Health Canada’s Experience on the Use of Nanotechnology in Drug Products

FDA/PQRI Workshop

Nanomaterial Drug Products:
Current Experience and Management of Potential Risks

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Outline

• Introduction
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• Current regulatory approach for nano-based health products
• Challenges
Introduction

• Nanotechnology based products are already marketed in a wide range of sectors (therapeutic products, electronics, paints, cosmetics, and more) and the numbers and complexity are expected to increase.

• It is recognized that nanomaterials exhibit unique physical and chemical properties which can be exploited for improved therapeutic benefits; however, these unique properties may lead to unanticipated behaviours.

• Health Canada acknowledges that new approaches may be necessary for risk assessment and risk management of nano-based health products to keep pace with advances in this area as there is inadequate information on risks associated with nanomaterials at this time.
Key Activities Related to Nanotechnology

- Number of working groups have been established at HC to raise awareness and address nanotechnology related issues:
  - The Health Portfolio Nanotechnology Working Group (HPNWG) was created in August 2004 to provide a broad-base of expertise and advice to senior Health Portfolio management on nanotechnology related issues and impacts specific to the Health Portfolio’s mandates.
    - Chaired by Science Policy Directorate
    - Co-ordinates activities and facilitates information sharing on nanotechnology and nanomaterials within HC
    - Includes representatives from Directorates regulating nanomaterials
The Health Portfolio Nanotechnology Working Group (HPNWG)
Health Canada's Health Products and Food Branch (HPFB) is responsible for regulation of the human health and safety aspects of health products, including pharmaceuticals, radiopharmaceuticals, biologics, natural health products, and medical devices.

Health products are regulated in Canada with a primary emphasis on product safety utilizing a risk/benefit analysis model. The regulations are product-centered and a number of Directorates within HPFB are organized along product-centred lines to oversee regulation of products for human use.
Health Products and Food Branch Directorate Responsibilities

- Drugs & Medical Devices
  - Pharmaceuticals (Rx), medical devices
- Biologics & Genetic Therapies
  - Blood, vaccines, recombinant drugs, tissues, organs, radiopharmaceuticals
- Natural Health Products
  - Vitamins, non Rx, herbs, minerals, disinfectants, etc.
- Veterinary Drugs
  - safety of foods from animals treated with drugs (eg: milk, egg, meat, eggs, etc.)
- Marketed Health Products
  - Post-Market Surveillance
- Inspectorate
  - Inspections, Investigations, Establishment Licenses

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The HPFB Nanotechnology Working Group was established in May 2007 to provide a broad-base of expertise and advice to senior management on nanotechnology issues and impacts specific to HPFB mandate.

- Currently chaired by the Therapeutic Products Directorate
- Co-ordinates activities and facilitates information sharing on nanotechnology based regulated health products (including pharmaceuticals, radiopharmaceuticals, biologics, natural health products, food and medical devices)
- Includes representatives from Directorates regulating health products
- Each Directorate is responsible for policies and guidances specific to their respective jurisdiction
The International Regulators Working Group on Nanotechnology was established in 2009 to discuss nanotechnology issues relevant to regulated products that may contain nanoscale materials. All discussions of this group are being conducted under the auspices of existing respective confidentiality arrangements.

Number of subgroups were formed to facilitate more detailed discussions in key product areas (including drugs, devices, food) to enable more detailed communication and collaboration among interested parties.

Key Activities Related to Nanotechnology (Cont’d)

• Currently Health Canada has no specific regulation for nanotechnology and does not have a product specific definition for nanomaterial containing regulated products.

• To identify regulated products and substances that may contain nanomaterials and to ensure a consistent approach across diverse regulatory programs Health Canada developed a general working definition which is described in the **Policy Statement on Health Canada’s Working Definition for Nanomaterial**.

• The working definition is relevant for all products and substances regulated by Health Canada.

Health Canada's Working Definition of Nanomaterial

- Health Canada considers any manufactured substance or product and any component material, ingredient, device, or structure to be nanomaterial if:
  - It is at or within the nanoscale in at least one external dimension, or has internal or surface structure at the nanoscale, or
  - It is smaller or larger than the nanoscale in all dimensions and exhibits one or more nanoscale properties/phenomena.

- For the purposes of this definition:
  - The term "nanoscale" means 1 to 100 nanometres, inclusive;
  - The term "nanoscale properties/phenomena" means properties which are attributable to size and their effects; these properties are distinguishable from the chemical or physical properties of individual atoms, individual molecules and bulk material; and
  - The term "manufactured" includes engineering processes and the control of matter.
The “Working Definition” is intended to be used as a tool to help the Department gather safety information about nanomaterials to improve the understanding of nanomaterials in its risk assessment and risk management activities.

