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Novel Aesthetic Treatments: Introduction to Exosomes – What We Know So Far

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Public Health Ontario Rounds

April 8, 2025

Disclosures

- Dr. Maureen Cividino does not have any conflicts of interest to disclose
- David Ryding does not have any conflicts of interest to disclose

Learning objectives

- Describe what exosomes are, how they are used and how they are derived
- Identify some of the challenges and concerns with the use of exosomes in personal service settings, medi-spas and other clinical settings
- Describe the current regulatory landscape in Canada related to the licensing, marketing and use of exosomes
- Identify key considerations and referral pathways when encountering exosomes

Outline

- Overview and background of exosomes
- Issues, concerns and unknowns with exosome use
- Public Health Unit experience
- Regulatory overview
- Question and answer period

What are exosomes?

- A form of extracellular vesicle, secreted by all cell types
- Very small (i.e., nano-sized) vesicles
- Involved in cell-to-cell communication by transporting complex cargo, such as genetic material (e.g., microRNAs, mRNAs, RNA, DNA), lipids, proteins
- The cargo is selectively taken up by local and distant recipient cells and influences various cellular processes (e.g., gene expression, cell-to-cell signaling, immune response, tissue repair)

Tienda-Vázquez, MA, Hanel, JM, Márquez-Arteaga, EM, Salgado-Álvarez, AP, Scheckhuber, CQ, Alanis-Gómez, JR., Espinoza-Silva, JI, Ramos-Kuri, M, Hernández-Rosas, F, Melchor-Martínez, EM, Parra-Saldívar, R. Exosomes: A Promising Strategy for Repair, Regeneration and Treatment of Skin Disorders. Cells. 2023 June; 12(12), 1625. Available from: https://doi.org/10.3390/cells12121625
Perocheau D, Touramanidou L, Gurung S, Gissen P, Baruteau J. Clinical applications for exosomes: Are we there yet? Br J Pharmacol. 2021; 178: 2375–2392. Available from: https://doi.org/10.1111/bph.15432

How are exosomes derived?

- Conventional sources (human/mammal)
  - Cells and tissues (e.g., adipose tissue, umbilical cord, placenta, bone marrow)
  - Body fluids (e.g., blood, saliva, urine, milk, amniotic fluids)
- Nonconventional sources (nonhuman/nonmammal)
  - Animal products (e.g., honey, venom)
  - Plants (e.g., fruits, seeds, pollen)
  - Bacteria, fungus, parasite

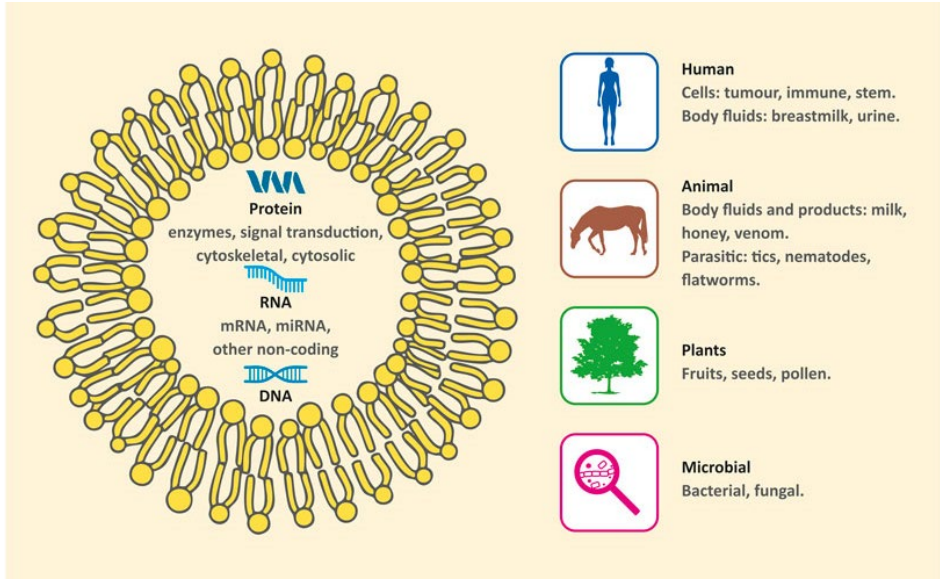


Image source: Janouskova O, Herma R, Semeradtova A, Poustka D, Liegertova M, Malinska HA and Maly J. Conventional and Nonconventional Sources of Exosomes–Isolation Methods and Influence on Their Downstream Biomedical Application. Front. Mol. Biosci. 2022 May; 9:846650. Available from: https://doi.org/10.3389/fmolb.2022.846650

Snake oil?

