Tumor Targeted Nanoparticles: Opportunities and Challenges for Advanced Drug Delivery Systems

PROF. DR. EREM BILENSOY

HACETTEPE UNIVERSITY FACULTY OF PHARMACY
DEPARTMENT OF PHARMACEUTICAL TECHNOLOGY
06100 ANKARA TURKEY
Presentation plan

• Cancer chemotherapy:
  • Problems,
  • Role of nanotechnology

• Nanomedicine:
  • Regulatory landscape
  • BE requirements (clinical and non-clinical)
  • Market status

• Case studies:
  1. Cationic coated nanocapsules for oral chemotherapy with camptothecin
  2. Injectable nanoparticles for folate receptor targeting to tumor cells with paclitaxel
Cancer

Cancer is a leading cause of death

- 24 million people diagnosed with the disease every year
- Causes **8 million deaths** each year with **32 million living with cancer**
- Overall cost for cancer treatment ; 157 billion USD
- Death rate from cancer in the USA has not changed between 1950 and 2001.

- In the last 10 years, death rate dropped by 1.8% in men and 1.5% in women each year due to new approaches in drug delivery and diagnosis (overall 20% improvement)

- However, dramatic increase in cancer incidence is expected by 2030 as population rises
- 21.5 million deaths per year estimated! **GLOBOCAN Report 2012**
Problems in chemotherapy

Toxicity and severe side effects
- Formulation factors
- Pharmacokinetic variability of anticancer drugs
- Non-selective cytotoxicity

Ineffectiveness of chemotherapy
- Drug properties (poor solubility and instability under physiological conditions)

• Drug resistance
  - Due to physiological barriers and tumor nature
  - Cellular mechanisms

• Lack of oral delivery
  - Very low oral bioavailability of anticancer drugs
Role of nanotechnology in cancer therapy

Strategy of nanotechnology for cancer therapy

1- To overcome cellular and non-cellular based mechanisms of resistance

2- To increase the selectivity of drugs toward cancer cells and reduce severe side effects and toxicity to normal tissues
Role of nanotechnology in cancer therapy
Role of nanotechnology in cancer therapy

Tumor Targeting

Passive targeting
- EPR effect due to size lower than 400 nm
- Prolonged Circulation and facilitated intracellular drug delivery of nanoparticles by surface modification/coating

Active targeting
- Targeting tumor cell surface receptors e.g. Folate or Integrin
- Targeting to blood vessels feeding the tumor tissue (Neoangiogenesis)

Selective Accumulation of Anticancer Drug in Deep Tumor Tissue
The term “Nanomedicine” refers to medicinal products using nanomaterials and nanotechnology during their development and for their manufacturing. A construct is classified as a nanomedicine if it has at least one dimension in the nanoscale (measured in nanometers up to 1000 nm) and exhibits properties dependent upon those dimensions.

European Commission recommended in 2011 to define nanomaterials as:

- 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.

- Alternatively materials should fall into this definition that have a specific surface area by volume greater than 60 m²/cm³.

Nomenclature and terminology still not homogenized and standard; food and cosmetics regulations more defined and regulated in terms of toxicity and thresholds.

S Tinkle et al, Ann NY Acad Sci, 1313, 35-56, 2014
Non-biological complex drugs (NBCD)

An NBCD is a medicinal product, not being a biological medicine, where the active substance is not a homomolecular structure, but consists of different (closely related and often nanoparticulate) structures that cannot be isolated and fully quantitated, characterized and/or described by physicochemical analytical means.

1- It consists of a multitude of closely related structures
2- The entire complex is the API
3- Properties cannot be fully characterized by physicochemical analysis
4- Well-controlled robust manufacturing process is fundamental to reproduce the exact product

*H Schellekens et al, AAPS Journal, 16(1), 15-21, 2014*
*DJA Crommelijn et al, Eur J Pharm Sci, 76, 10-17, 2014*
Nanomedicines
Regulatory landscape
Nanosimilars and follow-on nanomedicinal products
Generic approach relies on similarity and a stepwise approach of a full physicochemical characterization (PCC) to show pharmaceutical comparability regarding
- Quality
- Safety
- Efficacy

No harmonized approach exists for characterization with state of the art techniques.