It enables the Department to establish internal inventories, to ask for additional information, and to integrate new knowledge into regulatory decision making processes.

Although the Working Definition defines the term "nanoscale" as 1 to 100 nanometers (nm) inclusive, a product or substance that contains nanomaterial could measure beyond 1 micron in size. In these cases, regardless of the size, information may be requested for risk assessment purposes.

Therefore the Working Definition includes materials above the 100 nm size range to an upper limit of 1000 nm to maintain flexibility to take into consideration suspected nanoscale properties / phenomena.

Interpretation of the working definition regarding the "nanoscale properties/phenomena" will be addressed within the context of specific regulatory program areas.

As more evidence becomes available, program areas are expected to refine their information needs and produce program-specific guidance.
Current Regulatory Approach

• Health Canada relies on authorities within existing legislative and regulatory frameworks, which require the assessment of potential risks and benefits of products to the health and safety of Canadians before they can be authorised for sale.

• All health products, including those that contain nanomaterials are regulated by the *Food and Drugs Act*, and associated Regulations.

• The *Food and Drugs Act* and its associated regulations provide the authority to regulate all aspects of the life cycle of a health product, ranging from manufacturing (quality), non-clinical, clinical testing as part of the safety and efficacy assessment to the post-market surveillance of health products.

• Nanomaterial containing products are subject to the same rigorous health and safety regulations that apply to conventional health products.
Current Regulatory Approach (Cont’d)

• New health products can be sold in Canada once they have successfully passed a review process to assess their safety, efficacy and quality.

• Responsibility for this review process rests with Health Canada’s Health Products and Food Branch (HPFB).

• The HPFB evaluates and monitors the safety, efficacy and quality of thousands of human and veterinary drugs, medical devices, natural health products and other therapeutic products available to Canadians, as well as the safety and quality of food in Canada.
• To add visibility and transparency, the HPFB created a nanotechnology webpage entitled Nanotechnology-Based Health Products and Food.

• The webpage outlines applications of nanotechnology, and provides general guidance to stakeholders regarding health products containing nanomaterial. It is available on HC website at: http://www.hc-sc.gc.ca/dhp-mps/nano-eng.php

• The document advises sponsors and other stakeholders to communicate with responsible regulatory areas early in the development process if their products contain or make use of nanomaterial.

• It provides examples of the type of information that may be required for a nanotechnology-based product’s safety assessment.
Current Regulatory Approach (Cont’d)

- Section 2 of the *Food and Drugs Act* defines a drug as follows:

“drug” includes any substance or mixture of substances manufactured, sold or represented for use in

- the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,

- restoring, correcting or modifying organic functions in human beings or animals, or

- disinfection in premises in which food is manufactured, prepared or kept.
Current Regulatory Approach (Cont’d)

- **Product types regulated as drugs include:**
  - Pharmaceuticals (prescription, nonprescription, brand name, generic)
  - Biological drugs (vaccines, recombinant drugs, blood products)
  - Radiopharmaceuticals
  - Natural Health Products
  - Disinfectants for use on hard surfaces
  - Veterinary Drugs
Current Regulatory Approach (Cont’d)

- To facilitate identification and tracking of nanomaterial containing drug submissions Health Canada released a revised Drug Submission Application Form for Human, Veterinary, Disinfectant Drugs and Clinical Trial Application/Attestation (HC/SC 3011).

- The form asks the sponsor to self-identify when their application concerns a nanomaterial or 'nano-product'.

- To capture this information in electronic form, a “Nanomaterial” subclass code was added to the Drug Submission Tracking System (DSTS) to allow queries by subclass code “Nanomaterial”.
Current Regulatory Approach (Cont’d)

• Number of drug products have been assessed and authorized by Health Canada that may contain Nanomaterials.

• Pharmaceuticals and biologic products which may be regarded as products of nanotechnology or which contain nanomaterials include:
  - liposomal encapsulated drugs
  - albumin/polyethylene glycol (PEG) bound drugs
  - milled products
  - nanomaterial based sunscreens (ZnO or TiO2).

• Natural Health Products that may contain nanomaterials include:
  - Nano silver products.
  - Vitamin C liposomes.

• These applications were assessed under the existing regulatory framework using established principles of benefit/risk analysis.
Compared with conventional microparticulate formulation, nano-based drugs may demonstrate several advantages such as increased bioavailability, faster onset of action, dose uniformity, and reduction in fasted and fed variability.

