Nonclinical Perspective on Development of Drug Products Containing Nanomaterials

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

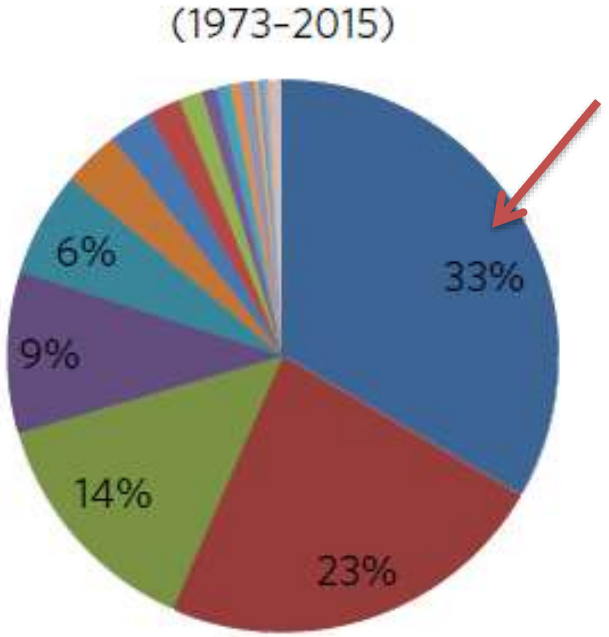
Outline

- Drug products containing nanomaterials for drug development
- Nonclinical development for drug products containing nanomaterials
- Case studies
- Additional resources and information

Submissions to the US FDA of Drug Products Containing Nanomaterials: Materials

a

- Liposome
- Nanocrystal
- Emulsion
- Iron–polymer complex
- Micelle
- Drug–protein complex
- Drug–polymer complex
- Dendrimer
- Polymeric NP
- Nanobubble
- Silica NP
- Drug–lipid complex
- Drug–metal complex
- Protein NP
- Drug NP
- Solid lipid NP
- Nanotube
- Metal–protein complex
- Metal–nonmetal complex
- Metal–polymer complex



(D'Mello S. et al., 2017)

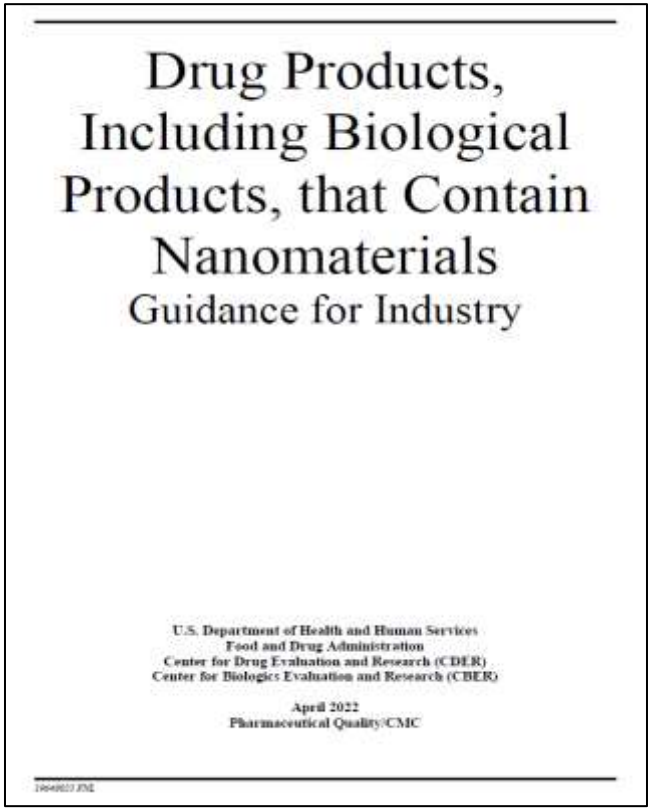
Cancer indications 30-40%
All routes of administration