Different authorities have different approaches for these submissions of follow-on products on nanomedicines

FDA: Case-by-case, flexible, adaptive but more general

EMA: Class-related and product-specific
Established nanomedicines with similarity guidelines

Iron-carbohydrates

Colloidal i.v. preparations
Core-shell structure
Used for treating iron deficiency
Similars differ in their carbohydrate shell and their electrostatic or covalent attachment to the core
Approved EU and US

- The central polynuclear mineral iron core is stabilized by sucrose
- Differences in core size, carbohydrate chemistry, and nanoparticle characteristics determine the drug profile in vivo (PK, PD safety, immunogenicity)
- The stability of the polymeric iron complex influences efficacy and tolerance of the intravenous iron preparation: iron dissociation, formation of reactive (labile) species
Nanomedicine Regulatory Landscape
Established nanomedicines with similarity guidelines

**Glatiramoids**

Synthetic copolymer mixtures of defined molar ratio of 4 natural amino acids found in myelin based protein (L-glutamic acid, L-alanine, L-tyrosine and L-lysine)

In the range of 1.5 to 550 nm

Used to treat multiple sclerosis

Approved in EU, US and Israel
Nanomedicine Regulatory Landscape
Established nanomedicines with similarity guidelines

**Doxil in US, Caelyx in EU**

Generic Lipodox of Sun Pharma, India approved temporarily in 2011 due to reference product shortage and received full approval in 2013 by FDA

Failed to demonstrate similarity to Caelyx in EU, Not approved by EMA
EMAs present scientific guidelines on nanomedicines

1- EMA/CHMP/SWP/620008/2012, March 2015, intravenous iron based nanocolloidal products development with reference to innovator product

2- EMA/CHMP/SWP/100094/2011, March 2011, Non-clinical studies for generic nanoparticle iron medicinal product applications

3- EMA/325027/2013, August 2013, Surface coatings: general issues regarding parenteral administration of coated nanomedicine products

4- CHMP/806058/2009/Rev.02, February 2013, Data requirements for intravenous liposomal products developed in reference to innovator liposomal product

5- EMA/CHMP/13099/2013, January 2014, Development of block copolymer micelle medicinal products
FDA Draft Guidance on Paclitaxel (Recommended Sept 2012) for Abraxane equivalence studies

1- 100 mg/vial (260 mg/m² dose administered in 30 minutes) BE study with PK endpoints, single dose, crossover, fasting, in vivo on breast cancer patients after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Analytes to measure: unbound and total paclitaxel in plasma. BE based on (90%CI) AUC and Cmax for unbound and total paclitaxel

2- In vitro particle size distribution: in vitro BE study on at least 3 lots of both test and reference products, 100 mg/vial, parameters to measure: D10, D50 and D90. BE based on 95%CI: based on D50 and span (D90-D10/D50) or polydispersity index

3- Waiver request for in vivo testing: not applicable

4- Applicants are encouraged to explore methods to characterize in vitro release
Nanomedicine
Bioequivalence studies
Unbound and total drug

Nanomedicine Drug fractions in the circulation:

I. NM encapsulated fraction

II. Unencapsulated fraction

- fu : unbound fraction
- 1-fu: protein bound fraction
Nanomedicine Bioequivalence studies
Unbound and total drug

Main Problems
- Process induced artifacts
- Difficult to accurately differentiate protein bound and encapsulated API

Current methods have inherent flaws, adding inaccuracy and variability to nanomedicine fraction quantitation
Nanomedicine
Bioequivalence studies
Number of subjects

