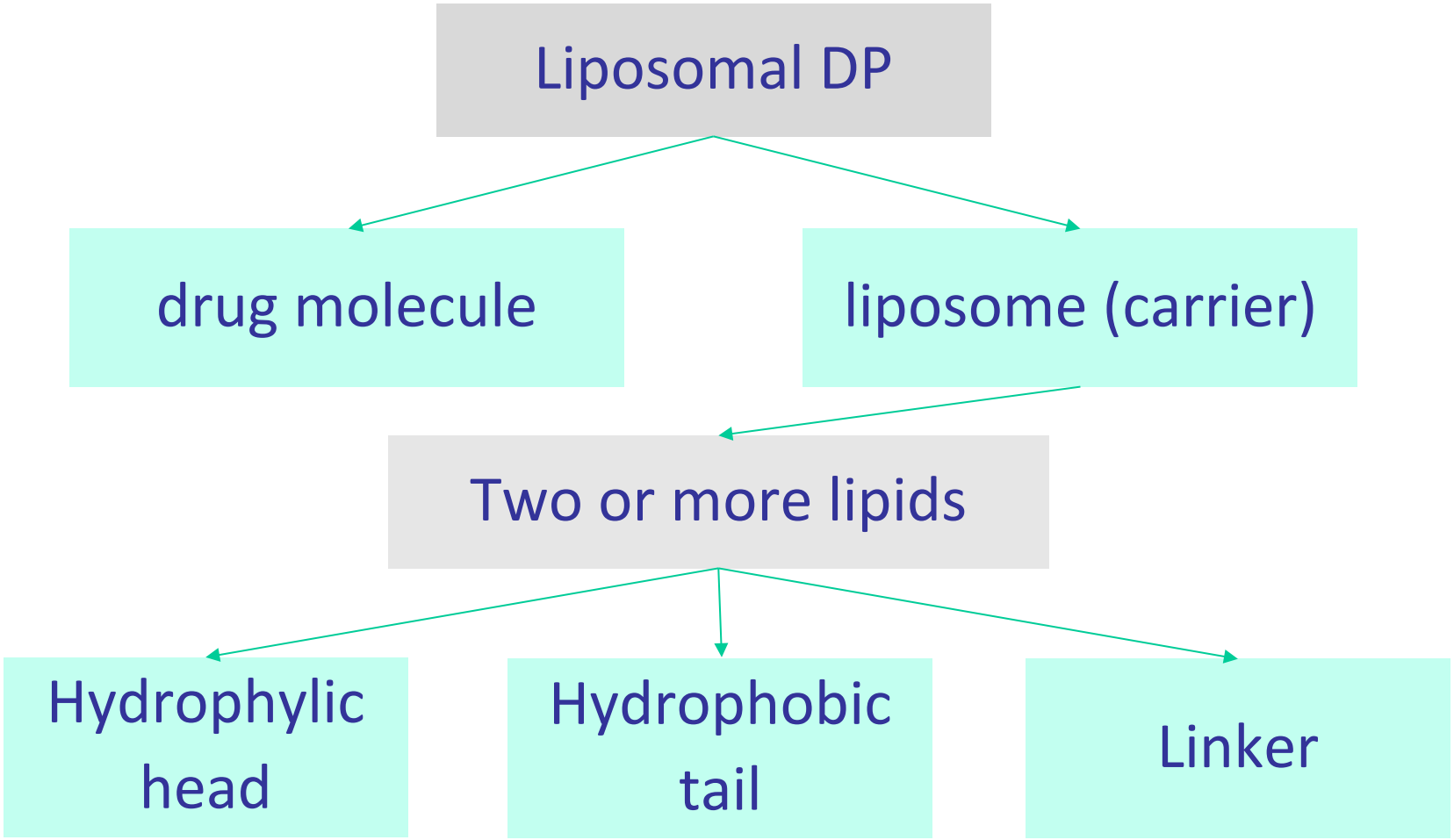
Characterization of Liposomes

- Liposome **D**rug **P**roducts (DP). FDA Guidance
- Most simple definition of a liposome:

  'a spherical vesicle having at least one lipid bilayer'
- DP is generally contained in the liposomes



Characterization of Liposomes ctd



Different parts/functions requires different characterization methods! FDA recommends methods

Characterization of Liposomes ctd, issues

The selections of lipids (as excipients) is therefore a critical factor determining safety, stability, and efficacy of a liposomal drug product.