Nanomaterials in Drug Products: Examples

Approval Year	Product	Nanoparticle material	Drug	Indication	Use
2017	Vyxeos	Liposome	Cytarabine/ Daunorubicin	Acute myeloid leukemia	Drug delivery
2015	Onivyde	Liposome	Irinotecan	Pancreatic cancer	Drug delivery
2012	Marqibo	Liposome	Vincristine	Acute lymphoid leukemia	Drug delivery
2005	Abraxane	Nanoparticle-bound albumin	Paclitaxel	Several cancers indication	Drug delivery
2004	Macugen	Polymer-based	Pegaptanib sodium	Macular degeneration	Drug delivery
1997	AmBisome	Liposome	Amphotericin B	Antifungal	Drug delivery
1996	Taxotere	Micelle	Docetaxel	Several cancers indication	Drug delivery

(Adapted from Foulkes, et al., 2020)

Nanomaterials in Drug Products: Guidance



Drug Products, Including Biological Products, that Contain Nanomaterials

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2022
Pharmaceutical Quality/CMC

https://www.fda.gov/media/157812/download

Nanomaterials in Drug Products: Guidance

- FDA regulatory framework and review processes adequately identify and manage potential risks associated with the use of nanomaterials in products
  - Further understanding may be needed regarding the interactions of nanomaterials in drug products with biological systems.
- Drug products containing nanomaterials are expected to meet the same standards of safety, efficacy, and quality as other drug products.
  - FDA asks relevant questions to understand any uncertainties that may exist concerning product safety, efficacy, quality, or other attributes in order to ensure that the product meets statutory and regulatory requirements.
- A risk-based approach for evaluating drug products containing nanomaterials. The approach is based on
  - Adequate characterization of the nanomaterial
  - Understanding of a nanomaterial's intended use and application
  - How the nanomaterial attributes relate to product quality, safety, and efficacy.

https://www.fda.gov/media/157812/download

Guidance for Industry
" Drug Products, including Biological Products, that contain Nanomaterials"

In vitro Tests with Human Biomaterials:

- Stability and Biocompatibility
- Plasma protein binding
- In vitro clearance and metabolism