Nano-formulations may function to overcome solubility or stability issues for the drug, limitations on route of administration, biocompartmentalization or side effect of generalized drug administration.

Information on the general method of manufacture for the drug substance, details on the technology and processes used in the manufacture of the drug substance and drug product and other relevant information is required to enable Health Canada perform its assessment to ensure that the drug can be produced consistently in high quality.
Current Regulatory Approach (Cont’d)

• The information submitted by the sponsor must demonstrate that the drug substance can be consistently manufactured to meet the intended specifications.

• The information must validate that the drug can be produced consistently and in commercial quantities within its required design space. For example, information on the description of the manufacturing process (such as reference to starting materials, critical steps, and reprocessing) and the controls that are intended to result in the routine and consistent production of material(s) of appropriate quality is evaluated.

• From a regulatory perspective, the evaluation of approved drugs which have been reformulated into nanoparticulate versions would involve determination of whether the nano-reformulation is significantly different from the non-nano approved version with respect to its safety, quality, and efficacy.

• For new chemical entities, the focus on their evaluation will be establishing from first principles: their safety, quality, and efficacy profile.
Current Regulatory Approach (Cont’d)

• It is expected that the existing regulatory pathway for a New Drug Submission (NDS) under *Food and Drug Regulations* would be appropriate and like all drugs, sponsors of nano-containing drugs must provide the necessary evidence to support all aspects of their submission.

• The onus will be on the sponsor to submit the necessary information.

• Regulatory decisions will be based on the *Food and Drugs Act* and *Regulations* and on the entire supporting evidence provided by the sponsor.
Currently there are no Health Canada guidance documents specific for nano-based health products. Maintaining a flexible approach is important to integrate new knowledge about risks and benefits related to nanomaterials into regulatory decision-making processes.

Health Canada believes that, in general, its current risk assessment methodologies are applicable for nanomaterials as they allow for sufficient flexibility. To address unique physical, chemical and biological properties of nanomaterials each product is assessed on a case-by-case basis.
Current Regulatory Approach (Cont’d)

• Basic physicochemical properties of nanomaterials including size, shape, charge, and stability could impart significant different physicochemical characteristics from those in its regular form.

• For nano-based health products, this becomes more critical given the unique properties and behaviour of the active pharmaceutical ingredient (API) at nano-scale.

• From regulatory perspective, it is important to clearly describe the extent to which the quality, non-clinical, and clinical data generated support the regulatory approval of these applications.
• During the review of nano-based health product applications, the special properties of nano-based products that are responsible for their activity such as their small size and high ratio of surface area to volume will be considered.

• Therefore, the new properties of nano-based health products may require additional product specific testing and manufacturing process controls.

• For product quality assessment (PQA) with respect to chemistry and manufacturing there are three main areas to consider:
  ≫ (1) Characterization (2) Manufacturing, and (3) Quality Control.
(1) Characterization

- As part of the regulatory process, the general properties of the health product, its characteristic features and characterisation data such as primary and higher order structure, biological activity, purity, and immunological properties are evaluated.

- Information on the potential and actual impurities arising from the synthesis, manufacture and/or degradation contributes to understanding the quality attributes of the product.

- For biotechnology derived products, results of characterization are compared with expected norms to decide on their acceptability.

- As part of the evaluation process, Health Canada verifies that there are no non-medicinal ingredients (excipients) which appear in the final product that are prohibited for use in drugs by the *Food and Drug Regulations*. 
(2) Manufacturing

- Manufacturing of nano-based health products has some of the similar challenges faced by regular health products such as control of critical process parameters (CPP), in-process control, and stability.

- However, there are additional critical factors that must be considered for a robust manufacturing process for nano-based health products such as consistent formulations with low batch-to-batch variability, manufacturing environmental conditions, manufacturing techniques, and scale-up.

- In product development, successful scale-up and manufacturing of a nano-based drug product is challenging as compared to conventional regular drug products. Each dosage form and route of administration (oral, parenteral, and inhalation) may require the use of a specific formulation and manufacturing technique.
(3) Quality Control

• To ensure, the high quality aspects of nano-based health products, it is important to have enhanced quality control measures. The application of “Quality by Design” could be a useful strategy to control the quality of nano-based health products.

• Another area of concern is the application of current pharmacopeial standards (such as USP, BP) to nano-based health products. The pharmacopeial standards are widely used for conventional health products which may not necessarily have all the specific critical material attributes (CMA) and critical quality attributes (CQA) required for achieving the quality of nano-based health products.