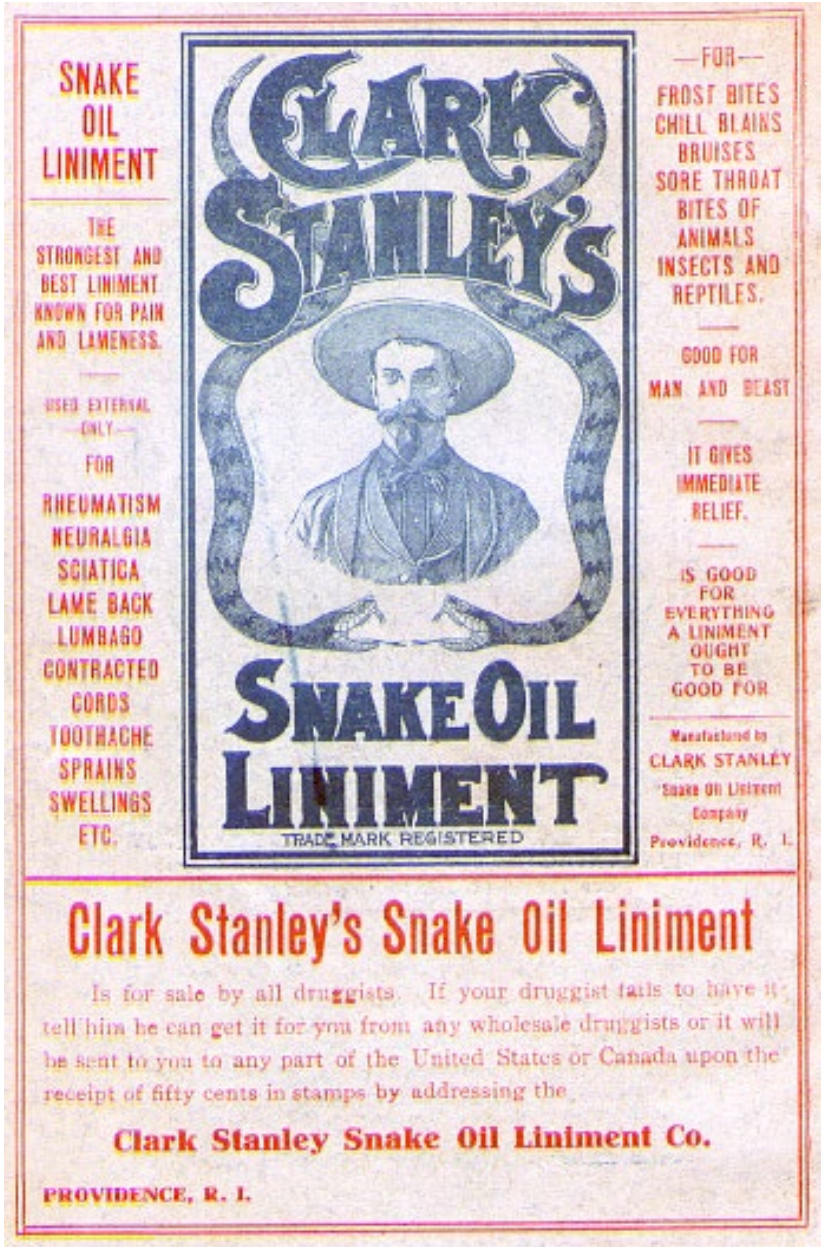


Image Source: Clark Stanley, Public domain, via Wikimedia Commons. Available from: https://www.nlm.nih.gov/exhibition/ephemera/medshow.html, attributed to: Clark Stanley's Snake Oil Liniment, True Life in the Far West, 200-page pamphlet, illus., Worcester, Massachusetts, c. 1905

What are exosomes used for?