Immunogenicity

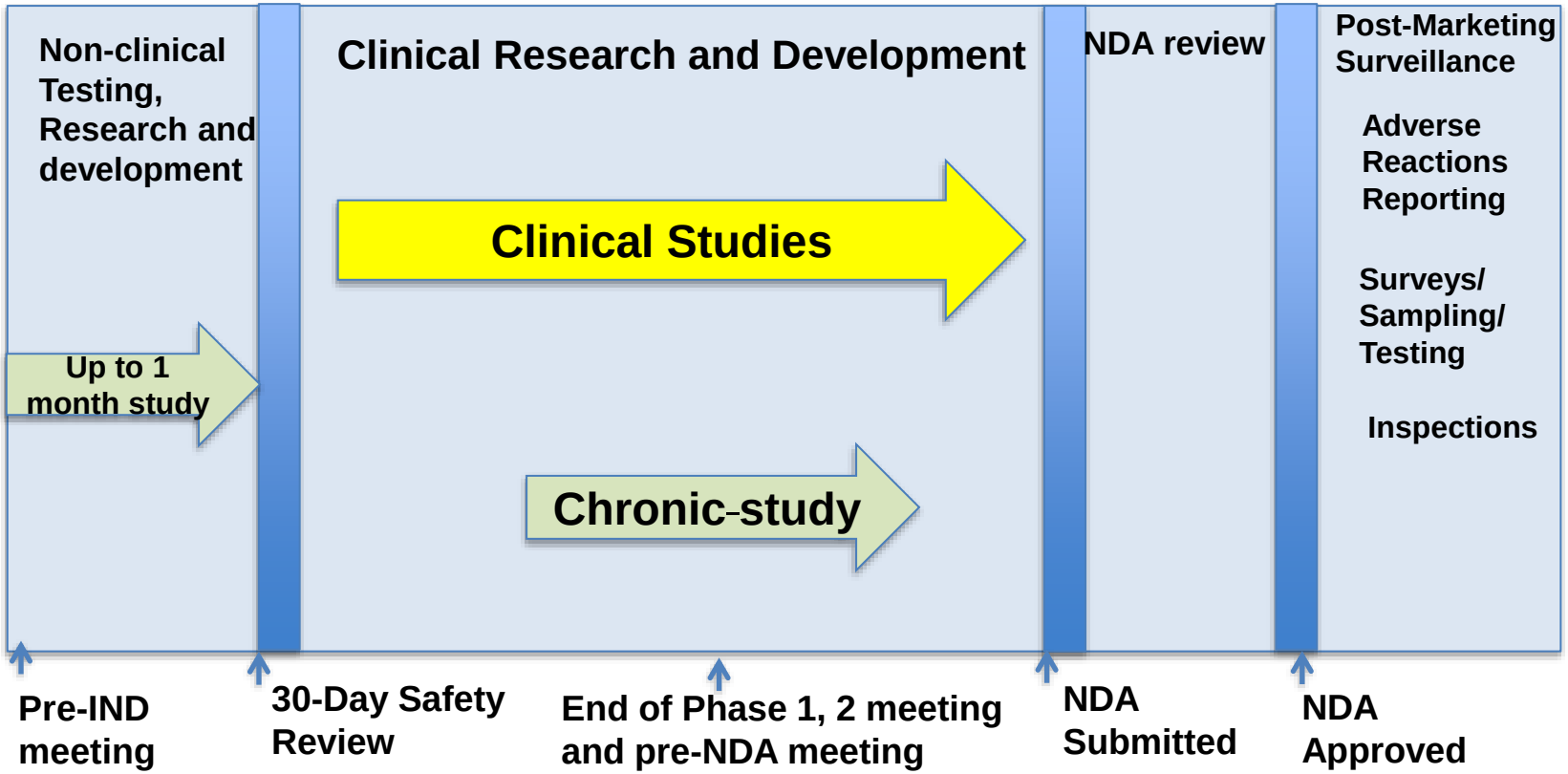
- It is recommended to use a risk-based approach to evaluate and mitigate adverse immune responses that may be associated with administration of products containing nanomaterials (refer to ICH S8 Immunotoxicity Studies for Human Pharmaceuticals).
- Risks for immunogenicity will need to be assessed on a case-by-case basis and considered at the earliest stage of product development as well as throughout the remainder of development.

https://www.fda.gov/media/157812/download

General Concerns for Safety Assessment of Nanomaterials

- Nanomaterials characterization
- Chemistry Manufacturing and Controls (CMC)
- Solubility and aggregation
- Route of exposure
- Toxicokinetic (exposure level)
- Biodistribution

General Drug Development Cycle



Common Reasons that Lead to a Clinical Hold of an IND Application

(1) Irrelevant or inadequate non-clinical studies

- Lack sufficient documentation
- Test too few animals
- Do not assess standard parameters or provide sufficient data
- Study inadequate doses
- Use a route of administration other than that proposed for the humans without adequate justification
- Study had an insufficient duration (single or repeat dose)

(2) CMC issue that requires non-clinical safety testing (impurities, novel excipient).

https://www.ncbi.nlm.nih.gov/books/NBK195047/

Non-clinical Development of Drug Products Containing Nanomaterials

- There are currently no nonclinical guidelines specific for development of drug products containing nanomaterials.
- Standard nonclinical safety testing usually follows ICH M3, ICH S9, and ICH S6 guidelines;
  - ICH M3 Guidance:
    - Describes which nonclinical studies to conduct and when data are needed, based on duration of clinical testing
  - ICH S9 Guidance:
    - Describes which nonclinical studies to conduct and when data are needed, based on duration of clinical testing
    - Applicable to oncology indications
  - ICH S6 Guidance:
    - Describes framework of the nonclinical safety studies to conduct for evaluation of biotechnology-derived pharmaceuticals
    - Advice on approaches to select relevant types of nonclinical studies (both in vitro and in vivo) for evaluating pharmacology and toxicology activities in relevant species
    - Advice about anti-drug antibody evaluations