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Dose/patient population</th>
<th>Reference product</th>
<th>Number analysed (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKD/08/038</td>
<td>50mg/m² ovarian cancer</td>
<td>Caelyx (Europe)</td>
<td>23</td>
</tr>
<tr>
<td>PKD/09/031</td>
<td>30mg/m² multiple myeloma</td>
<td>Caelyx (Europe)</td>
<td>26</td>
</tr>
<tr>
<td>PKD/09/030</td>
<td>50mg/m² ovarian cancer</td>
<td>Doxil (US)</td>
<td>41</td>
</tr>
</tbody>
</table>

- From Doxil comparison study report: ‘Expecting +/- 5% variation in T/R Ratio with expected intra subject CV of around 22.5%, 24 subjects were required to prove bioequivalence. However based on the variability of free doxorubicin sample size was increased from 24 to 36 evaluable subjects in order to improve the result and meet the BE criteria for free doxorubicin’

- From the EMA Assessment report: Free (un-encapsulated) doxorubicin is comparable, within 80.00-125.00% to Doxil (US reference product), but not Caelyx. This may be due to insufficient power of the Caelyx studies.
Nanomedicine Pitfalls for in vitro BE Full physicochemical characterization

1. Sterility and endotoxin

2. Physicochemical characterization: no standard approach, based on formulation, reagents and API should be analyzed, measurements should be in biorelevant media, thorough understanding of NP composition (API? Polymer?, Free drug? Encapsulated drug?)

3. Residual manufacturing components

4. Biocompatibility of components

5. Batch to batch consistency

6. Nanoparticle in vivo stability

7. Drug release rate
# Nanomedicines Regulatory Landscape

Table 1. Comparability requirements of nonbiological complex drugs and their nanosimilars.

<table>
<thead>
<tr>
<th>NBCD product categories</th>
<th>Generic follow-on pathway</th>
<th>Additional NBCD similar requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Specs of ref. product</td>
<td>Clinical PK (BE)</td>
</tr>
<tr>
<td>Liposomes</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Glatiramoids</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Iron carbohydrates</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

+: Required; -: Not required; ?: Case-by-case differences or differences between EMA and US FDA regulations; BE: Bioequivalence; NBCD: Nonbiological complex drugs; PD: Pharmacodynamics; PK: Pharmacokinetics; TE: Therapeutic equivalence. Adapted with permission from [7].
Nanomedicine Market

Biopharmaceuticals account for 25% of all pharmaceuticals in the pipeline

<table>
<thead>
<tr>
<th>nanopharmaceutical</th>
<th>2020 (US$ billions)</th>
<th>2025 (US$ billions)</th>
<th>targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>protein-based</td>
<td>14 ± 7</td>
<td>28 ± 14</td>
<td>cancer/inflammatory/CNS</td>
</tr>
<tr>
<td>nucleic-acid-based</td>
<td>7 ± 3</td>
<td>14 ± 7</td>
<td>cancer/inflammatory/CNS</td>
</tr>
<tr>
<td>small-molecule-based</td>
<td>3 ± 3</td>
<td>6 ± 3</td>
<td>cancer/inflammatory/CNS/cardiovascular/infections</td>
</tr>
</tbody>
</table>

*a Does not include diagnostic nanoparticles/theranostics (e.g., magnetic and luminescence-based optical contrast agents) for in vivo imaging (cell tracking, anatomical, functional) and/or combined therapy (e.g., hyperthermia). Source: Roadmaps in Nanomedicine, Toward 2020; Joint European Commission/ETP Nanomedicine Expert Report 2009.

