Radiopharmaceutical Regulations: Changing the Tide
International Nuclear Medicine Community Collaboration

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Impetus

- evident that regulatory practices are one of the most significant factors limiting affordable access to new and existing radiopharmaceuticals and hindering further development
- Jurisdictions around world have problems but creative solutions have been already explored and in many cases implemented

Radiopharmaceutical Regulation History

- RP's somewhat of an orphan (foster child)
- Initially governed under medical devices (likely because of Mo/Tc generators)
- Canada assessed and partially harmonized with other jurisdictions designated RP's as drugs
- Currently reside with *Biologics and Genetics and Therapeutics Directorate (BGTD)* possibly as a result of monoclonal antibody work?
- oversight of production facilities is with a different section now called *Regulatory Operations and Regions*

Canadian Radiopharmaceutical Regulation History

- They fall under the Federal Ministry of Health and are guided by regulations derived from the Food and Drug Act
- Somewhat antiquated legislation although there has been some regulatory reform over time and a significant effort now under way

Radiopharmaceutical Regulation

- Don’t fit well into much largercold pharma system
  - Radioactive
  - Short lived
  - Small batch (especially in PET and hospital based production)
  - Subphysiologic dosing
    - Diagnostics
    - But case for therapeutics as well because still nanomolar; rads strong
  - Negligible/minimal side effects or adverse events

Canadian RP Regulatory Status

- Manufacturing (mostly PET)
  - Federal falls under Food and Drug Act and the resultant regulatory schema
  - Similar for cold kit production
- Compounding (largely SPECT agents)
  - Practice of pharmacy which has provincial oversight
  - Exception of larger Centralized radiopharmacies

Canadian RP Regulatory Approval

- Basic Research Applications for Positron agent
  - Proof of concept for PET agent;<30 human patients;15 day review

  No SPR equivalent although under review
- CTA (clinical trial application)
  - clinical use of RP not approved in jurisdiction
  - More detailed review; 1 month review
- Therapeutic CTA
  - Variation to allow access to agents not otherwise approved but available in other jurisdictions
  - Relatively new and limited RP use to date

Canadian RP Regulatory Approval

- NDS (new drug submission)
  - approval of new tracer, clinical data
  - 12 months (priority 6 months)
- All aspects of these are dealt with by BGTD
- Issue of NOC (Notice of Compliance)

Production/ Manufacturing

- Separate Division
- Own rules and guidance
- Looks after ALL pharmaceutical production facilities from huge pharma to small unit production
- No specific regulations related to RP but adaption of cold pharma

Facility Requirements

- For manufacturing
  - GMP
  - Obvious issues around unique nature of RP's especially related to radioactive decay
  - Issues of small volumes and in many cases small area of distribution

Facility Requirements

- For compounding only related to larger commercial central radiopharmacies
  - GMP based
  - Again issues with the unique nature of RP's
- economic viability difficult with significant consolidation over the last decade and now have only one Canadian commercial provider in essentially a monopoly situation

Perspective of the $ Problem

- Market of therapeutic drugs world wide is close to $962.1 billion
- Market of Diagnostic agents worldwide is $3.8 billion (0.3%)
- Pfizer alone is $6.5 billion

The Negative Evolution

- when began practice a quarter-century ago, many more radiopharmaceuticals were available
- over time there has been a significant loss
  - 57/58-Colbalt B12 for Schillings test
  - 51Cr EDTA for GFR
  - 51Chromate for Red Cell Mass
  - Iodine based hipporate renal agent
  - Antimony Collloid lymphoscintigraphy

Still clinically relevant

Loss of RP's During 21st Century

Year	Market name	Compounded radiopharmaceutical
2015	MDP-Bracco	Tc^{99m} medronate
2009	Technetope II Generator	Tc^{99m} sodium pertechnetate sterile generator
2009	Tesuloid	Tc^{99m} sulfur colloid kit
2009	Renotec	Tc^{99m} ferpenetate kit
2009	TechneColl	Tc^{99m} sulfur colloid kit
2009	TechneSca Pyrophosphate	Tc^{99m} pyrophosphate kit
2009	Technescan Gluceptate	Tc^{99m} gluceptate kit
2008	Gluceptate Kit	Tc^{99m} gluceptate injection
2008	NeutroSpec	Tc^{99m} fanolesomab kit
2007	Sodium Pertechnetate	Sodium pertechnetate Tc^{99m} solution
2007	Glucoscan	Tc^{99m} gluceptate kit
2007	Lung Aggregate Kit	Tc^{99m} macroaggregates of albumin kit
2007	Technescan HIDA	Tc^{99m} HIDA kit for preparation of lidofenin injection
2007	AcuTect	Tc^{99m} apticide kit
2007	NeoTect	Tc^{99m} depreotide kit
2005	Sodium Pertechnetate	Sodium pertechnetate Tc^{99m} solution
2005	Tc^{99m} MAA Kit	Tc^{99m} macroaggregates of albumin kit
2005	Tc^{99m} Medronate Kit	Tc^{99m} medronate MDP kit
2003	HEDSPA Multidose Kit	Tc^{99m} etidronate kit
2003	HSA Kit	Tc^{99m} human serum albumin kit
2003	TSC Kit	Tc^{99m} sulfur colloid kit
2003	RBC Kit	Tc^{99m} red blood cell kit
2002	Sulfur Colloid	Tc^{99m} sulfur colloid kit
2002	Osteoscan	Tc^{99m} etidronate kit
2002	Pyrophosphate Kit	Tc^{99m} pyrophosphate kit

And Approvals since 1990?