- FDA Guidance: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers

Pharmacology Studies

- Define mechanism of action biochemically, in cultured cells, and/or in animals
  - Try to identify a marker of activity (e.g., downstream signal-modulation) that can be used in in vivo studies to correlate with overall pharmacodynamic (PD) activity (Useful but not required)
- May help define optimal dose and schedule for potential clinical administration
- Helps to assess the therapeutic window early in development
  - Collect tolerability information (body weight, clinical observations) in animal pharmacology studies
  - Collect pharmacokinetic (PK) data in pharmacology studies to perform PK/PD modeling
  - Perform in vitro/in vivo modeling using in vivo maximum tolerated dose (MTD) vs. in vitro potency (e.g., effective dose (ED) 50)

General Toxicology Studies

- **Purposes:**
  - To identify target organs
  - To characterize the dose-toxicity relationships
  - To characterize the reversibility of effects
  - To determine the relationship between pharmacology and toxicity
  - To determine the exposure level of drug metabolites and impurities
- **General recommendation**:
  - For small molecule drugs: two species are needed for First-in-Human (FIH): rodent and non-rodent
  - For biologics: two relevant species, could be in one relevant species based on scientific data justification
  - Dose selection: 3 dose levels to evaluate dose-response relationship (low, mid, and high dose levels)
    - Dosing regimen and route of administration follows the proposed clinical trial
  - Duration of toxicology study: based on stage of drug development and the pharmaceutical indications
    - Single dose toxicity study: acute dose toxicity
    - Repeat dose toxicity studies: up to 1 month for initial development and 3-9 months for later development

Other Nonclinical Studies: Supporting Continued Development and Marketing Application

- **Genotoxicity studies:** standard battery testing follows ICH S2 (R1) guidance
  - In vitro bacterial reverse mutation test (Ames Test), in vitro chromosomal aberration test in mammalian cells, and in vivo micronucleus test in rodent per applicable ICH guidance
  - See ICH M3(R2) and ICH S9 for timing of genotoxicity studies
- **Reproductive and Developmental Toxicity studies:** follows ICH S5 (R3) guidance
  - Fertility and Early Embryonic Development (FEED) studies in one pharmacologically relevant species (rodent, rabbit, dog, or non-human primate)
  - Embryo-fetal development toxicity (EFD) studies should be conducted in 2 species; but could be in a single species if there is clear positive results for the induction of malformations or embryo-fetal lethality.
  - Pre- and Postnatal Development (PPND) studies in rodent; but may consider other species on a case-by-case basis
  - Literature-based risk assessment may be acceptable on a case-by-case basis
  - See ICH M3, ICH S6, and ICH S9 for timing of reproductive and developmental studies

Other Nonclinical Studies: Supporting Continued Development and Marketing Application

- **Carcinogenicity studies:** follows ICH S1A and S1B guidance
  - Usually conduct in rodents (i.e., rat, mouse) for 2 years
  - Can be conducted in a 6-month transgenic mouse study
  - Can submit a request for recommendations on carcinogenicity study to CDER's Executive Carcinogenicity Assessment Committee (ECAC)

Still have questions on which nonclinical studies are needed?

Contact the appropriate review division based on your proposed indications to determine which types of nonclinical studies that would be needed to support the drug development.

Non-clinical Development of Anticancer Pharmaceuticals (ICH S9)

Non-clinical development programs for anticancer pharmaceutical should be conducted in accordance with ICH S9: applicable to both drug products containing nanomaterials and non nanomaterial products

First-In-Human:

- Up to 28-day toxicology studies in 2 species (relevant species) to support dose selection for FIH trials; similar dosing regimen and route of administration with the proposed clinical trial
- Safety pharmacology can be incorporated into the repeat-dose toxicity studies
- Information on Absorption, Distribution, Metabolism, and Excretion (ADME) in animals should normally be generated in parallel with clinical development
- Start dose selection: Severely Toxic Dose (STD) in 10% in rodents
  Highest Non-Severity Toxic Dose (HNSTD) in non-rodents

