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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

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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?

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Expedited Review Pathways in Canada

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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
  - https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/priority-review/drug-submissions.html

- 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) [1] of the *Food and Drugs Act* [2], 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

https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/interim-order-import-sale-advertising-drugs.html

- 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.

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CMC Challenges for Clinical Vaccine Development

Build Quality in **Early**!!

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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

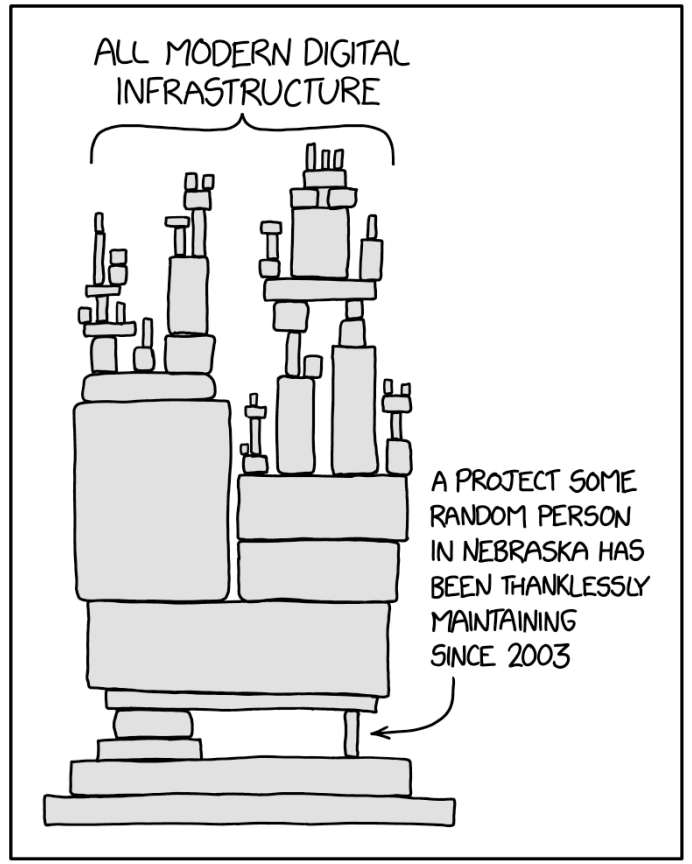
- Formulation changes during development
  - Specifications (changes to posology, bridging between studies)
  - Stability (what assays, what conditions)

- 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

"Dependency"