- Therapeutic potential
  - Drug delivery
  - Vaccination
  - Immunomodulation
  - Gene therapy
- Disease diagnosis
  - Biomarkers
  - Disease progression

- Cosmetic application
  - Skin rejuvenation
    - Wrinkles
    - Photoaging
    - Scars
  - Wound healing
  - Hair growth

There are <u>no</u> exosomes of any kind, delivered by any route that are approved for use in Canada

Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science. 2020 Feb 7;367(6478):eaau6977. Available from: https://doi.org/10.1126/science.aau6977
Yousefian F, Espinoza L, Yadlapati S, Lorenc ZP, Gold M. A comprehensive review of the medical and cosmetic applications of exosomes in dermatology. J Cosmet Dermatol. 2024 Apr;23(4):1224-1228. Available from: https://doi.org/10.1111/jocd.16149
Harsha Sreeraj, R. AnuKiruthika, K.S. Tamilselvi, D. Subha, Exosomes for skin treatment: Therapeutic and cosmetic applications, Nano TransMed. 2024; (3) 100048. Available from: https://doi.org/10.1016/j.ntm.2024.100048.

How are cosmetic-related exosomes prepared and administered?

- Topically without disruption to skin barrier
  - Face mask, serums, combined with creams and rubbed in
- Topically with disruption to skin barrier
  - Microneedling
  - Radio Frequency (RF) microneedling
  - Laser/RF skin resurfacing
  - Chemical peels
  - Mesotherapy
  - Dermabrasion
- Intradermal, subcutaneous or intravenous routes

Zhang Y, Bi J, Huang J, Tang Y, Du S, Li P. Exosome: A Review of Its Classification, Isolation Techniques, Storage, Diagnostic and Targeted Therapy Applications. Int J Nanomedicine. 2020 Sep 22;15:6917-6934 Available from: https://doi.org/10.2147/ijn.s264498

How safe are they?

- May promote infection or play an anti-infective role
  - Exosomes can either accelerate or inhibit the process of infection
  - In both cases, exosomes make possible connections between host cells or between pathogens and host cells
- Participating in the immune escape of pathogens
  - Some pathogens can escape the host immune system with the help of exosomes and this favors their spread
- Manufacturing process issues; handling and administration errors
  - May also be implicated in infection transmission

Zhang W, Jiang X, Bao J, Wang Y, Liu H, Tang L. Exosomes in Pathogen Infections: A Bridge to Deliver Molecules and Link Functions. Front Immunol. 2018 Feb 12;9:90. Available from: https://doi.org/10.3389/fimmu.2018.00090

What are the challenges with producing exosomes?

- Exosome source influences the types of pathogens that may be present in products
- Thorough screening of exosome donors is essential for human and animal sources
- Manufacturing techniques must ensure sterility and properly filter out potential pathogens
- Quality control measures to ensure purity of the product, such as testing the final product

Ahn SH, Ryu SW, Choi H, You S, Park J, Choi C. Manufacturing Therapeutic Exosomes: from Bench to Industry. *Mol Cells*. 2022;45(5):284-290. Available from: https://doi.org/10.14348/molcells.2022.2033

Food and Drug Administration (FDA) warning letters

- Since 2020, the US FDA has issued several warning letters related to the manufacture and distribution of exosomes
- This includes the results of 4 inspections conducted at 3 facilities that were manufacturing exosomes without regulatory approval
- They identified a total of 50 infractions across 25 different offences
- Types of offences included:
  - Poor quality control
  - Poor aseptic technique
  - A failure to screen donors

The U.S. Food and Drug Administration. Warning Letter: Invitrix Therapeutics Inc. Silver Spring, MD: FDA: 2020. Available from: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/invitrx-therapeutics-inc-581182-03162020
The U.S. Food and Drug Administration. Warning Letter: EUCYT Laboratories LLC. Silver Spring, MD: FDA: 2020, Available from: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/eucyt-laboratories-llc-607182-06042020.
The U.S. Food and Drug Administration. Warning Letter: Invitrix Therapeutics Inc. Silver Spring, MD: FDA: 2022 Available from: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/invitrx-therapeutics-inc-630712-11092022
The U.S. Food and Drug Administration. Warning Letter: Kimera Labs Inc. Silver Spring, MD: FDA: 2024 Available from: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/kimera-labs-inc-649343-09012023

Pathogens noted in FDA warning letters

- Gram positive cocci
- Gram negative rods
- *Acidovorax temperans*
- *Clostridium perfingens*
- *Enterococcus faecalis*
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Kocuria varians*
- *Streptococcus spp*
- Hepatitis B virus