Later Development:

- 3-month toxicology studies in 2 species to support Phase 3 (or pivotal) clinical programs

Marketing:

- For small molecules: mutagenicity and clastogenicity testing prior to marketing and embryo-fetal development toxicity studies to support labeling

https://www.fda.gov/media/73161/download

Toxicology: Typical Rodent Study Design for FIH Study

Group	Dose*	# Main Study	# Recovery
Control	0	10M/10F	5M/5F
Low	X	10M/10F	**
Mid	3X	10M/10F	**
High	10X	10M/10F	5M/5F

*High dose should be MTD/maximum feasible dose (MFD); low dose should cover the proposed starting dose; mid-dose should be the log-linear mid-point
**Recovery cohorts are needed in control and high-dose groups for FIH studies; Recovery groups in mid-dose groups are recommended if significant high-dose mortality is anticipated

- ICH S9 Guideline
https://www.fda.gov/media/73161/download
- FDA CFSAN Red Book:
http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm078315.htm
- OECD 28-Day repeat-dose toxicology guideline
https://www.oecd.org/chemicalsafety/testing/37477972.pdf

Novel Excipients in Drug Products: Safety Evaluation

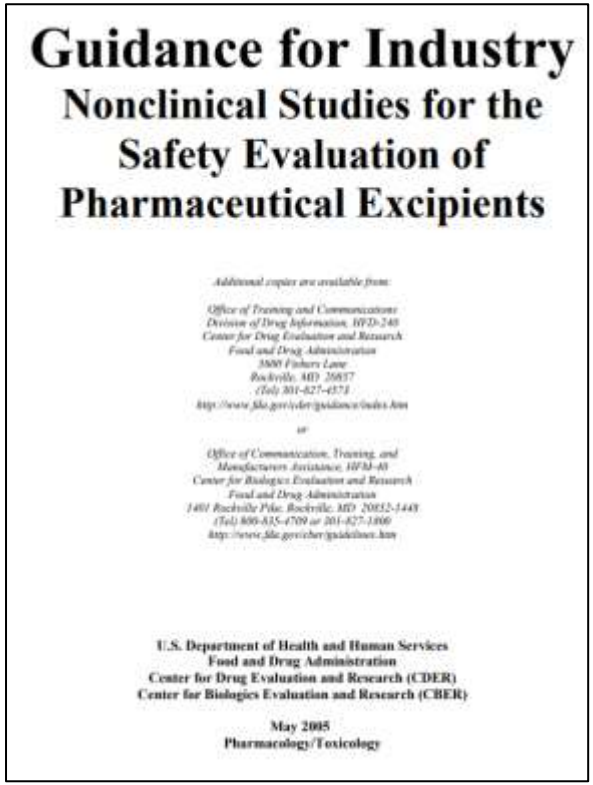
Novel excipient means

(1) Not intended to exert therapeutic effects at the intended dosage (may improve drug delivery)

(2) Not fully qualified by existing safety data at the proposed level of exposure, duration of exposure, or route of administration

Safety data supports IND/NDA

- Refer to the guidance for more details and contact the appropriate review division regarding safety evaluation of a novel excipient.


Guidance for Industry

Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients

Additional copies are available from:

Office of Training and Communications
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
3880 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

or

Office of Communication, Training, and Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
(Tel) 800-835-4709 or 301-827-1800
http://www.fda.gov/cber/guidelines.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2005
Pharmacology/Toxicology

https://www.fda.gov/media/72260/download

Case Studies

Vyxeos (CPX-351)
(Daunorubicin and Cytarabine liposome injection)

This NDA was submitted as a 505 (b)(2) application (Reference drugs: DepoCyt ® and DaunoXome ®).

