Decision Making and Clinical Nuclear Medicine

A Canadian Pharmacists’ Perspective

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A Canadian Pharmacists’ Perspective on:
(Radiopharmacist, Regulator, Industry Regulatory Affairs)

1. Impact of Regulatory Agencies
2. Changing landscape of radiotracers
3. Economic impact on nuclear medicine
Nuclear Medicine in Canada

250 Nuclear Medicine departments
- Private clinics
- Hospitals

Provision of Radiopharmaceuticals
- Commercial Radiopharmacies
- Radiopharmacies
- Hospitals based NM services
- Industry

Provision of PERs
- Commercial Radiopharmacies
- In-house Cyclotron facility

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Agencies Impacting on Nuclear Medicine and its Related Industry

Canadian Nuclear Safety Commission (CNSC)

- Protects the health, safety and security of Canadians as well as the environment, and respects Canada's international commitments on the peaceful use of nuclear energy.

- The Atomic Energy Control Board was established in 1946; CNSC was established in 2000 under the Nuclear Safety and Control Act and reports to Parliament through the Minister of Natural Resources.

- Issues licences/certificates for:
  - Facilities
  - Nuclear medicine facilities and clinics, uranium mines and mills, fuel fabricators, labs
  - Medical devices
  - Radioactive sources
  - Transport containers

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Agencies Impacting on Nuclear Medicine and its Related Industry

Health Canada

- **Guardian/Regulator** through a stewardship role that involves both protecting Canadians and facilitating the provision of products vital to the health and well-being of our citizens.

- Regulating and approves the use of thousands of products, including:
  - Biologics,
  - Consumer Goods
  - Foods
  - Medical Devices
  - Natural Health Products
  - Pesticides
  - Pharmaceuticals, and
  - Toxic Substances

- Under the Canadian Food and Drugs Act, reports to Parliament through the Minister of Health
Agencies Impacting On Nuclear Medicine And Its Related Industry

Provincial Health Authorities

- Guide and enhance the province's health services to ensure the public are supported in their efforts to maintain and improve their health.
- Improve the health and wellness of the public.
- Provide high quality patient care.
- Ensure the health care system remains sustainable, affordable and publicly funded.
Agencies Impacting On Nuclear Medicine And Its Related Industry

Change:

• Any changes in the Acts or introduction of a new Act giving authority to agencies

• A crisis or world event can precipitate a change

• A local or regional event highlighting an issue to an Agency

• An agencies participation on a international body with a view to global harmonization
Provision of Radiopharmaceuticals – Today

- **Commercial Radiopharmacies (including PET)**
  - for profit

- **Radiopharmacies (including PET)**
  - hospital-based offering a regional service to under a single administration – not for profit

- **Nuclear Medicine - hospitals based services**

- **Industry**
The Central Radiopharmacy

Pre-1980
- No interest by Health Canada
- The concept begins to evolve
- Colleges of Pharmacy will not be involved

1980s
- Centralized radiopharmacies developing
- Many hospital based radiopharmacies were formulating their own kits, etc.
- Health Canada had made informal visit to assess the standard of practice
- Managers:
  - Radiopharmacists
  - Radiochemists
  - Nuclear medicine technologists

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1980s

Health Canada implements a ‘change’: 
(*Through informal visit to sites HC collected information on practices*)

- All radiopharmacies must have licences listing products
- All formulated radiopharmaceuticals must be approved:  
  - ‘Notice of Compliance’ - drug approval
- Managers – “responsible, qualified”
The Central Radiopharmacy

Problems:

• Health Canada did not implement regulations or extensive guidance's.

• Central radiopharmacies were asked to apply the spirit of the GMP based on GMP regulations for drugs; industry had accepted this direction.

• No regulations were becoming a problem when site GMP issues arose for radiopharmacies.