2019 Nebraska outbreak

- Following IV administration, five *E.coli* sepsis cases occurred within hours of receiving exosome treatment
- The exosomes were sourced from harvested human placentas
- The product was unregulated, not FDA approved and not associated with any clinical trials
- The company relied on internal protocols for safe production
- Bacterial isolates from contaminated product matched the clinical specimens
- Resulted in state-wide health alert and FDA notice

Salehi, Susanne. Congratulations to Dr. Maureen Tierney, 2020 Inaugural McKnight Prize for Healthcare Outbreak Heroes Recipient [Internet]. CDC Foundation. 2020. [Cited Feb 24, 2025] Available from: https://www.cdcfoundation.org/blog/dr-maureen-tierney-receives-mcknight-prize-healthcare-outbreak-heroes-award

Other case reports

- Papules and nodules
  - 8 individuals developed erythematous indurated papules or nodules at the site of exosome injections
  - Onset ranged from 2 weeks to 3 months post treatment
- Foreign body granuloma
  - A 50-year-old woman developed papules and nodules 7 weeks after receiving exosome injections with a product that had not been officially released
  - Patient was diagnosed with foreign body granuloma
- Skin necrosis
  - A 36-year-old man received intradermal injections of an exosome product that was mixed on site
  - Three days later he presented with skin necrosis

Nahm, W.J.; Thunga, S.; Yoo, J. Complications After Exosome Treatment for Aesthetic Skin Rejuvenation. Dermatol. Rev. 2024, 5, e242. Available from: https://doi.org/10.1002/der2.242
Hoon Choi, Jun Ho Kwak, Bong Seok Shin, Chan Ho Na, Min Sung Kim, Foreign body granuloma caused by an injection of exosomes, JAAD Case Reports, April 2024, Available from: https://doi.org/10.1016/j.jdcr.2024.03.026
Tawanwongsri W, Vachiramon V. Skin necrosis after intradermal injection of lyophilized exosome: A case report and a review of the literature. J. 2024 May;23(5):1597-603. Available from: https://dx.doi.org/10.1111/jocd.16206

Risk at point of administration

- On site mixing
- Dosing
- Improper handling
- Storage issues

E. Tzng, N. Bayardo, P.C. Yang, Current challenges surrounding exosome treatments, Extracell. 2023 Dec; 100023. Available from: https://doi.org/10.1016/j.vesic.2023.100023

Conclusion

- Exosomes offer exciting promise in cancer and neurological disease research, use as a potential vehicle for drug delivery and there is growing interest in their application in the field of aesthetics
- Despite exosomes having no Health Canada approval for any type (human, animal or plant) or approval for any route of administration (topical, injectable) they are currently widely in use in aesthetic services in Ontario
- There remain significant safety considerations in the sourcing and manufacturing of exosomes as well as handling, administration and storage
- There are reports of serious infection and adverse health outcomes, including sepsis with intravenous use

Communicable Disease Control Portfolio: Communicable.DiseaseControl@oahpp.ca

Public Health Ontario keeps Ontarians safe and healthy. Find out more at **PublicHealthOntario.ca**

BodySafe

Toronto Public Health: Discovery of Exosomes In Personal Services Settings

Cecilia Alterman, Manager

Herveen Sachdeva, AMOH

Toronto Public Health

Inspectors Discovery

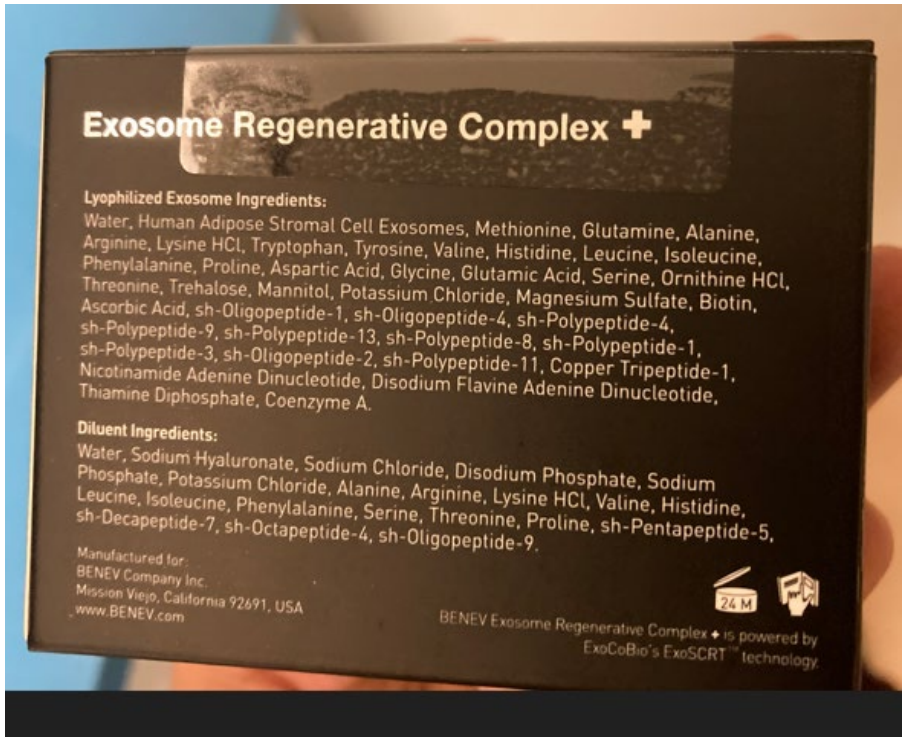
Exosome serums can be used topically or with micro-needling style devices.