- **Indication:** Treatment of adults with newly-diagnosed therapy related acute myeloid leukemia (t-AML) or AML with myelodysplasia related changes (AML-MRC)
- **Mechanism of Action:** After cellular internalization, the liposomes undergo degradation which releases cytarabine and daunorubicin intracellularly to induce DNA damage resulting in cell death
- **Formulation:** Injection, lyophilized [(44 mg daunorubicin and 100 mg cytarabine) liposome]
- **Route of administration/dosing schedule:**
  - **Induction:** Vyxeos (daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) liposome via intravenous (IV) infusion over 90 minutes on Days 1, 3 and 5 and on Days 1 and 3 for subsequent cycles of induction, if needed.
  - **Consolidation:** Vyxeos (daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2) liposome via IV infusion over 90 minutes on Days 1 and 3

Non-clinical Toxicity Studies

- **Pharmacology studies: provide mechanisms (proof of concept and biodistribution):**
  - The 1:5 molar ratio of daunorubicin: cytarabine has been shown to have synergistic effects of killing leukemia cells in vitro and in murine models.
  - Daunorubicin has anti-mitotic and cytotoxic activity and cytarabine is a cell cycle phase-specific anti-neoplastic agent, affecting cells only during the S-phase of cell division (inhibits DNA polymerase).
  - Based on animal data, the liposomes enter and persist in the bone marrow, where they are taken up intact by bone marrow cells. In leukemia-bearing mice, the liposomes are taken up by leukemia cells to a greater extent than by normal bone marrow cells.
  - After cellular internalization, the liposomes undergo degradation releasing cytarabine and daunorubicin within the intracellular environment.

Non-clinical Toxicity Studies

- **Toxicology Studies: provide toxicological profile of pharmaceuticals:**
  - Repeat-dose toxicity studies of CPX-351 (cytarabine:daunorubicin) in rats and dogs (IV once every 2 days x 3 in 3-week cycles with 28-day recovery period)
    - Mid and high dose levels were associated with morbidity which was attributed to hypocellularity of the bone marrow and lymphoid organs in both rats and dogs.
    - In dogs, epithelial necrosis of the large and small intestinal mucosa was observed.
    - A drug-related decrease in white blood cell differential was observed that correlated with hypocellularity of the bone marrow and lymphoid organs and reduction in thymic and spleen weight and size.
    - Reversibility could not clearly be evaluated due to premature deaths and early terminations.
    - Primary target organs: bone marrow, lymphoid organs, and small and large intestine.
    - **Relevant to clinic adverse effects:** febrile neutropenia, mucositis, diarrhea, constipation, decreased appetite

Genotoxicity, carcinogenicity, and reproductive and developmental toxicity studies relied on the reference drugs DepoCyt ® and DaunoXome ® ([505 (b)(2)].

Drug X

- **Drug X** is a specific membrane antigen-targeted nanoparticle (~ 100 nm) encapsulating the active pharmaceutical ingredient (API)
- **Proposed mechanism:** anti-microtubule/anti-mitotic compounds
- **Formulation:** API is physically encapsulated (not covalently bound) in a matrix derived from polymeric components. The polymer matrix is composed of the biodegradable and biocompatible polymer (polylactic acid covered with a coating of polyethylene glycol) with ligands that target prostate-specific membrane antigen.
- **Route of administration/dosing schedule:** IV infusion, once every 3 weeks

Drug X

- **Dose escalation magnitude:** cohort 2 was 100%, cohort 3 was 114%, cohort 4-5 were 100%, cohort 6 was 25%, cohort 7 was 33% and cohort 8 is 25% increase until the MTD was reached.
- **No. of patients**: 20-60
- **Previous clinical experience:** None

Non-clinical Studies

Pharmacology and Pharmacokinetic studies: provide mechanism (proof of concept and biodistribution):

- In vivo, drug X inhibited tumor growth in various murine xenograft models (human breast, lung and prostate cancer).

- In vivo PK studies in rats and monkeys, drug X has higher volume of distribution for API when compared to administration of API alone, indicating rapid and extensive distribution beyond the vascular compartment.

- The apparent terminal half-lives for drug X in rats and monkeys were shorter than the API alone.