Result:

• Exemption for radiopharmaceuticals in GMP regulations was removed, now GMP regulations apply.
  • Annex for radiopharmaceuticals.
  • Annex for positron emitting radiopharmaceuticals (PERS).
Today

• **Canadian Establishment Licence** is issued annually.
  • Based on a GMP compliant inspection every two years
  • Also applies to all
    • Manufacturers
    • Wholesalers
    • Distributors
    • Packagers
    • Labellers
    • Testers
The central radiopharmacy is now held to the same standards as industry.
## PET In Canada

<table>
<thead>
<tr>
<th>Province</th>
<th>PET/ CT</th>
<th>Cyclotrons</th>
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<tbody>
<tr>
<td>British Columbia</td>
<td>1</td>
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<td>Manitoba</td>
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<td>Nova Scotia</td>
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<tr>
<td><strong>Research</strong></td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>32</strong></td>
<td><strong>12</strong></td>
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</table>
PET Facilities

Early 2000
Expert Advisory Committee struck to develop a policy on regulating Position Emitting Radiopharmaceuticals (PERS)

- Sites are urged to file one NDS for F-18 FDG, & other PET sites can cross reference; No one wishes to do this.
- Clinical Trial Applications (CTAs) are required for all new products

2005
GMPs for PERs
- Existing radiopharmaceutical GMPs were not appropriate and did not address PER issues

2009
Health Canada differentiates research & clinical products
- clinical diagnosis - requires a CTA
- research products - Research Ethics Board responsibility is mandatory and only notification to Health Canada is required.

PET facilities with additional sites
- Notifiable Change required when processes and conditions of manufacture are same as existing product & same source of F-18 was being used
- However, SNDS required if source of F-18 is a different cyclotron
Health Canada

Radiopharmaceuticals include drugs either of chemical or biological origin which are intentionally made radioactive for the purpose of diagnosing illness or treatment.

Include:
- Finished dose form radiopharmaceuticals
- Kits for the preparation of radiopharmaceuticals
- Radionuclide generators

Radiopharmaceuticals are always prepared and administered by health care professionals; they are never self-administered.
1970 - 90
Self contained regulatory group in Environmental Health
  • Submission review
  • Annual establishment licence issuance
  • Inspection of all licenced manufacturers every two years
  • Quality control testing laboratory = program parallel the Australian TGA program
    • closed 1992

Adverse event reporting
  • Directly to Drugs Directorate
  • Confusion with terminology – database input was often in incorrect
  • Nuclear Medicine community does not know about the program

1995
Program moves to be aligned with drugs and biologics
  • Inspections are now performed by the Inspectorate
Section 12: Canadian Food and Drugs Act

No person shall sell any drug described in Schedule C or D unless the Minister has, in prescribed form and manner, indicated that the premises in which the drug is manufactured and the process and conditions of manufacture therein are suitable to ensure that the drug will not be unsafe for use.

Regulations Specific to Radiopharmaceuticals: Division 3 of the Canadian Food and Drug regulations

Inner and outer label requirements & package insert content
  • Radiopharmaceuticals
  • Kits
  • Generators

Prescriptive
Probably the best labelling regulations for radiopharmaceuticals in the world

Additional references for Tc-99m generator specifications & 2009 – PER research
Health Canada: Regulations

- Division 1: Licencing
- Division 2: Good Manufacturing Practices
- Division 3: Radiopharmaceuticals
- Division 4: Biologics
- Division 5: Clinical Trials
- Division 8: New Drug Submission Requirements
Global Direction: Impact Of Health Canada

International Conference on Harmonization (ICH)

Mutual Recognition Agreements

Memorandums of Understanding
"International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use".

• ICH is a joint initiative involving both regulators and industry as equal partners in the scientific and technical discussions of the testing procedures which are required to ensure and assess the safety, quality and efficacy of medicines.

• The focus of ICH has been on the technical requirements for medicinal products containing new drugs.
The industry was becoming more international and seeking new global markets, but the registration of medicines remained a national responsibility.

Different regulatory systems were based on the same fundamental obligations to evaluate the quality, safety and efficacy, but the detailed technical requirements had diverged over time to such an extent that industry found it necessary to duplicate many time-consuming and expensive test procedures, in order to market new products, internationally.

