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

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Outline

- Expedited review pathways in Canada
- CMC challenges for accelerated Clinical Development
- How can “platform” technologies speed up development
- How can regulators be “agile?”

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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
  - 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 Development

Build Quality in **Early**!!

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CMC Challenges for 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?
    - What are relevant antigens?

- In a rush, building quality in early is crucial
  - Proof of concept, especially for novel products/processes
    - Tie to immunogenicity endpoints, correlates of protection (or lack thereof)
  - Correlation between *in vitro* and *in vivo* assays
  - Antigen design

CMC Challenges for Accelerated Development

- Unqualified/unvalidated assays
  - Products with unique testing reagent requirements
  - What is a nucleic acid potency test?

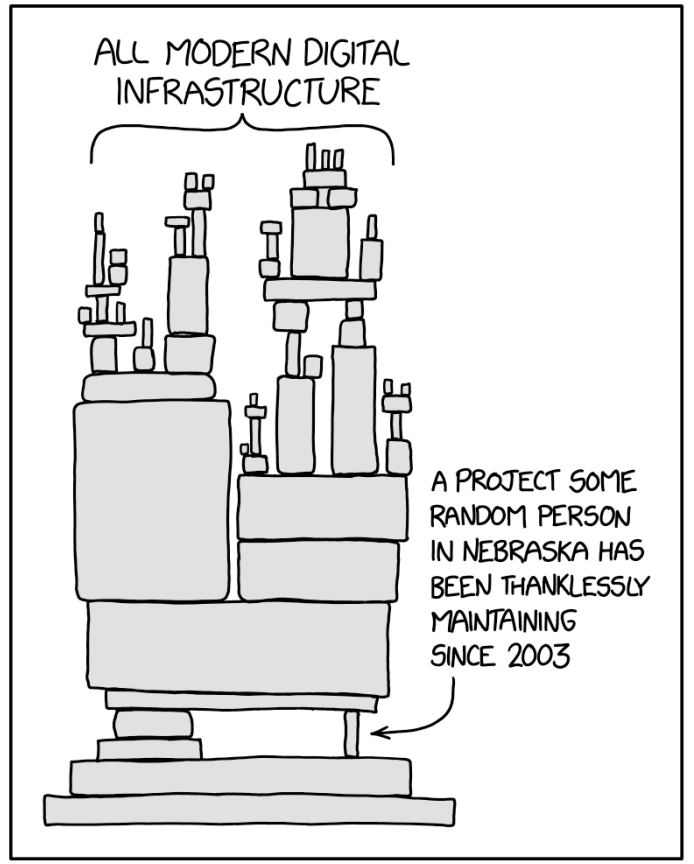
- Formulation changes during development
  - Specifications (posology, bridging)
  - Stability (assays, conditions)

- For new products, product/process knowledge is often limited
  - Especially true for smaller manufacturers
  - Attribute criticality, process parameters
  - Wide acceptance criteria/specifications

How can CMC Regulators Expedite Clinical Development

- Help build in quality from the outset
- Communicate expectations early and often
- Enhanced guidance
- Early requests for information, especially from smaller sponsors
  - formulation, assays
  - Access to MF/DMF, as appropriate
  - Information on CMOs

“Dependency”