Non-clinical Studies

Toxicology studies: provide toxicological profile of pharmaceuticals:

- Drug X was IV administered (low, mid and high dose levels) once every 3 weeks (total of 2 doses) in GLP compliant repeat-dose toxicity studies in rats and cynomolgus monkeys. Animals were euthanized four days following the second dose, and recovery was evaluated after Day 43 after a 3-week recovery period.

- These GLP studies included placebo (nanoparticles without encapsulated API) and positive control (other FDA approved drug with similar mechanism) arms in order to distinguish between the toxicities associated with the API and particle component of drug X.

- In addition, a repeat-dose GLP toxicity study was also performed in rats at a higher dose and on a more frequent dose schedule than that used in clinic to evaluate possible differences in toxicities of drug X due to dosing schedule.

Non-clinical Studies

- **Toxicology studies: provide toxicological profile of pharmaceuticals:**
  - No drug X-related mortality was observed in rats.
  - Mid and high dose levels were associated with morbidity (13% and 80% with unscheduled death on Days 6 and 10, respectively) which was attributed to degeneration of the gastrointestinal tract in monkeys.
  - In rat and monkey studies, there were no apparent effects of placebo particles on any of the parameters evaluated in the study.
- **Target organs of toxicity in rats and monkeys:**
  - Bone marrow (hypocellularity), lymphoid tissues (lymphoid depletion in thymus, spleen and lymph node), small intestines (increased diameter and length of crypts populated by cells with increased mitotic activity and single cell necrosis of epithelial cells), ovaries (persistent corpora hemorrhagic), and seminal vesicles (increased mitotic activity and single cell necrosis of epithelial cells).

Relevant clinical adverse effects

- **Non-clinical adverse effects:** bone marrow and lymphoid tissue depletion and degeneration of GI tract.

- **Reviewer recommendation:**

Based on the rats and cynomolgus monkey toxicity studies, the proposed clinical start dose is acceptable.

- **Clinical experience:** the clinical trial enrolled 263 adult patients in 4 different clinical trials with advanced solid tumors and MTD was reached at ~10X from the proposed start dose.

- **The most common adverse reactions (≥ 10%) in patients:**

fatigue, nausea, diarrhea, anemia, alopecia, decrease appetite, neutropenia, vomiting, dehydration, constipation, dysgeusia, dyspnea and arthralgia.

Drug Y

- **Drug Y** is a colloidal dispersion of nanoparticles containing the active pharmaceutical ingredient
- **Proposed mechanism:** antioxidant. It may involve the stimulation of the mitochondrial, pro-apoptotic bcl-2 proteins, causing death in the oncolytic cells.
- **Formulation:** A 4% (w/v) compound Y nano-suspension (30-80 nm) for injection. The formulation had been specifically developed to stabilize the nanoparticle.
- **Route of administration/dosing schedule:** IV infusion for 4 hours, 3 times per week for 26 days

Drug Y

- **Dose escalation magnitude:** Cohort 2 was 100%, cohort 3 was 50%, and cohort 4 and beyond 25% increase until the MTD was reached.
- **Indication:** Patients with solid tumors
- **No. of patients planned**: 63
- **Previous clinical experience:** Yes, with a different route of administration.

Do we need additional nonclinical data?

Non-clinical Studies

Pharmacology and Pharmacokinetic studies: provide mechanism (proof of concept and biodistribution):

- In vitro, drug Y induced apoptosis in various human tumor cells lines (liver cancer, breast adenocarcinoma, prostate cancer, pancreatic cancer, and melanoma).
- In vivo, drug Y inhibited tumor growth in murine xenograft models and increased the lifespan of the tumor-bearing mice.
- Drug Y accumulated in high concentrations in cynomolgus monkey liver tissues and smaller amounts in the lungs, pancreas, heart, and brain tissues. In mice, drug Y accumulated in high concentrations in the liver and spleen.
- No formal metabolism and excretion studies of drug Y have been conducted in animals. The Sponsor provided data based on previous published literature.

