Progressive Licensing and the Modernization of the Canadian Regulatory Framework

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Disclaimer

- Disclaimer: the information within this presentation is based on the presenter's expertise and experience, and represents the views of the presenter for the purposes of a training workshop.
A Word on Regulation

- Regulators are entrusted to protect and promote public health
- Regulators are also on the drug development/access critical path
- The effectiveness of a regulatory authority in fulfilling its mandate is critical to the achievement of desired public health outcomes
- This in turn depends in large part on the adequacy of the legal framework within which a regulator must operate
A Word on Regulation (2)

- Laws and regulations should:
  - Provide regulators with the necessary authorities and tools to carry out their mandate
  - Define conditions to be met
  - Define prohibitions
  - Provide sufficient flexibility to deal with new or evolving practices and science
  - Take into consideration international norms and best practices
A Word on Regulation (3)

- Laws and regulations should not:
  - Pose unnecessary burden on those regulated
  - Become a barrier to access, innovation and trade
Guidances

- Devil in the details: regulatory expectations for the most part defined at level below laws and regulations, through policies, guidances and procedures
- Laws are regulations define the “what”, guidances and procedures the “how” to comply
- Guidances:
  - Not legally binding: alternate approaches may be acceptable if scientifically justified
  - Provide two way flexibility
  - Easier to change than laws and regulations
  - Cannot override or contradict laws and regulations
Adoption versus Implementation

Finalized guideline or standard

Implementation Issues

Regulatory Framework

Adoption or “Intent to Adopt”

Complete integration / implementation
Implementation Considerations

- Regulatory implications
- Collateral policy/guidance work
- Scope/phase-in considerations
- Readiness of those regulated
- Training requirements
- Skill sets – right people?
- System/infrastructure requirements
- Organizational/mandate issues
- Inherent complexity of product
- Translation: equivalent terms/concept?
- Resources

...in other words, true, consistent implementation of a guideline represents much more than its publication
Regulating Drugs in Canada: The Need for Change

- Current framework governing regulation of pharmaceuticals over 40 years old
- Represents patchwork of amendments over time, resulting in systems of regulations that do not work well together
- Current framework also reflects outdated approaches and concepts, including “point in time” regulation of products
- Recognition that comprehensive modernisation of legislation was needed to deal with both current and anticipated needs of the regulatory system
- New Bill (C-51) introduced in Parliament in Spring of 2008: proposes sweeping changes to the Canadian *Food and Drugs Act*
Modernization of Food and Drugs Act

- Modernization initiative embodies concepts established under “Progressive Licensing” project

- Three objectives have in turn guided the design of the Progressive Licensing framework:
  - Alignment with the system of health care in Canada to achieve positive health outcomes
  - Ensure new regulatory structure enables Health Canada to implement best international regulatory practices and maintain appropriate oversight without unduly increasing regulatory burden
  - Encourage and make best use of evolutions in the science of drug development and regulation
Good Time to Modernize

- Take advantage of
  - Review of recent and ongoing legislative changes in the EU and US
  - Extensive consultations with stakeholders on Progressive Licensing concepts
  - International developments, notably
    - Evolving science and practices (pharmacogenomics, adaptive trial designs, Benefit/Risk initiatives, etc.)
    - Key ICH guidances and standards that provide tools for newer, more modern approaches to drug development and regulation (such as E2E and Q8,9,10 suite of Quality guidances)
    - Growing number of arrangements with key regulatory counterparts and international organizations
What is “Progressive Licensing”? 

- “Progressive” as recognizes that there is an ongoing progression of knowledge about a medicinal product over time, from initial research through development, marketing and eventual product removal.

- As a consequence, benefit/risk assessment is not static and should also be assessed throughout product life cycle.

- Represents a fundamental shift traditional “point-in time” model.

- Progressive Licensing also provides conceptually for alternate licensing models that consider broader B/R factors and Health Care needs.
Progressive Licensing – a Vision for the Future

- Key elements of the Progressive Licensing Framework have been tested with stakeholders:
  - Life-cycle approach
  - Evidence-based
  - Good planning
  - Accountability
Current Point-in-Time Process
Progressive Licensing Model

Life cycle approach

Pharmacovigilance and Benefit-Risk Management

- Drug Discovery
- Pre-Clinical Studies
- Pre-Submission Meeting
- Clinical Trials
- Clinical Trial Review
- Re-Evaluation of Authorization and Commitments
- Monitoring and Intervention
- Ongoing Reporting of New Information
- Early Post-Market Period
- Authorization
- Drug Submission
- Post-Submission Meeting
- Pharmacovigilance Activities: Health Canada, Industry, Health Professionals, Public