These products do not have a drug identification number or natural product number on the label. Some websites indicate these products are USA FDA approved.

Products can be derived from human cell origin or made from animal or synthetic means.

BodySafe

Products Found



Human Exosomes

Synthetic Exosomes

Animal Exosomes

Health Canada Referral

No exosome products are approved by USA FDA or Health Canada for consumer use.

Would be regulated as a drug or biologic health product.

Canadian suppliers are purchasing USA non-FDA approved products & claiming it is approved as a “topical cosmetic”.

Actions

- Consulted with Public Health Ontario & Ministry of Health.
- Continue to issue Verbal Orders under Section 13 (7) of the Health Protection and Promotion Act, R.S.O. 1990, c. H.7 to immediately stop use and remove all products with exosome ingredient.
- Recommend to stop all advertising of product and services using product as indicated in the Order.

Actions

- PHIs to continue taking pictures of exosome products, document manufacturer and supplier.
- Continue to refer products/suppliers to Health Canada, PHO and MOH.
- Posted general information for public on BodySafe.ca.

BodySafe.ca

Do not purchase products or provide services with products that contain human exosomes. For more information, visit our aesthetics page. If you have these products at your premises or see these products in the City of Toronto please contact BodySafe at bodysafe@toronto.ca.

Exosomes

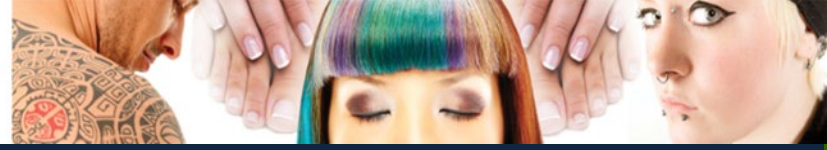
Exosomes are tiny sac-like structures that are formed inside a cell. Exosomes leave the cell and carry RNA, DNA, lipids, and proteins from one cell to another for communication. Products with exosomes are classified as a drug and must be Health Canada approved with a Drug Identification Number (DIN) or Natural Product Number (NPN). This includes if it is applied topically or used in combination with any other invasive procedure.

What you need to know

- Currently there are NO products containing human exosomes approved for sale or use in Canada.
- Do not purchase products or provide services with products that contain human exosomes.
- Toronto Public Health recommends not to purchase products or provide services with animal and synthetic exosomes.
- Long term studies are required to determine the safety of these products.
- Exosome products can become contaminated in the manufacturing process and have been linked to bacterial sepsis and notices advising clients of potential exposures to bloodborne pathogens in the United States.

If you have these products at your premises or see these products in the City of Toronto please contact BodySafe at bodysafe@toronto.ca.

BodySafe



Suggested Next Steps

Inform health units of risks associated with these products.

Communicate to regulatory colleges.

Advocate to Health Canada to issue warning on purchase, sale, use of these products.