Non-clinical Studies

Toxicology studies: provide toxicological profile of pharmaceuticals:

- Repeat-dose toxicity studies were conducted in rats and dogs (three times per week IV bolus for 4 weeks with 2-week recovery, 3 dose levels)
- No mortality in rats at all dose levels tested, but early euthanasia in female dogs at the highest dose level. Thus, the high dose in rats was the severely toxic dose in 10% animals (STD10), and the mid dose in dogs was the highest nonseverely toxic dose (HNSTD).

Reviewer recommendation:

- Based on the rat and dog toxicity studies, the proposed clinical start dose is acceptable.

Non-clinical Studies

- **Toxicology studies: provide toxicological profile of pharmaceuticals:**
  - **Target organs of toxicity:**

    •**Rats:** Liver (increased liver aspartate aminotransferase (AST), alanine aminotransferase (ALT) level and hepatocellular necrosis), spleen (enlargement), and bone marrow (an increase in erythropoiesis was observed in the sternal bone marrow).

    •**Dogs:** Liver (glycogen accumulation) and bone marrow (increased erythrocytic hyperplasia at all doses). Significant reductions in reticulocytes and platelets in both sexes at mid and high doses. On Day 24 in male dogs, the heart rate was slower at all dose levels. The RR interval was longer in male dogs (no remarkable changes following 2-week recovery).

Relevant clinical adverse effects

- **Non-clinical adverse effects:** anemia, reduction in platelets, tachycardia

- **On-going clinical trials:** there are 6 completed and 2 on-going clinical trials enrolling 217 adult patients with advanced solid tumors as monotherapy and combination therapy. The MTD of Drug Y as monotherapy was reached at ~50X from the proposed start dose.

- **The most common adverse reactions (≥ 30%) in patients:** anemia, fatigue, nausea, dyspnea, pyrexia, decreased appetite, vomiting, hyperglycemia, hypoalbuminemia, hypocalcemia, thrombocytopenia, increased AST and blood alkaline phosphatase level. Elevated international normalized ratio (INR) and partial prothrombin time (PTT) were noted.

Summary

- Generally, nanomaterial drug products are less than 100 nm and are developed to enhance the safety and effectiveness of an active pharmaceutical ingredient.

- Currently, most nanomaterial drug products in clinical development are in the form of liposomal carriers.

- There is no formal guidance for the types and extent of non-clinical studies needed specifically for nanomaterial drug products, which may vary based on the clinical experience with the active pharmaceutical ingredient and how extensively nano-sizing changes its properties.

Resources and Additional Information

Additional Resources for Toxicology and the Safety Assessment

- **Redbook 2000**

https://www.fda.gov/downloads/Food/GuidanceRegulation/UCM222779.pdf

- **ICH S9, nonclinical evaluation for anticancer pharmaceuticals**

S9 Nonclinical Evaluation for Anticancer Pharmaceuticals | FDA

- **ICH S9, nonclinical evaluation for anticancer pharmaceuticals- Questions and Answers**

S9 Nonclinical Evaluation for Anticancer Pharmaceuticals--Questions and Answers | FDA

- **Safe Starting Dose Guideline**

https://www.fda.gov/media/72309/download

- **ICH M3 (R2), nonclinical safety studies**

https://database.ich.org/sites/default/files/M3_R2__Guideline.pdf

Additional Resources for Toxicology and the Safety Assessment

- **ICH S1A Carcinogenicity studies**
https://database.ich.org/sites/default/files/S1A%20Guideline.pdf

- **ICH S2, Genotoxicity studies**
https://database.ich.org/sites/default/files/S2%28R1%29%20Guideline.pdf

- **ICHS5 (R3) Reproductive studies**
https://www.ich.org/page/safety-guidelines

- **ICH S6, Biotechnology products**
https://database.ich.org/sites/default/files/S6_R1_Guideline_0.pdf

- **ICH S8, Immunotoxicity studies for human pharmaceuticals**
https://database.ich.org/sites/default/files/S8_Guideline_0.pdf

- **ICHS10, Photosafety evaluation**
https://database.ich.org/sites/default/files/S10_Guideline.pdf

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Questions/Discussion