Pandemic Preparedness: Regulatory Agility in the Era of COVID-19

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*The views and opinions expressed herein do not represent the official policy or perspective of Health Canada
Outline

- Expedited review pathways in Canada
- CMC challenges for accelerated clinical development
- How can “platform” technologies help expedite vaccine development?
- How can regulators be “agile” in a pandemic?
Expedited Review Pathways in Canada
Expedited Review Pathways

• Priority Review
  – Fast-tracked review (25 days screening, 180d review) for New Drugs intended for the treatment, prevention, or diagnosis of severe, life-threatening, or severely debilitating diseases or conditions

• Access to Drugs in Exceptional Circumstances Pathway
  – Urgent Public Health Need identified by federal/provincial/territorial Chief Public Health Officer
  – Must have received market authorization in Europe, Switzerland, or USA
  – Does not grant market authorization in Canada

• Special Access Programme
  – Initiated by HCP
  – Access for drugs to treat patients with serious/life-threatening conditions where conventional tx failed/are unavailable
COVID-19 Interim Order

Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19

Whereas the Minister of Health believes that immediate action is required to deal with a significant risk, direct or indirect, to health, safety or the environment;

Therefore, the Minister of Health, pursuant to subsection 30.1(1) of the Food and Drugs Act, makes the annexed Interim Order Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19.

Ottawa, September 16, 2020

Minister of Health
Patricia Hajdu


• Provides flexibility for regulatory requirements for filing
  – A similar IO is in place for clinical trials (signed May 23, 2020)

• Similar approach to Canada’s response to the H1N1 pandemic
COVID-19 Interim Order

• Normal NDS pathway requires substantial evidence of clinical effectiveness, detailed reports of tests made to establish safety for the purpose and under conditions of use recommended
  – No rolling review
  – Can use foreign reviews in our review but no pathway for approval based on foreign decisions
  – Limited authority to compel information post-authorization

• IO pathway: Sponsor required to submit known information regarding CMC, safety, and efficacy
  – No cost recovery; no formal performance standards
  – A distinct pathway for drugs approved by a trusted foreign regulatory authority
  – Allows for rolling submissions
  – Authority to compel information/material (including samples) both pre- and post-authorization
Operational Considerations

Hope is that the IO provides a more flexible pathway, fosters communication between HC and sponsors, and will help make COVID-19 vaccines available to Canadians in the shortest time possible.
CMC Challenges for Clinical Vaccine Development

Build Quality in **Early!!**
CMC Challenges for Accelerated Clinical Development

• Pandemic = ultra-rapid development
  – Not just product development - global knowledge shifts week to week CMC issues may go beyond the norm
    • What’s the mechanism of action?
    • What’s the relevant animal immunogenicity/challenge model?
    • How are you assaying your molecule/clinical endpoints?

• In a rush, important not to rush to FIH trials
  – Proof of concept, especially for novel products/processes
    • Tie to immunogenicity endpoints, correlates of protection (if available)
  – Does the antigen design match the proposed MoA?
  – Correlation between *in vitro* and *in vivo* assays
  – Protection/disease enhancement
CMC Challenges for Accelerated Clinical Development

- Unqualified/unvalidated assays
  - Products with unique testing reagent requirements
  - Critical element for early scrutiny

- Formulation changes during development
  - Specifications (changes to posology, bridging between studies)
  - Stability (what assays, what conditions)

- For new products, product/process knowledge is often limited
  - Especially true for smaller manufacturers
  - Attribute criticality, process parameters
  - Wide acceptance criteria/specifications
How can Regulators Support Expedited Clinical Development

- Communicate expectations early and often
- Provide consistent guidance, published where possible
- Request information early, especially from smaller sponsors
  - Formulation, assays
  - Forced degradation studies
  - Container closure compatibility
- Even in a pandemic, expediency isn’t worth sacrificing quality

https://xkcd.com/2347/
What can platforms do for you?
Platforms can Expedite Authorization/Licensure

CEPI: “A technology was defined as a platform if an underlying, nearly identical mechanism, device, delivery vector, or cell line was employed for multiple target vaccines”

- Vaccine Platforms: State of the Field and Looming Challenges, Center for Health Security
How can Platforms Speed Development

**Process**
- Validated unit operations (predictable CPPs, CQAs)
- Rapid phase-to-phase process improvement
- Predictable yields and scale-up

**Safety**
- Safety record of platform-related impurities
- Qualification of cell banks, reagents
- Clinical experience with adjuvants

**Control**
- Translating specifications
- Applicability of existing assay validations
- Stability, container-closure compatibility
Platforms: Is there anything they can’t do?

Quite a lot, actually…

- **Good:** “Hot-swapping” antigens, sponsor has substantial experience  
  - shared mechanism of action, clear proof of concept, stability

- **Bad:** Limited pre-clinical/clinical development history, but CMC experience  
  - MoA limitations, but supported by good quality (or vice versa)

- **Ugly:** Broad similarities to other products, little (or no!) manufacturing/clinical experience  
  - Unproven MoA, little to no CMC/clinical development data
The caveat…

“Regulatory Agencies License Products, Not Platforms”

Risk-based decisions are supported by data, not concepts

Platform technologies can make a regulator’s job easier and get products to market faster, IF they help fill in gaps for the data you need!
Platforms, we hardly knew ye

- **Does platform knowledge:**
  - Reflect and validate proposed mechanism of action? ✓
  - Demonstrate control of a highly similar process? ✓
  - Show pre-clinical/clinical experience with a highly similar formulation? ✓
  - Indicate control of materials used in manufacture? ✓
  - Help predict stability? ✓
  - Inform on quality systems?
How can regulators be agile?
Regulatory Agility = Regulatory Flexibility

• Guidance documents – official and targeted, ad hoc advice

• Emphasize phase-appropriate CMC concerns
  – Front-loading clinically-relevant control
  – Back-loading characterization/validation for licensure

• Reference standard qualification for key assays
  – Is there a plan in place?

• Container closure systems, multi-dose considerations
  – Supply constraints
  – In-use stability
Front-loading Safety and Efficacy

- Identify criticality for early phases of development:
  - Proof of concept
    - WHO International Serology standard
  - Control of materials
    - Novel manufacturing process?
  - Control assays for potency
    - ASAP

- Forced degradation studies
  - Links back to control assays
- Impurities
  - Expected/detected
- Container closure compatibility
  - Supply issues
Back-loading control

- How do you balance risk/benefit due to data gaps?
  - Leverage platform data
  - Plan, plan, plan!

- Comparability
  - Scale up/scale out

- Assay validation
  - Key assays should be validated
  - Assay transfers

- PPQ
  - Supportive data
  - PPQ Protocols

- Stability
  - Informed by clinical trial material
Risk-based decisions are supported by data, not concepts
Pandemic development challenges scrutiny

- Time crunch (sponsors + regulators)
- Knowledge gaps
- Material/supply chain challenges
- Fewer opportunities for input

As a regulator, recognizing how and where to be flexible is the key to supporting expedited development.

Know what your tools are!
Build Quality In Early!

Modified from: https://xkcd.com/2347/