Industry Activities
Health Canada Activities
Pre-submission Meetings:

- Not required for every drug
- Could be relied upon subject to amendment only where the science underpinning the advice has demonstrably changed
Highlights

Submission Requirements:

- Will vary across drug lines (eg. Rx, non-Rx)
- Information necessary to establish a favourable benefit-risk profile
- New requirements can include risk management plans, including pharmacovigilance plans
- Also new requirements to publicly register any clinical trial relied upon in a drug submission
Demonstration of a favourable benefit-risk profile

The favourable benefit-risk profile must be maintained throughout the life-cycle of the therapeutic product

The authorization would be capable of supporting ongoing obligations upon the market authorization holder following the release of the drug into the Canadian market
Obligations for filing of safety reports, active surveillance, post-market studies would be assigned within the authorization.

Obligations could be amended, depending upon benefit risk profile of the drug.
Re-evaluation:

- Not for all drugs only where necessary based upon risk or nature of drug
- Period determined based upon drug, and would be identified as an obligation within the authorization
- Extent of re-assessment would similarly be based upon the drug and specified within the authorization
How Does This Relate to a New Quality Paradigm and Why is Regulatory Oversight Necessary?

- Starting with the second question:
  - Quality equally important to achieving drug’s intended effect as the drug’s inherent safety and efficacy
  - Case for regulatory oversight: end user cannot independently judge drug’s quality, as past tragedies attest
  - Issue is *how* best to ensure quality
Link to Progressive Licensing

- Quality an essential element of pharmaceutical regulation and Progressive Licensing
- Newer ICH Quality concepts align well with Progressive Licensing themes
Life Cycle Management

- Knowledge gained over life-cycle allows for process and product improvement
- Quality by Design (QbD), risk management and quality system important enablers to achieving enhanced confidence in consistent product quality – and regulatory flexibility
- Regulatory flexibility also conditional on knowledge transfer - ‘telling the critical story’
- Desired change will also require common understanding and better coordination between reviewers and inspectors
Good Planning

- Planning essential element of QbD:
  
  “Deliberative design effort from product conception through commercialization”  
  (M. Nasr, FDA, 2007)

- Drug quality considerations form part of proposed life-cycle management plan

- Importance of early communication:
  
  - Provides regulator with a better understanding of proposed strategy
  
  - Reduces risk of comments at submission evaluation stage
Accountability

- Responsibility for producing drugs of suitable quality ultimately rests with industry

- Demonstration of enhanced product and process knowledge, combined with implementation of an effective quality management system, makes possible a greater shift in ‘ownership’ of post-approval changes to industry

- *Not de-regulation* – same obligation to comply with regulatory requirements
Accountability (2)

- Health Canada also accountable to Canadians by virtue of regulatory mandate
- Accordingly, risk management and quality systems should also be hallmark of a modern regulator, thereby enabling sound decision-making, use of resources and continual improvement
Build upon Best Practices

- Submission review:
  - Long-established request to file pharmaceutical development information
  - Use of QOS as review template; CPID as basis for documenting ‘regulatory agreement’
- Leveraging international cooperation:
  - Effective use of MRAs, PIC/S
  - Contribution and adherence to ICH guidances
  - Recent MOU with EDQM
- Risked-based approach to lot release (biologics)
Elements of A Desired State

- Manufacturers (and regulators) have extensive knowledge about critical product and process parameters and quality attributes
- Manufacturers strive for continuous improvement
- Regulator’s role:
  - initial verification, subsequent audit
  - creating a regulatory environment conducive to innovation, continuous improvement…and ultimately, access to high quality medicines

- adapted from various FDA presentations
Elements of a Desired State (2)

- Regulatory oversight commensurate with risk and product knowledge
- Effective internal, national and international cooperation
Quality Framework within Progressive Licensing

- Courtesy K. Tirunellai
Conclusion

- A well designed, flexible and modern regulatory framework is essential to meeting the current and future regulatory challenges and opportunities
- Progressive Licensing concepts form foundation of Health Canada’s legislative and regulatory modernization efforts
- PL concepts aligned with new ICH Quality paradigm and QbD, risk management and continuous improvement principles
- Together, will encourage a more science and risk based approach to the regulation of pharmaceutical quality over the product life cycle
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