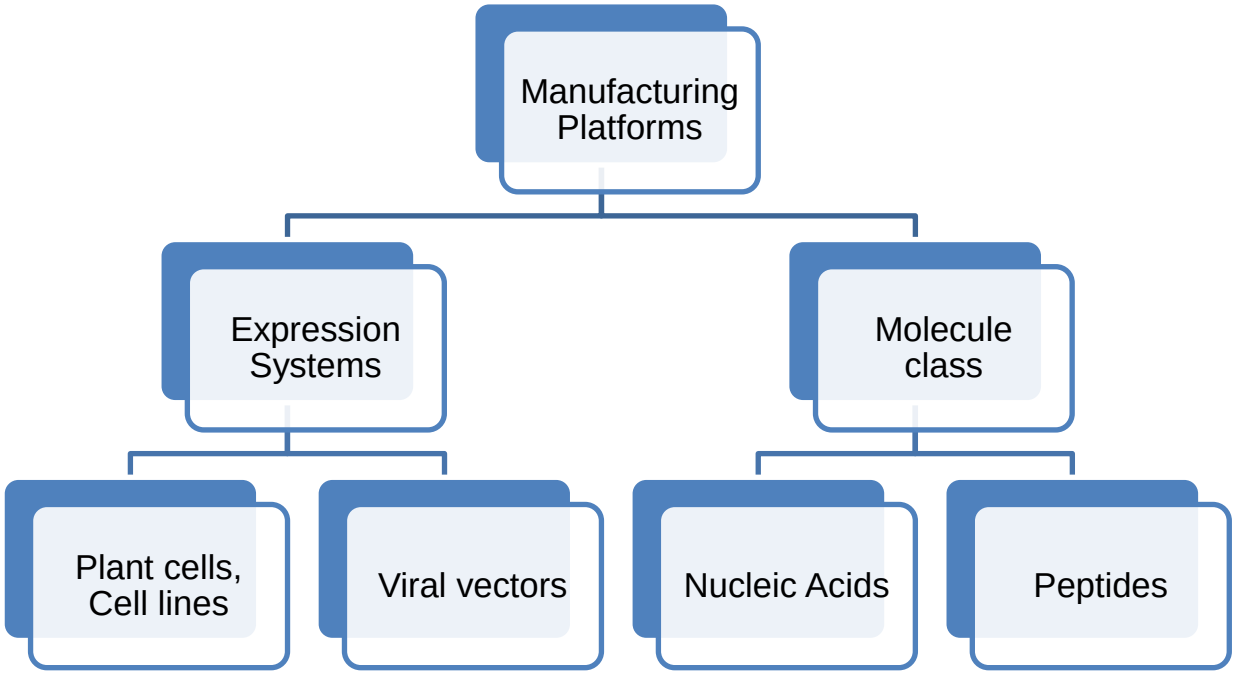
https://xkcd.com/2347/

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…

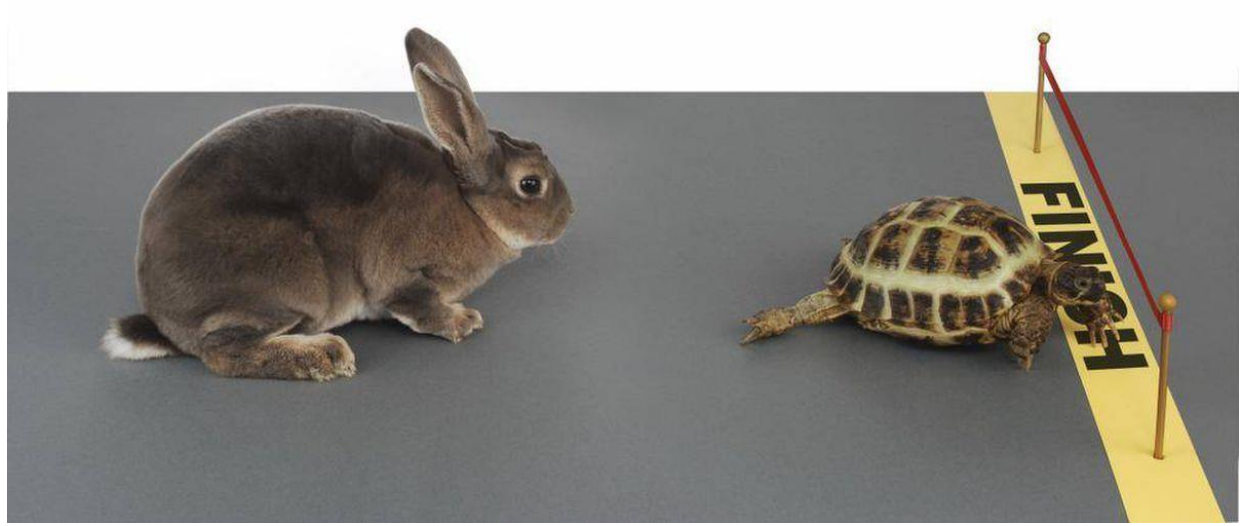
"Regulatory Agencies License Products, Not Platforms"

<u>Risk-based decisions are supported by data, not concepts</u>

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

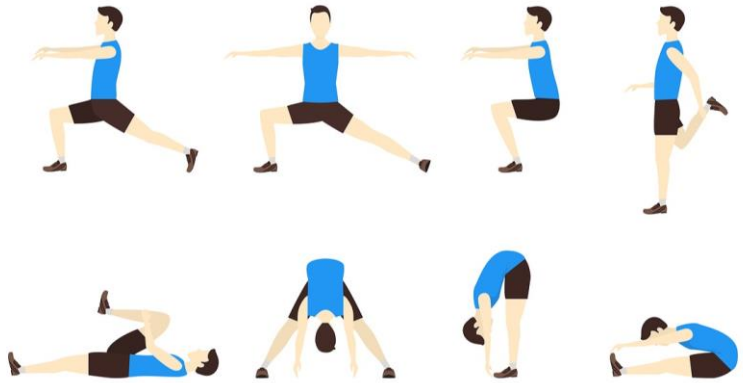
- **Does platform knowledge:**
  - Reflect and validate proposed mechanism of action? ✓
  - Demonstrate control of a highly similar process? ✓
  - Show pre-clinical/clinical experience with a highly similar formulation? ✓
  - Indicate control of materials used in manufacture? ✓
  - Help predict stability? ✓
  - 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 balidated
    - 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

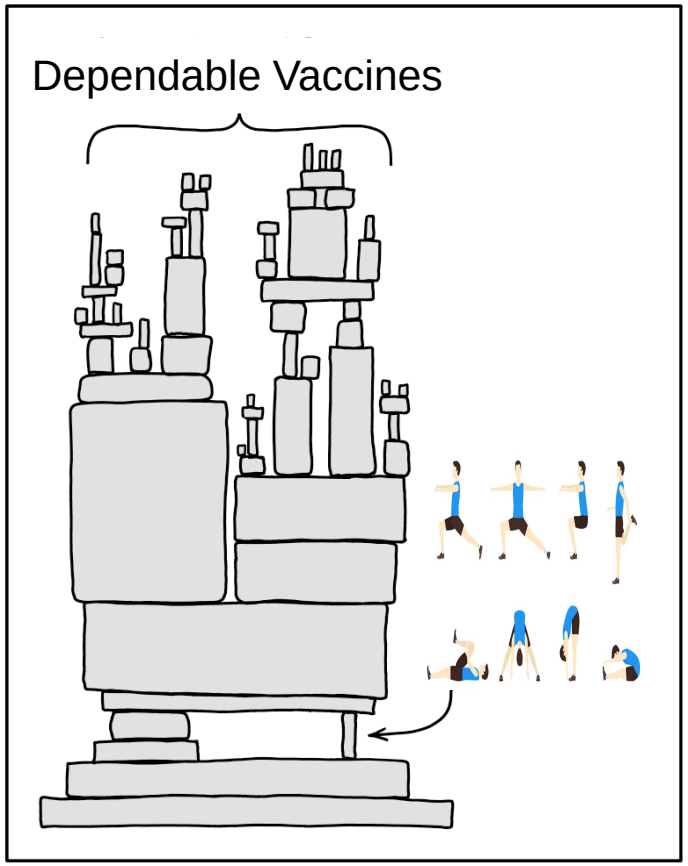
- Time crunch (sponsors + regulators)
- Knowledge gaps
- Material/supply chain challenges
- Fewer opportunities for input

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!

"Dependency"



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Thank you!