Due to the significant role of lipid excipients on the quality, safety, and efficacy of liposomal DP's, lipid excipients should be characterized in as much details as the drug substance itself.

Liposome DP's are complex formulations and usually small changes in the formulation may significantly affect clinical results.

Characterization of liposomes ctd, issues

Changes in the physicochemical properties of liposomes may affect the PK/PD performance of the product

- Develop a strategy to determine the Critical Quality Attributes (CQAs) (Risk factor FDA)
- CQA = physical, chemical, biological, or microbiological property that may influence finished product quality or performance
- Examples: lamellarity, internal volume, lipid phase transition T, free and encapsulated drug proportions, lipid degradation products, zeta potential, particle size, and drug release kinetics

Characterization of liposomes ctd, issues

- Interaction of liposomes with filter matrix; clogging
- Fusion; (i.e., irreversible coalition of smaller liposomes to form larger liposomes),
- Aggregation (i.e., reversible conglomeration or pooling of two or more liposomes without fusion)
- Leakage of the contained drug substance during storage.
- Double tailed lipids -> single tailed -> lysolipids -> apoptosis
- PS and PSD measured before but not after a size reduction step, as these are CQA's it is a liposome specific quality issue

Characterization of liposomes
FDA, common pain points:

- PS and PSD impact the biodistribution and drug PK
- parameters used for reporting PS/PSD may vary per method and instrument parameters. E.g., DLS results may vary based on the algorithm and weighting parameters (intensity, volume or number)
- Lipid degradants; complete degradation profiles of liposomal products were often not fully determined -> lysolipids -> hemolysis and/or apoptosis
- *In vitro* release test should be done in order to discriminate between acceptable and non-acceptable batches;
- Lack of knowledge of properties of lipid excipients; e.g., non-acceptable degradation products

Conclusions

- Most novel formulations can be considered as complex formulations too and their characterization is pretty complex and extensive.
- FDA gives some guidance in how to approach the characterization (risk factors, CQA's) and which properties should be characterized. Some common pitfalls are described from which we can learn, but there is much more to learn.
- Characterization is very important as this is the key to identify the proper risk factors required for a good efficacy and safety evaluation.
- Protocols should be developed to guide the characterization per type of (novel) formulation, including mentioning the defined CQA's and risk factors. => translated to white papers (EBF) => Guidance

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Acknowledgment

- Amanda Wilson – session lead
- Google
- Key literature:
  - Guidance for Industry. Considering whether an FDA-regulated Product involves the application of Nanotechnology. FDA June 2014.
  - Quality aspects of Nano-based medicines. EMA April 2014
  - Product quality for nanomaterials; current U.S. experience and perspective. Katheryne M. Tynes et al. WIREs Nanomed Nanobiotechnology 2015, 7: 640-654
  - Scientific and Regulatory Considerations for Generic Complex Drug Products Containing Nanomaterials. Nan Zheng et al. The AAPS Journal 19, (3), May 2017, 619-631.
  - Liposomal Drug Product Development and Quality: current U.S. experience and perspective. The AAPS Journal 19, (3), May 2017, 632-641.
  - Drug Products, Including Biological Products, that Contain Nanomaterials. Guidance for Industry. FDA DRAFT GUIDANCE. Dec 2017.
  - Liposomal Drug Products. Chemistry, Manufacturing, and Controls: Human Pharmacokinetics and Bioavailability; and Labeling Documentation. Guidance for Industry. FDA April 2018.

The End

Thank you for your attention

Questions?