SM Moghimi et al, ACS Nano, 5(11), 8454-8458, 2011
Nanomedicine Market

<table>
<thead>
<tr>
<th>Nanocomponent</th>
<th>Investigational</th>
<th>Commercial</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Therapeutic</td>
<td>Device</td>
</tr>
<tr>
<td>Hard NP</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Nanodispersion</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Polymeric NP</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Protein NP</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Liposome</td>
<td>53</td>
<td>0</td>
</tr>
<tr>
<td>Emulsion</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Micelle</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Dendrimer / Fleximer</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Virosome</td>
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<td>0</td>
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<tr>
<td>Nanocomposite</td>
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<td>0</td>
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<tr>
<td>NP Coating</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Nanoporous Material</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Nanopatterned</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Quantum Dot</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Fullerene</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hydrogel</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Carbon</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nanotube</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>122</td>
<td>25</td>
</tr>
</tbody>
</table>
Case Study 1
Orally administered nanocapsules for chemotherapy
Oral cationic nanocapsules

API:
- Camptothecin

Polymers:
- PCL, CS-PCL
- CD, CS-CD

*Published in;*

*BJOC, 11, 204-215, 2015*

Nanomaterial used
Amphiphilic Cyclodextrin

Primary face
OH (6)

Apolar cavity

OH (3)

OH (2)

Modification sites

Secondary face

OH (3)

OH (2)
Oral cationic nanoparticles
Gastrointestinal stability

<table>
<thead>
<tr>
<th>Media</th>
<th>Mean diameter (nm)</th>
<th>Polydispersity Index</th>
<th>Zeta Potential (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
<td>Initial</td>
</tr>
<tr>
<td>SGF pH 1.2</td>
<td>208.6</td>
<td>214.4</td>
<td>0.043</td>
</tr>
<tr>
<td>SIF pH 6.8</td>
<td>208.6</td>
<td>230.7</td>
<td>0.043</td>
</tr>
</tbody>
</table>

PCL-CPT
| SGF pH 1.2 | 220.4   | 239.3 | 0.21    | 0.144 | +6.2    | +14.6 |
| SIF pH 6.8 | 220.4   | 264.9 | 0.21    | 0.184 | +6.2    | +12.1 |

CS-PCL-CPT
| SGF pH 1.2 | 187.3   | 189.4 | 0.091   | 0.121 | -10.4   | -5.92 |
| SIF pH 6.8 | 187.3   | 199.7 | 0.091   | 0.175 | -10.4   | -7.68 |

CD-CPT
| SGF pH 1.2 | 197.8   | 185.9 | 0.102   | 0.123 | +17.1   | 19.20 |
| SIF pH 6.8 | 197.8   | 203.7 | 0.102   | 0.115 | +17.1   | 18.45 |

CS-CD-CPT
Oral cationic nanoparticles
Mucosal penetration

<table>
<thead>
<tr>
<th></th>
<th>24 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCL</td>
<td>40 ± 5</td>
</tr>
<tr>
<td>PCL-CS</td>
<td>50 ± 5</td>
</tr>
<tr>
<td>CD</td>
<td>60 ± 5</td>
</tr>
<tr>
<td>CD-CS</td>
<td>70 ± 5</td>
</tr>
</tbody>
</table>

Mucosal penetration of anionic and cationic CD nanocapsules in comparison to polymeric nanocapsules
Oral cationic nanoparticles
Caco-2 permeability

<table>
<thead>
<tr>
<th>Formulations</th>
<th>$P_{\text{app}} \times 10^6 \text{ cm/s} \pm \text{SD}$ $(n=3)$</th>
<th>Increase in permeability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free CPT solution</td>
<td>$2.88 \pm 0.39$</td>
<td>---</td>
</tr>
<tr>
<td>CPT-CD nanocapsules</td>
<td>$7.88 \pm 1.40$</td>
<td>274</td>
</tr>
<tr>
<td>CPT-CS-CD nanocapsules</td>
<td>$9.95 \pm 1.42$</td>
<td>345</td>
</tr>
</tbody>
</table>

Permeability through Caco-2 cells is a major indicative of oral bioavailability according to the BCS

Permeability of CPT in nanocapsules form significantly increased by CD nanocapsules