• Establishment of acceptable physical and chemical data, evidence of product performance *in vivo*, and limits for process impurities could be helpful to support application of a nano-based health product for approval. It is essential to use validated analytical methods for product characterization.
Current Regulatory Approach (Cont’d)

- For biologic drugs, an evaluation of the control of endogenous and adventitious agents in the production is also performed.

- Data from final batch analyses are reviewed to ensure they are acceptable based on the specification of the drug product.

- Health Canada’s lot release testing and evaluation program for biologic drugs tests and evaluates a specific number of lots of consecutively manufactured final product lots to ensure that the product satisfies the specifications of the drug product and that the product can be consistent during manufacture.

- For biologic drugs, Health Canada may perform on-site evaluations (OSEs) for the manufacturing facilities.
Like all drugs, nano-based drugs are expected to be supported by clinical data. As such clinical trials are expected to be conducted.

Clinical trials conducted in Canada involving human drugs are subject to Part C, Division 5 of the FDR or Part 4 of the NHPR that outline the requirements applicable to the sale and importation of drugs for use in human clinical trials.

Clinical Trial Applications (CTAs) should be submitted in accordance with Health Canada’s Guidance for Clinical Trial Sponsors: Clinical Trial Applications, the Clinical Trials Manual and Guidance Document for Clinical Trials for Natural Health products.

Information and/or data from clinical trials are evaluated as part of the safety and efficacy evaluation for the drug.
Current Regulatory Approach (Cont’d)

• Sunscreens are regulated as drugs in Canada, subject to either the FDR or the NHPR depending on the active ingredient and claim and must meet the appropriate regulatory requirements before they may be imported, advertised, or sold in Canada.

• The use of nanomaterials as UV filters such as nano-titanium dioxide (nano-TiO2) and nano-zinc oxide (nano-ZnO) in sunscreens, offers certain benefits to the consumer.

• As the risk assessment of nanomaterials is still evolving, Health Canada takes a precautionary approach in addressing potential safety concern with the use of nanomaterials as UV filters.

• Health Canada is continuing to monitor the emerging scientific studies to ensure appropriate action is taken should any substantial safety concerns be identified.

• Health Canada reserves the right to request information, material or define conditions in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product.
Challenges

- There are many regulatory and scientific issues that must be addressed before nano-based health products are authorised for sale in Canada.
- The state of science around nanomaterials is evolving. Joint efforts are needed to accelerate the achievements promised by Nanotechnology.
- Health Canada continues to work closely with domestic and international partners toward consistency with relevant international norms.
International cooperation

- Health Canada is actively involved internationally to ensure application of sound regulatory practices and standards which are consistent, whenever possible, with international norms, strengthen and facilitate existing mutual cooperation with international jurisdictions in scientific and regulatory areas; address the challenges of globalization, new technologies and timely approval of new medicines and reduce risks associated with therapeutic products marketed in Canada.

- Health Canada’s international engagements have taken many forms ranging from informal information exchanges to multilateral harmonization initiatives.

- Strong relations and dialogue with international counterparts are important in achieving program objectives in an increasingly complex regulatory world.
International cooperation (Cont’d)

• HC is involved in various key international initiatives, including:
  - International Organization for Standardization (ISO) Technical Committee (TC) 229 on Nanotechnologies
  - Organisation for Economic Co-operation and Development (OECD) Working Party on Manufactured Nanomaterials (WPMN)
  - Canada-US Regulatory Cooperation Council (RCC)
  - International Cooperation on Cosmetic Regulation (ICCR)
  - International Regulators Nanotechnology Working Group
Conclusions

• Currently, there are no regulations specific to nanotechnology-based health products. Health Canada relies on authorities within existing legislative and regulatory frameworks, which require the assessment of potential risks and benefits of products to the health and safety of Canadians before they can be authorized for sale.

• Health Canada encourages sponsors and other stakeholders to communicate with the responsible regulatory authority early in the development process, especially for combination products that are, contain or make use of nanomaterials.

• In order to identify and assess potential risks and benefits of nanotechnology based health products, the Department encourages manufacturers to request a pre-submission meeting with the responsible regulatory authority to discuss type of information that may be required for their product's safety assessment.

• As the risk assessment of nanomaterials is still evolving, Health Canada takes a precautionary approach in addressing potential safety concerns with the use of nanomaterials in health products. Therefore, for the assessment of nano-based health products additional/different data may be required and/or requested on a case-by-case basis depending on the developments in methodological risk assessment approaches and nano-specific testing requirements.
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Thank you