- 3 SPECT agents
  - MIBI 90’s
  - 123I MIBG
  - 1234I Datscan
- 3 PET agents
  - FDG 2000’s
  - Rubdium 2015
  - Amyvid 2016

Issues

- good science is not sufficient to bring a drug on the market
- Radiopharmaceutical industry is fully mature but does not have the funds to fully develop RPs
- Today Conventional Pharma Industry (CPI) is not interested in RPs (and absolutely not in diagnostics)
- industry consolidation/ loss of competition/low R&D investment

Regulation Further Fallout

- Each production site needs to develop their own products
- Huge duplication of
  - Workload
  - Costs
  - Patient accrual
  - Chemistry and Quality expertise

Example: Canadian FDG Licensing

- Required multiple 8 separate NDS's for essentially a generic physiologic agent with two decades of prior use
- Only last couple were reviewed as generic (ANDS) and that change occurred during process
- Had to produce Canadian clinical data
- Huge resources expended by the community and the regulator
- Currently multiple licensed products with differing indications

Example: Radiation Synovectomy

- Decades of use although relatively limited patient numbers
- 90Y became primary around 1995
- with regulatory changes, access only through Special Access Program in late 1990s

Example: Radiation Synovectomy

- 2012 abrupt termination of approvals for 90Y
- Told doesn’t meet criteria
- CANM helped organize a multicenter CTA to help provide access
- Viewed by BGTD as therapeutic access CTA
- Several hundred patients in 7 active sites

BUT

- Rigorous requirement for patient testing and follow up deterred many centres and patients
  - To meet safety data requirements
  - Due diligence
- Utilizing same RP utilized in Europe in countless patients
- Summer 2017 Inspectorate Review of a site
  - ‘countless breeches of GCP and CTA requirements’
  - Study ended

Bilateral Work

- Consultative work between Nuclear community and regulator for years in various formats
- Current iteration began around 2011
- Initiated by BGTD as an information seminar every 2 years
- Now a formalized as a Working Group led by CANM and CARS with community members
- Direct contact with BGTD
  - Unfortunately other areas of bureaucracy (SAP; Inspectorate) with oversite not directly plugged in but do link

Current Bilateral Work

- Provides a venue for consultation and discussion of issues
- A WIP that now involves 2 meetings with working group and HC annually and larger scale biennial conferences

Future

- Regulations reflecting Radiopharmaceutical uniqueness allowing affordable safe access
- Canadian government announced 2017 that $71 million to HC improving access and use of necessary Therapeutic products
- Hopeful for modifications and recognition of the unique nature of RP's but the project covers all Pharma
- Affordable access???

But More Needed

- From discussions became evident regulators not wanting to be out of step internationally
- Pharma and radiopharma are largely international
- Context of ICH catch term in Health Canada discussions
- Discussions of regulations with members of sister nuclear medicine organizations around globe

International Nature of Radiopharmaceutical Regulations

- Despite himself:

- Living in an international world
- trying to improve the regulatory framework look at the international picture

Moreover; with evolution, not just a Canadian issue

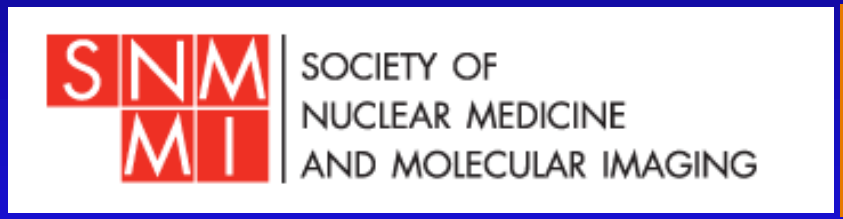
Further Impetus

- International Collaboration on Harmonization (ICH)
- Interest in radiopharmaceutical regulation on an international scale expressed by IAEA
  - Harmonization for major players
  - Develop a floor for developing members

Hopes

- Sharing info can improve regulatory practices in the involved countries
- Sharing of information between organizations/regions will provide others with insight to positively engage their respective regulators
- Bring new ideas to regulatory table for RP’a

Inception of a Working Group of the Nuclear Community



?Others

International RP Working Group Structure

- Began May 2017
- Inclusive group of of the world nuclear medicine community looking at RP regulatory structures and administration
- Assessing areas of common interest and work that can facilitate affordable, safe access to nuclear medicine agents
- Critical assessment of different international regulatory structures seeking “Best Pragmatic Practice”

Operations

- Ongoing
- face to face (facetime too) at the major international nuclear medicine conferences
  - EANM
  - SNMMI
  - WFNMB
  - ?others
- Tcon and electronic linkage to forward work

Work

- Discussion of position/white papers and other methods to help member organizations deal with regulatory bodies
- Working groups on specific issues
- Evaluate regulatory regimes and member organization issues seeking solutions
- Sharing of how Regs applied, evolving
- Involvement in international efforts on RP regs
  - IAEA
  - ICH?

Summary

- RP's especially diagnostic have an extraordinary safety record
- RP's maintain significant importance to diagnosis and RX
- RP regulation is important but the balance and application is important
- Significant differences of regs and application around the world
- Room for improvement
- Sharing of information is vital to aid this
- Incorporation of practitioners into regulation discussion formulation and reform