Regulatory Landscape of Exosomes

Ministry of Health

April 8, 2025

Ontario

Objectives

- Describe the existing regulatory landscape in Canada related to the licensing, marketing and use of exosomes
- Identify key considerations and referral pathways when encountering exosomes

Food and Drug Act

- Health Canada is responsible for the regulation of personal care products (*Food and Drugs Act*)
  - Cosmetics → Cosmetic Regulations
  - Drugs → *Food and Drugs Regulations*
  - Natural Heath products (subset of Drugs) → *Natural Health Products Regulations*
- Section 2 of the Food and Drugs Act
  - **Cosmetic:** any substance or mixture of substances manufactured, sold or represented for use in cleansing, improving or altering the complexion, skin, hair or teeth, and includes deodorants and perfumes
  - **Drug:** any substance or mixture of substances manufactured, sold or represented for use in
    - (a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,
    - (b) restoring, correcting or modifying organic functions in human beings or animals, or
    - (c) disinfection in premises in which food is manufactured, prepared or kept;

Health Canada. Guidance Document Classification of Products at the Cosmetic-Drug Interface [Internet]. Available from: https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/industry-professionals/guidance-document-classification-products-cosmetic-drug-interface.html

Cosmetic-Drug Interface

- Classification of a product as a cosmetic or a drug is done on a case-by-case basis in accordance with a list of set criteria:
    - **Representation for use** (explicit or implied)
        - e.g., indications of use, claims presented as a word, a sentence, a picture, a symbol, a paragraph or an implication on product labels, package inserts or advertisements.
    - **Composition**
        - i.e., the ingredients, components, structure of the product, and their contribution to the therapeutic representation
    - **Level of Action**
        - Cosmetics must lack percutaneous absorption and should not have to be absorbed below the skin to achieve the effect
        - Cosmetics cannot be administered via ingestion, inhalation, or by injection (except tattoo ink)
- Risk alone does not qualify a substance as either a cosmetic or a drug.
- Ultimately the intended purpose of the product takes precedence in the classification decision.

Health Canada. Guidance Document Classification of Products at the Cosmetic-Drug Interface [Internet]. Available from: https://www.canada.ca/en/health-canada/services/consumer-product-safety/reports-publications/industry-professionals/guidance-document-classification-products-cosmetic-drug-interface.html

Microneedling Involving Topical Products

- If the product is administered by microneedling, it would **not** be considered a cosmetic
    - Guidance Document: Classification of Products at the Cosmetic-Drug Interface
- If the product is applied to the skin **prior** to microneedling it could be considered a cosmetic
    - Applied **before and not at the time** of the microneedling procedure
    - If the product claims to prepare the skin for microneedling but limits its claims to a cosmetic function (e.g. moisturizing, cleansing, conditioning), then it may be a cosmetic
    - If the product suggests a therapeutic claim prior to the microneedling, it would be considered outside the scope of a cosmetic.
        - Examples of therapeutic/ health claims for drugs: Guidelines for the Nonprescription and Cosmetic Industry Regarding Non-therapeutic Advertising and Labelling Claims.
        - Therapeutic/ health claims cannot appear on the labels or advertising of cosmetics. Products for which therapeutic claims are made are classified as drugs.
    - If the substance is applied before microneedling but will be absorbed into deeper layers of the skin during the procedure, then it could be considered beyond the scope of a cosmetic.

Health Canada Authorization

- **Drugs**

- **Clinical Trials**: No Objection Letter (**NOL**) is required
    - To verify authorized drugs under clinical trials, refer to Clinical Trials Database

- **Market Distribution**: Notice of Compliance (**NOC**) and Drug Identification Number (**DIN)** is required
    - To verify authorized drugs, refer to Health Canada's Drug Product Database

Cosmetics

- All manufacturers and all importers are required to notify Health Canada within 10 days after they first sell a cosmetic in Canada.

- Not subject to pre-market review of approval but are regulated in a post-market system

- Evidence of a completed/successfully submitted "Cosmetic Notification Form" from a manufacturer/seller does **not**:
    - Constitute approval for sale by Health Canada;
    - Provide agreement that the product is appropriately classified as a cosmetic and not a drug;
    - Confirm that the product complies with all legislative requirements.