The urgent need to rationalise and harmonize regulation was impelled by concerns over:

- rising costs of health care
- escalation of the cost of R&D
- the need to meet the public expectation that there should be a minimum of delay in making safe and efficacious new treatments available to patients in need.
International Conference on Harmonization (ICH)

Six Parties
- European Medicines Agency (EMEA)
- European Federation of Pharmaceutical Industries and Associations (EFPIA)
- Ministry of Health, Labour and Welfare, Japan (MHLW)
- Japan Pharmaceutical Manufacturers Association (JPMA)
- US FDA
- Pharmaceutical Research and Manufacturers of America (PhRMA)

Non-voting members
- Acts as a link between ICH and non-ICH countries and regions
- WHO
- European Free Trade Association (EFTA)
- Canada (Health Canada)
International Conference On Harmonization (ICH)

Goal

• To promote international harmonization by bringing together representatives from the three ICH regions (EU, Japan and USA) to discuss and establish common guidelines.

• To make information available on ICH, ICH activities and ICH guidelines to any country or company that requests the information.

• To promote a mutual understanding of regional initiatives in order to facilitate harmonization processes related to ICH guidelines regionally and globally.

• To strengthen the capacity of drug regulatory authorities and industry to utilize them.
Examples Of Impact Of ICH

Common Technical Document (CTD) for drug submissions
Now adopted globally – US, EU, Japan, Canada, Australia, etc.)

Prescribes the layout & content of a drug submission.

• All drug manufacturers are to preparing submissions to health agencies in the CTD format. This facilitates a submission to another agency accepting the same format.

• *In the next 10 years, all submissions to developed countries will be electronic.

Health Canada
• CTD format is applicable to industry & radiopharmacies.
• Developed guidances on radiopharmaceuticals as a tool to complete the CTD

Issues:
• Some countries have modified the format somewhat adding their own unique requirements.
• Some countries – not part ICH – have not adopted the CTD format as yet
Examples of Impact of ICH

Q7A - Guidance on GMP for Active Pharmaceutical Ingredients (APIs)

Now adopted by US, EU, Japan

EU bring guidance to Europe and Parliament legislates implementation by member states by a specified date.

US and Japan adopt the guidance into their own country format and it is implemented.

Guidance states –” not applicable to radiopharmaceuticals”.

**US**

US FDA instructs radiopharmaceutical providers of APIs: “you have the choice to apply this guidance or the drug GMPs, to those APIs you manufacture”.

**Health Canada**

Has not adopted Q7A because the Act and regulations do not give them the authority to regulate APIs.
Memorandums of Understanding (MOU)

• Formal memorandums are often in place between two agencies covering the sharing of information:
  • Post market surveillance
  • Investigational applications
  • Marketing applications
  • Orphan designation
  • Recalls
  • And more

• More than ever agencies are talking to one another to share information

• Canada has MOUs with Australia, United States, European Union, France, India, Mexico, Singapore, South Africa, Russia, ……

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Mutual Recognition Agreements (MRA)

2003 MRA

- Allows a foreign country to recognize a Canadian company’s GMP compliance if Health Canada has inspected that site. Health Canada will then issue to the foreign health agency a Drug GMP Compliance Certificate.

- For a Canadian company, this means that the foreign health agency will no longer need to inspect the Canadian company for GMP compliance on a regular basis or prior to granting a product marketing authorization in that country ….. and vice versa.
Mutual Recognition Agreements (MRA)

• It's important that company’s understand that these agreements do exist.

• Some companies and foreign agency representatives are not aware that their health agency has this MRA in place with Canada.

• Canada hold Agreements with:
  • 18 EU countries
  • Switzerland
  • Australia

• What does this mean:
  • Since the implementation of the MRA, many Canadian companies have not been inspected by the EU.
  • Financial benefit to industry and the regulatory agencies.
Health Canada Initiatives

Good Manufacturing Practices

  - Prescriptive
  - Annexes are specific to:
    - Radiopharmaceuticals
    - Positron emitting radiopharmaceuticals

Drug Master Files

- 2009 Draft Guidance Document - Drug Master Files (DMFs)
Health Canada Initiatives