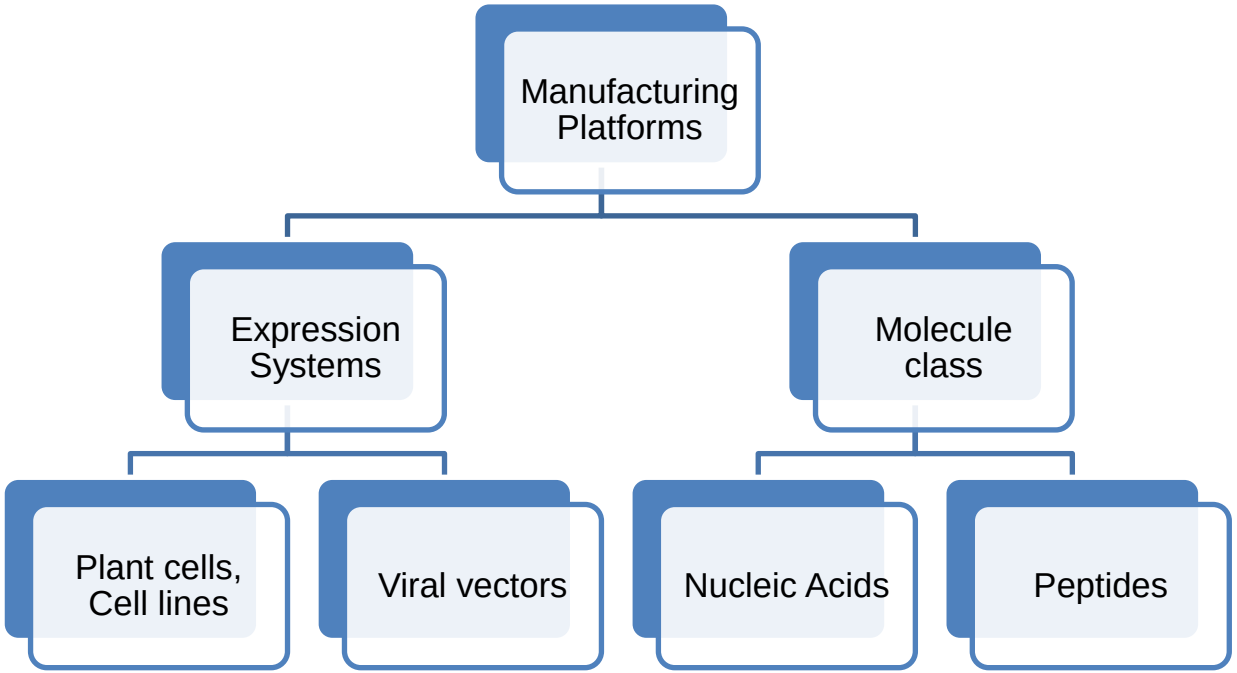
https://xkcd.com/2347/

What can platforms do for you?

Platforms can Expedite Development

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
- Stability, container-closure compatibility
- Applicability of existing assay validations

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: Leveraging limited clinical experience with similar types of products
  - **Process knowledge limitations, proof of concept lacking**

- Ugly: Very broad similarities to other publications but little manufacturing/clinical experience
  - **unknown mechanism of action**, **unproven concept**

The caveat…

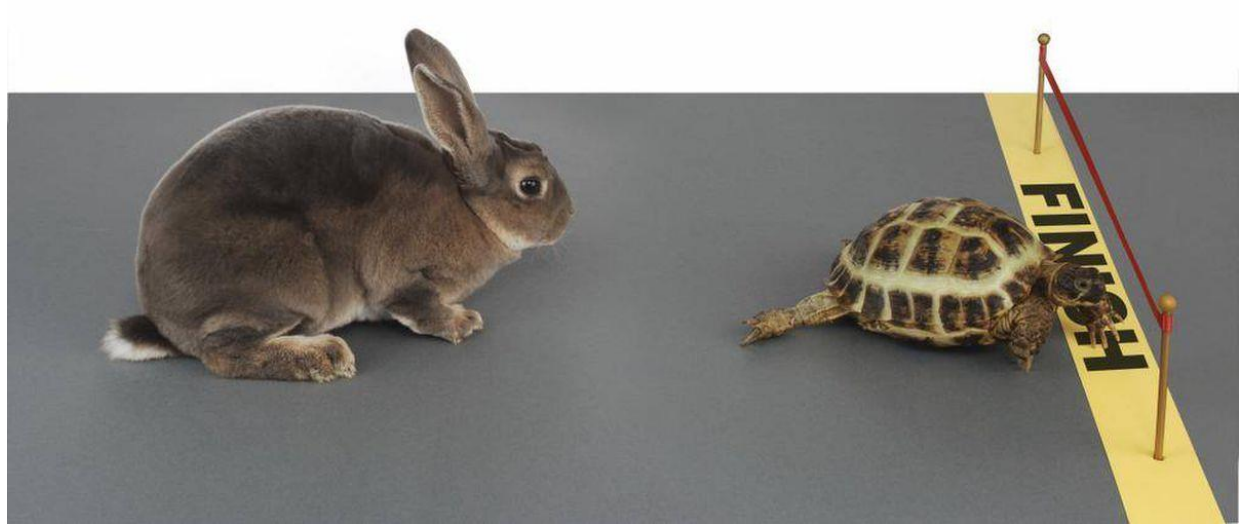
"Regulatory Agencies License Products, Not Platforms"