CS coating contributes to increased permeability
Oral cationic nanoparticles

Cytotoxicity vs. cancer cells

Improvement of cytotoxicity for CPT bound to cationic nanocapsules
Oral cationic nanoparticles
Animal Studies

Oral administration of CD nanocapsules with and without coating to healthy mice

Quantification of active load (Nile Red) in the stomach and intestines (4 segments)

Tested groups:
CD-NR-Nanocapsules
CS-CD-NR-Nanocapsules
Blank CD-Nanocapsules
Blank CS-CD-Nanocapsules
Case Study 2
Folate-targeted injectable nanoparticles

ACD-2

Molecular weight: 1767 g/mol
Highly soluble in ethanol
Surface charge close to neutral in PBS

ACD-1

Molecular weight: 3565 g/mol
Highly soluble in DMSO
Surface charge is close to neutral in PBS
### Table of Independent Variables

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
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</thead>
<tbody>
<tr>
<td>X₁: Surfactant percentage</td>
<td>0</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>X₂: CD concentration (mg/mL)</td>
<td>1.5</td>
<td>3</td>
<td>4.5</td>
</tr>
<tr>
<td>X₃: Ratio CD/PCX</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
</tr>
</tbody>
</table>

#### Dependent Variable

<table>
<thead>
<tr>
<th>Code</th>
<th>X₁</th>
<th>X₂</th>
<th>%X₁</th>
<th>X₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-1</td>
<td>-1</td>
<td>%0</td>
<td>1.5</td>
</tr>
<tr>
<td>2</td>
<td>-1</td>
<td>0</td>
<td>%0</td>
<td>3</td>
</tr>
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<td>3</td>
<td>-1</td>
<td>1</td>
<td>%0</td>
<td>4.5</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>-1</td>
<td>%0.25</td>
<td>1.5</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td>%0.25</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>1</td>
<td>%0.25</td>
<td>4.5</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>-1</td>
<td>%0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>0</td>
<td>%0.5</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>1</td>
<td>%0.5</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Factorial design to optimize critical parameters for manufacturing nanoparticle of desired final characteristics.

- Mean diameter <100 nm
- Possible lowest surfactant %
- Zeta potential neutral for prolonged circulation
<table>
<thead>
<tr>
<th>c</th>
<th>X₁</th>
<th>X₂</th>
<th>Particle size (nm)</th>
<th>Polydispersity Index</th>
<th>Zeta Potential (mV)</th>
<th>EE (%)</th>
<th>PCX amount per CD (μg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>331</td>
<td>0</td>
<td>2.64</td>
<td>84.8</td>
<td>0.187</td>
<td>-5.12</td>
<td>60.38</td>
<td>85.49</td>
</tr>
<tr>
<td>361</td>
<td>0</td>
<td>2.74</td>
<td>85.14</td>
<td>0.183</td>
<td>-5.08</td>
<td>62.3</td>
<td>82.81</td>
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<tr>
<td>362</td>
<td>0.0172</td>
<td>2.74</td>
<td>90.06</td>
<td>0.184</td>
<td>-5.02</td>
<td>60.43</td>
<td>85.06</td>
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<tr>
<td>391</td>
<td>0</td>
<td>2.84</td>
<td>85.84</td>
<td>0.18</td>
<td>-5.05</td>
<td>64.02</td>
<td>80.64</td>
</tr>
<tr>
<td>392</td>
<td>0.0172</td>
<td>2.84</td>
<td>90.9</td>
<td>0.181</td>
<td>-4.99</td>
<td>62.12</td>
<td>82.86</td>
</tr>
<tr>
<td>393</td>
<td>0.0345</td>
<td>2.84</td>
<td>95.75</td>
<td>0.181</td>
<td>-4.92</td>
<td>60.43</td>
<td>84.76</td>
</tr>
<tr>
<td>422</td>
<td>0.0172</td>
<td>2.95</td>
<td>92.1</td>
<td>0.178</td>
<td>-4.95</td>
<td>63.61</td>
<td>81.16</td>
</tr>
<tr>
<td>423</td>
<td>0.0345</td>
<td>2.95</td>
<td>97.1</td>
<td>0.179</td>
<td>-4.88</td>
<td>61.9</td>
<td>83.04</td>
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<tr>
<td>453</td>
<td>0.0345</td>
<td>3.05</td>
<td>98.8</td>
<td>0.177</td>
<td>-4.84</td>
<td>63.16</td>
<td>81.81</td>
</tr>
<tr>
<td>483</td>
<td>0.0345</td>
<td>3.15</td>
<td>100.9</td>
<td>0.177</td>
<td>-4.85</td>
<td>64.21</td>
<td>81.09</td>
</tr>
</tbody>
</table>