Drug Identification Numbers for Radiopharmaceuticals

- 2007 Possible future Amendment to Food and Drug Regulations
- Drug Identification Number (DIN)
- Requirements for Schedule C Drugs (Radiopharmaceuticals)

Impact:
- All manufacturers will need to update product labels to include unique DIN identifiers.
- DIN will be used to track adverse events and for post market surveillance activities
Health Canada Initiatives

Additional New Manufacturing Sites for PERs (F-18 FDG)

- May, 2009 - Letter to Canadian Society of Nuclear Medicine
- Applies to F-18 FDG, where the manufacturer adds a new manufacturing site.
- If F-18 shipped from a cyclotron to a different location for processing to make F-18 FDG
  - Processes and conditions of manufacture are the same
  - Then Notifiable Change is required
- If F-18 FDG is produced from a new cyclotron
  - Then a Supplement to their New Drug Submission (SNDS) is required.
Health Canada Initiatives

Investigations / Basic Research

- March 2009  Canadian Gazette Part 1
  Regulations Amending the Food and Drug Regulations (Positron Emitting Radiopharmaceuticals)
- Proposed the REB accept responsibility for research in humans decreasing Health Canada’s oversite and the need for Clinical Trial Applications (CTAs).

Impact:
- A less burdensome approach to physicians and researchers

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New Market Entry Products

- **Generic Radiopharmaceuticals will continue to enter market**
  - Industry will carefully plan for market entry at patent expiry

- **Industry critically assess costs to obtain market entry**
  - Certain products will selectively be discarded
  - Smaller companies will look for partnerships or to sell promising new products
  - Companies may look to bundle products for a clinical application to decrease submission fees
  - Companies may seek approvals for orphan indications to circumvent high submission costs
### Fees Impacting on Industry

<table>
<thead>
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<th>New Drug Applications (US Dollars)</th>
<th>European Union</th>
<th>Canada</th>
<th>United States</th>
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<tr>
<td></td>
<td>$500,000</td>
<td>$200,000</td>
<td>$1+ million</td>
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New Market Entry Products

- **Industry critically assess costs to obtain market entry (cont’d)**
  - Companies may work closer with cancer organizations and focus on collaborative trials
  - Companies will work closer with health agencies to develop effective clinical plans
  - Companies will lobby health agencies to share submission reviews with other agencies in an effort to expedite approvals
  - Professional associations will lobby government to perform confidence building exercises to lead to mutual recognition of drug approvals
New Market Entry Products

• There may be a greater focus on PERs, that do not suffer from issues relating to reactor isotope shortage
  
  • Companies will develop new PERs and make wise use of patents to protect technology.
  
  • Researchers will critically assess potential new PET isotopes.
  
  • Synthesis modules will be streamlined and simplified.
  
  • Industry will establish partnerships with key research groups to identify important new compounds.
  
  • Use of special access/compassionate use programs will increase.
  
  • Physician sponsored CTAs/IND will increase.
Economic Impact on Nuclear Medicine

- Continued focus by Health Agencies on Position Emitting Radiopharmaceuticals may increase operational costs for PET facilities engaged in product development.

- Health Agencies will look for ways to regulate radiopharmaceuticals, PERs and industry in the less burdensome way.

- Health care facilities may need to develop a resource to manage product CTA's for new products.

- High costs of R & D and increase in drug submission fees could result in a decline in industry’s interest to develop innovative products, where higher product costs would need to be passed on to Nuclear Medicine.
Working Cooperatively With Health Agencies

Health Canada clearly demonstrates the desire to work collaboratively with Nuclear Medicine & manufacturing facilities including industry

• Biannual meeting with associations representing stakeholders.
• e.g. Nuclear Medicine Alliance.

Open and continued communication will be necessary to maintain an effective partnership.

Opportunities to educate all parties on new challenges faced by Health Canada, Nuclear Medicine and manufacturers should be welcomed.

The importance of developing and maintaining highly, qualified staff with applied education/training/experience in radiopharmaceuticals must continue to be encouraged and challenged for all parties.
Our Mutual Goal .......

to ensure that the Canadian public has access to

the best Nuclear Medicine products and technology available in the world.