<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

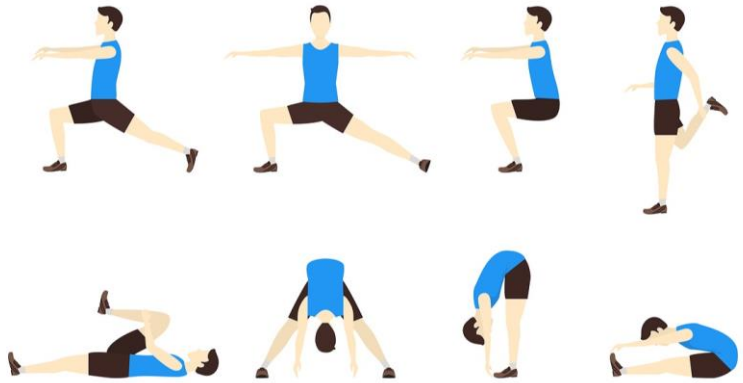
- **Does platform knowledge:**
  - **Reflect** and validate proposed mechanism of action? ✓
  - **Similarly** demonstrate induction of the desired immune response? ✓
  - Show pre-clinical/GLP tox/clinical experience with a **related** formulation? ✓
  - Demonstrate process/product **experience**? ✓
  - Help **predict** stability? ✓



How can regulators be agile?

Regulatory Agility = Regulatory Flexibility

- Guidance documents – official and targeted, ad hoc advice
- Emphasize phase-appropriate CMC concerns
  - Front-loading safety/efficacy
  - Back-loading characterization/product knowledge for licensure
- Process/assay validation, reference standards
- New container closure systems, multi-dose considerations

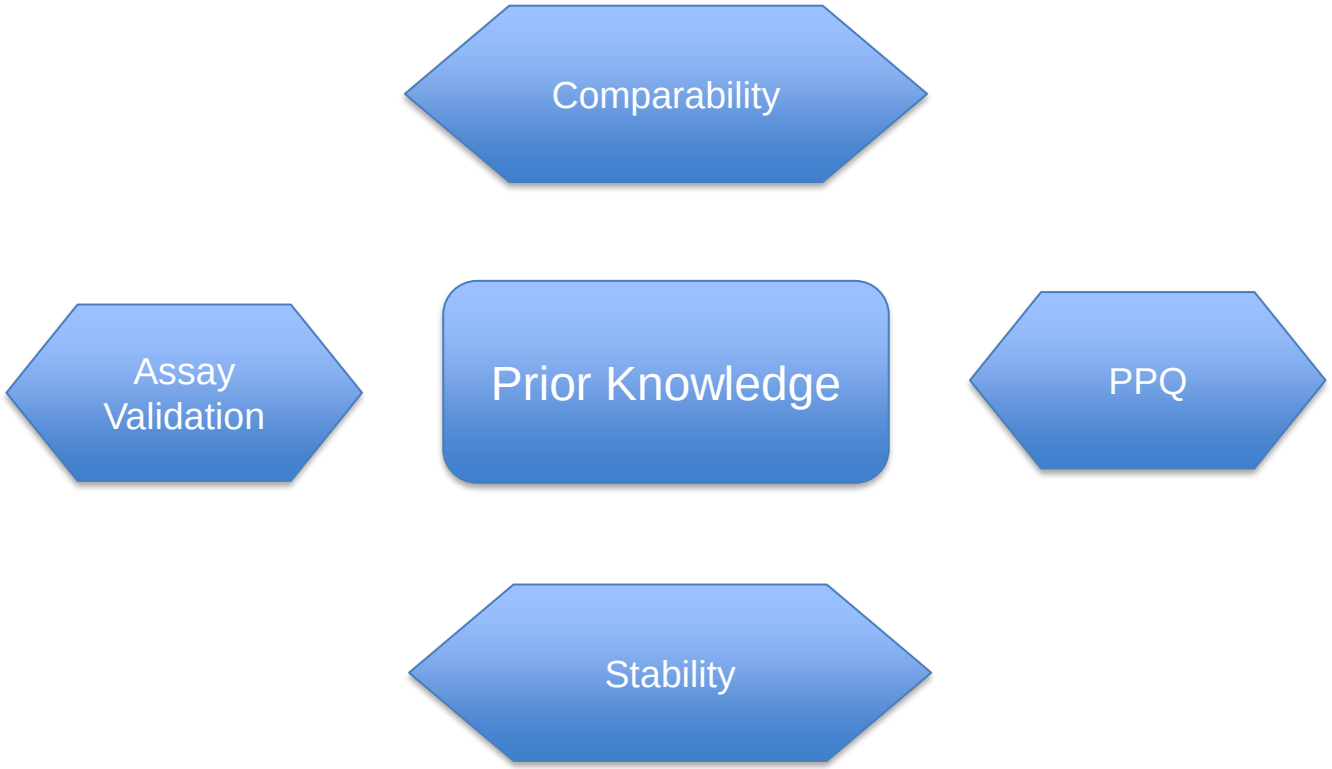


Front-loading Safety and Efficacy

- Part of pandemic development includes assessment of criticality at different phases…

Back-loading control

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



An example of Agile Regulation: Lot Release

- Lot release activities explicitly protected in Health Canada's COVID-19 IO

  "HC can request at any time additional information or material (including samples) in order to determine if HC will move forward with issuance, amendement, or cancellation of the authorization"

Question: How do we fulfill lot release activities and ensure consistency?