**From these results, 2.64 mg cyclodextrin and no surfactant % was selected for ACD-1 and 1.5 mg cyclodextrin and no surfactant for ACD-2 for an optimum formulation.**
Physicochemical characterization

DSC, XRD, FTIR for PCX-ACD interaction
Cell culture
Cytotoxicity and anticancer efficacy

L929 fibroblast cells

Folate positive cell line 4T1
Animal studies in mice with mammalian tumor induced with 4T1 instillation at the mammalian gland.
Ongoing studies

Comparative antitumor efficacy studies with Abraxane in mammalian tumor induced mice model

Physicochemical (PCC) comparison to Abraxane
Take home message

“Nanosimilars” ≠ Generics, Biosimilars

API Identity is Known

Common Requirements for Approval of Generics
- Thorough PCC
- Bioequivalence studies + others as deemed appropriate

API Identity is a Complex Mixture

Common Requirements for Approval of Biosimilars
- Thorough PCC
- Nonclinical studies? Clinical PK/PD/Efficacy
- Post market evaluation
- Clinical immunogenicity + others as deemed appropriate

Take home message

- Nanomedicines, combine different technologies ending up in complex heteromolecular products

- Head-to-head comparison to reference product through physicochemical, non-clinical and clinical studies for nanosimilarity

- Regulatory landscape still changing and developing; case by case approach required

- Science-based regulation is key to elucidate the quality, efficacy, safety and similarity of nanomedicinal product as a result of manufacture process parameters
EUFEPS Annual Meeting 2016
13-15 June 2016 Istanbul
www.eufepsannualmeeting.org

ANNUAL MEETING
Clinical Outcome and Regulation of Advanced Drug Delivery Products
JUNE 13-15, 2016
THE MARMARA HOTEL, ISTANBUL, TURKEY

SCIENTIFIC TOPICS

Meeting topics to be covered by the organization of active EUFEPS Networks include:

- Advanced drug delivery ranging from small molecules, biologics, gene therapy, cell therapy, tissue engineering
- Non-biological complex drugs
- Inhalation products
- Modified release
- Combination products
- Drug devices
- Therapeutic proteins and biosimilars
- Personalized medicine
- Manufacturing and upscaling issues
- Safety and toxicity of advanced therapeutics
- Regulatory approaches for advanced technologies in the pharma sector
- Reimbursement and pricing for advanced drug products
Thank you

Collaborating Partners:

**Uni Sevilla, Spain**
Juan Manuel Benito
Carmen Ortiz Mellet

**Uni Aalborg, Denmark**
Thorbjorn Terndrup Nielsen
Kim Lambertsen Larsen

**Uni Naples Federico II, Italy**
Fabiana Quaglia
Francesca Ungaro

**Uni Hacettepe, Turkey**
Levent Öner
Güneş Esendağılı
Hakan Eroğlu
Alper B İskit
Mustafa F Sargon
Ayşe Ercan
Murat Şen
İmran Vural

**PhD Students:**
Hale Ünal
Nazlı Erdoğan
Gamze Işık
Cem Varan
Demet Daşkın

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