Anticipation of regulatory needs for nanomedicines

1st EU-NCL survey with regulators

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Interaction with the European Nanomedicine Characterisation Laboratory

- to ensure the relevance of EU-NCL methods for decision making in particular for regulatory needs
- a series of questionnaires addressed to regulatory working groups experienced
Survey with regulatory agencies

The objectives of the survey

- to get an overview on the experiences of regulators with nanomedicines in the various regions
- To anticipate information needs
- To identify future priorities to support the translation of nanomedicines towards clinical applications

<table>
<thead>
<tr>
<th>No</th>
<th>Governmental organisation</th>
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<tbody>
<tr>
<td>1</td>
<td>Health Canada (market health products), Canada</td>
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<tr>
<td>2</td>
<td>European Medicines Agency</td>
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<tr>
<td>3</td>
<td>Swiss Agency for Therapeutic Products (Switzerland)</td>
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<td>4</td>
<td>Health Canada (health products and food branch), Canada</td>
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<td>5</td>
<td>United States Food and Drug Administration, USA</td>
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<td>6</td>
<td>Pharmaceuticals and Medical Devices Agency, Office of New Drug II; Japan</td>
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<td>7</td>
<td>Brazilian Health Surveillance Agency, Brazil</td>
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<td>8</td>
<td>Ministry of Food and Drug Administration, Korea</td>
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<td>9</td>
<td>Center for Drug Evaluation, Taiwan</td>
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<td>10</td>
<td>National Institute for Public Health and the Environment, Netherlands</td>
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<td>11</td>
<td>Federal Institute for Drugs and Medical devices, Germany</td>
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<td>The Medicines and Healthcare products Regulatory Agency, United Kingdom</td>
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<td>National Health laboratory, Luxembourg</td>
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<td>Spanish Medicines Agency, Spain</td>
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<td>15</td>
<td>Ministry of Health, Labour and welfare, Japan</td>
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<td>16</td>
<td>Australian Government, department of Health therapeutic goods administration, Australia</td>
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<td>17</td>
<td>National Agency for food and drug administration and control, Lagos</td>
</tr>
<tr>
<td>18</td>
<td>Health Science Authority, Singapore</td>
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Overview on the number of nanomedicines requesting regulatory approval

Applications for regulatory approval

- Regional differences of nanomedicine applications for the approval of clinical trials and market authorisation
- Knowledge sharing of regulatory bodies with more experiences required in order to prepare regions with less nanomedicine applications
Challenge: Regulation of „Nanosimilars“

Did you receive applications for follow-on nanomedicines that claim to be similar to an innovator product in the last 36 months?

Regional differences demonstrating that follow-on products might be an upcoming challenge also for the European regulatory bodies.
Challenge: Identification of the Regulatory Path

Did you regulate or were involved in discussions related to products containing nanomaterial that raises challenges regarding the regulatory pathway e.g. combination or borderline products?

- Borderline and combination products will require special regulatory awareness in the future
- Flagged as a priority in EMAs strategy document 2020

Validation status of characterisation methods

Were the characterisation methods used for quality assessments well described and sufficiently validated?

- only very few standards specifically addressing the application of nanotechnology in the health sector are available
Regulatory needs

Which physicochemical properties do you consider relevant for the preclinical characterization of nanomedicines that are not applicable to other pharmaceutical product classes?

- Chemical reactivity/catalytic activity
- Density
- Solubility and partition properties
- Redox potential
- Stability
- Surface charge
- Surface chemistry
- Physical form/morphology/shape
- Size and size distribution

The graph shows the number of agencies that consider each property relevant, depending on the nature of the nanomedicine, not relevant, or have no answer. The color coding indicates:
- Red: always
- Gray: depends on the nature of the nanomedicine
- Light gray: not relevant
- White: no answer
Did a specific property of the nanomedicine trigger any additional testing in vivo/in vitro in applications that you have reviewed?

- Specific properties of nanomedicines can trigger additional in vitro and in vivo testing.
- Understanding if what kind of information is needed in order to make tailor made in vitro tests available before introducing additional laborious and expensive animal experiments.
Is there a need to develop additional testing methods to assess the environmental effects of medicinal nanoparticles (ecotoxicology)?

- some product classes might need to demonstrate the safety for the environment
- better understanding what kind of environmental tests have to be developed
Pitfalls for toxicity testing

How do you value potential pitfalls for toxicity testing (in vitro/in vivo) in **market authorisations**?

- Solubilised fraction before and during the testing of metals and...
- Interaction between test reagent and the nanomaterial
- Stability and uniformity of the nanomaterial in the test medium
- Endotoxin assessment
- Agglomeration/aggregation behavior

How do you value potential pitfalls for toxicity testing (in vitro/in vivo) in **clinical trial applications**?

- Solubilised fraction before and during the testing of metals and...
- Interaction between test reagent and the nanomaterial
- Stability and uniformity of the nanomaterial in the test medium
- Endotoxin assessment
- Agglomeration/aggregation behavior
Harmonisation needs

Do we need to harmonise the characterisation of nanomaterials used in medical devices (free nanomaterial administered to the patient) and medicinal products?

Is it relevant to harmonise testing requirements of medicinal products and medical devices for nanomedicines in the various regions?
Functions of the EU-NCL

What functions could an EU-NCL fullfill to support regulatory authorities?

- Testing laboratory
- Extended consultancy service
- Technology scouting
- Scientific advice
- Test method validation
- No answer

The strategic partnership of the EU-NCL and the NCI-NCL can support regulatory by

- Providing expertise on information needs
- The development and validation of new test methods
- Supporting the harmonisation of methods
Conclusion

• Survey confirmed the regional differences
• Upcoming challenges might be „nanosimilars“ as well as borderline and combination products
• Additional toxicity tests might be required
• Currently only few standards for nanomedicine testing are available but consensus finding on future standardisation needs is ongoing
• Harmonisation of information requirements
• Alliance of EU-NCL and NCI-NCL can support the evaluation of methods
Next steps

- Publication of 1st EU-NCL survey in the format of a JRC technical report
- 2nd questionnaire with the EU Innovation Network
- Focus on requested information of European Agencies related to quality and safety of products in clinical trials

EU-NCL is funded by the European Union's Horizon 2020 Framework Programme, under grant agreement no. 65419
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Thank you for your attention
1st survey with the Nanomedicine Working Group of the international pharmaceutical regulators forum

- **Objectives:**
  - Non-confidential information and work sharing, regulatory harmonization or convergence focused on nanomedicines / nanomaterial in drug products, borderline and combination products.
  - Promotion of potential consensus finding on standards

- **JRC contribution**
  - Compilation, mapping and discussion on terminology and definitions with focus on the classification of nanomedicines / nanotechnology in drug products
  - Exchange and mapping of general Critical Quality Attributes for nanomedicines / nanotechnology in drug products
  - Survey with regulatory agencies
Which physicochemical properties do you consider relevant for the preclinical characterization of nanomedicines?

- Drug release
- Photocatalytic activity
- Functionality of targeting moieties
What will be the reference for comparison of nanoparticle-delivered drugs from a...

- cost/benefit perspective?
- safety/efficacy perspective?

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<thead>
<tr>
<th>Reference</th>
<th>No of Agencies</th>
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<tbody>
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<td>free drug</td>
<td>2</td>
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<tr>
<td>best medicine currently on the market</td>
<td>4</td>
</tr>
<tr>
<td>&quot;gold standard&quot; not necessarily commercially available</td>
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<tr>
<td>other standards</td>
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<tr>
<td>no answer</td>
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