Health Canada. Health Canada's Clinical Trials Database. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/health-canada-clinical-trials-database.html
Health Canada. Guidance Document: Regulatory Requirements for Drug Identification Numbers (DINs). Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/regulatory-requirements-drug-identification-numbers/document.html
Health Canada. Notification of Cosmetics [Internet]. Available from: https://www.canada.ca/en/health-canada/services/consumer-product-safety/cosmetics/notification-cosmetics.html

Authorization of Human-Derived Exosomes

- All human-derived exosomes intended for administration (including topically applied products) to humans are considered **drugs** under the FDA
  - Rationale: associated with inherent therapeutic potential and biological activity
  - Requires authorization under the Food and Drug Regulations as biologic drugs prior to sale.
- To the Ministry's knowledge,
    - As of April 2, 2025, Health Canada **has not approved or authorized any exosome-based products** for use in Canada.
    - Neither a NOL or NOC and DIN have been provided for exosome-based products and therefore they cannot be legally marketed or sold

Exosomes From Other Sources

- Classification and authorization on a **case by case** basis
- Depends on factors like the source, representation, composition, route of administration, and therapeutic activity

Product 1

- 100% synthetic
- Purported claims from cosmetic sponsors; the validity of which has not been evaluated by Health Canada:
- Establishes intercellular communication bridges to enhance and activate skin cells
- Emulates the signaling biological qualities and capabilities of human mesenchymal cell-derived exosomes
- Penetrates skin cells, triggering physiological processes that promote tissue repair and regeneration
- **Assessed as a Drug (can be subject to change)**

Product 2

- Milk exosome
- Applied immediately after aesthetic treatments such as microneedling, laser/RF skin resurfacing, dermabrasion
- **Assessed as a Drug (can be subject to change)**

Response

- **Health Canada**

- Under the *Food and Drugs Act,* Health Canada has the authority to take compliance and enforcement actions related to non-compliance with the *Food and Drugs Act* or its associated regulations
    - Verify if a non-compliance has occurred
    - Take compliance and enforcement actions in line with the Compliance and Enforcement Policy
        - Type of action depends on facts of each case and appropriate for the situation
        - Can include site visits, stop sales, recalls and/or seizing products and advertising materials
- In response to the information provided on exosomes, Health Canada Health Product Compliance Directorate has opened a case for further follow up
    - Status: ongoing
- **Ministry**
- Collaborate with PHO and local public health units
- Liaise with Health Canada
- Raise awareness

Ontario Legislative Overview- Public Health

- *Health Protection and Promotion Act*, 1990
    - Section 13 Order
    - O. 136/18: *Personal Service Settings Regulation*
- Ontario Public Health Standards and Protocols
    - Duty to inspect personal service settings
    - Duty to investigate complaints (e.g., personal service settings, clinical offices not routinely inspected)

Key Considerations

- Are there IPAC concerns?
- Is there a health hazard?
    - Section 13 Orders under the HPPA are an enforcement action that can be utilized if exosomes are found.
    - This decision is made at a local level.

Ontario Legislative Overview- Regulatory Colleges

- In Ontario, regulated health professions are governed under:
  - The *Regulated Health Professions Act*, 1991 (RHPA)
  - Health profession-specific Acts (for example, Medicine Act, 1991)
- ***Regulated Health Professions Act*, 1991 (RHPA)**
  - Creates a legislative framework for governing health professions in Ontario (26 regulatory colleges overseeing 28 professions).
  - It establishes one set of rules and procedures that all colleges must follow.
  - Is a "self-regulation" model that assumes professions are best placed to regulate themselves
  - Makes regulatory colleges responsible for:
    - Regulating their members in the public interest
    - Ensuring members provide health services in a safe, competent, and ethical manner
    - Developing and maintaining standards of practice, education requirements, complaints, discipline and fitness to practice processes, among other requirements

Key Considerations

What are regulatory colleges' positions regarding their members using, prescribing, administering, and/or dispensing products (e.g., drugs/devices) that are not specifically approved for use by Health Canada?

Next steps

- **Key considerations**

- There are potential risks associated with using unauthorized products that have not been assessed for safety, effectiveness and quality by Health Canada, including human-derived exosomes. These risks include transmission of infectious disease and adventitious agents, and toxic effects.

- **Public Health:**
  - Need to consider the evidence and information available as to whether there are violations of O. Reg 136/18 when it comes to IPAC concerns and whether a health hazard exists
  - Educate operators

- **Regulatory Colleges:**
  - Members of the profession may consult with regulatory colleges to determine if using an unauthorized drug conflicts with practice standards
  - Educate members of the profession, if needed.

Referral pathways

- Refer to Health Canada any concerns or questions on classification of a product (e.g., drug, cosmetics)
- Report sale, advertising, manufacturing, clinic offering exosome-based therapies or any other non-complaint or unauthorized health products to Health Canda using the online complaint form