Issues:

- Assays not yet validated
- Delayed supply
- Regulatory burden
- Different jurisdictional approaches
- Different situation than H1N1

Approaches:

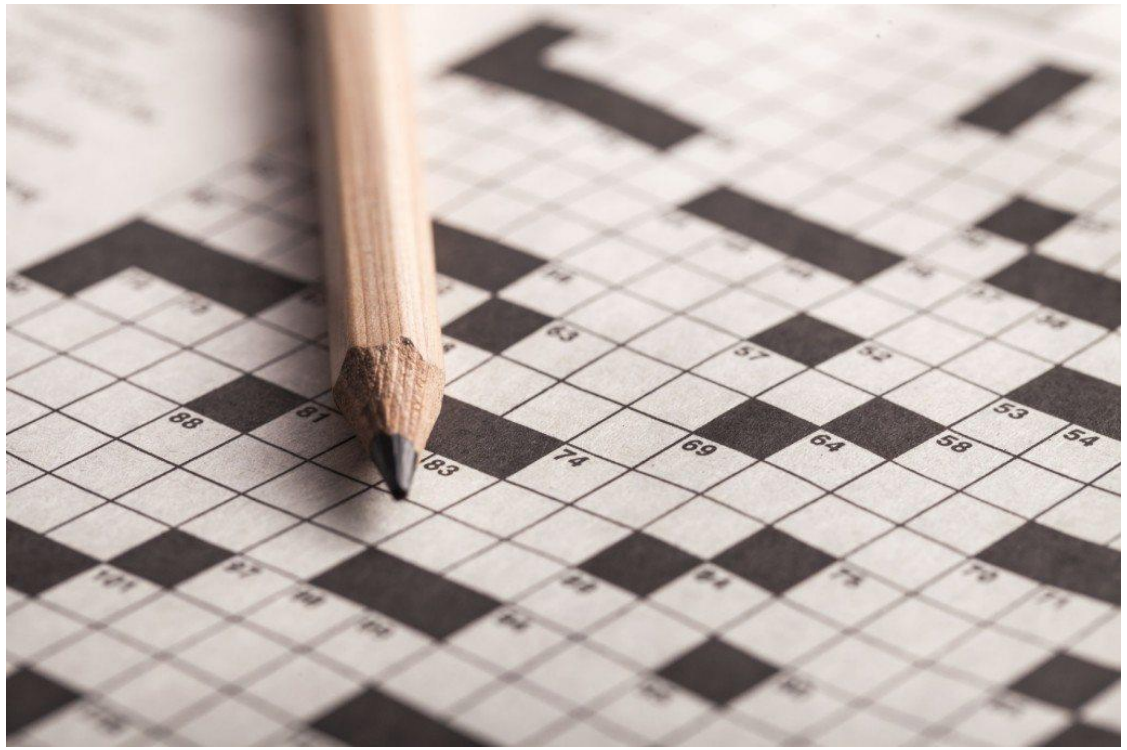
- Early assay transfers/material requests
- Test bulks vs final containers?
- Release on documentation
- Batch disposition records
- Surveillance model
- Class-specific testing where possible, product-specific where necessary

How can we be agile, but risk-based?

- Build a plan to address gaps:
  - Early phases:
    - Focus on issues that confirm proof of concept and impact safety
    - Request forced degradation studies during development
    - Request samples and protocols during development
    - Start comparability/specification discussions early
  - Later phases:
    - Identify how sponsors will bridge knowledge between manufacturing processes
    - Request risk assessments for expected gaps at submission
    - Request plans for validation and consider rolling data submissions
    - Identify alternate approaches to consistency assessment
- Where else can you get the information?
  - OSEs: Are inspection reports from other NRAs available?

How can we be agile, but risk-based?

Risk/benefit under the IO is not set in stone



Our approach can **complement** the sponsor's!

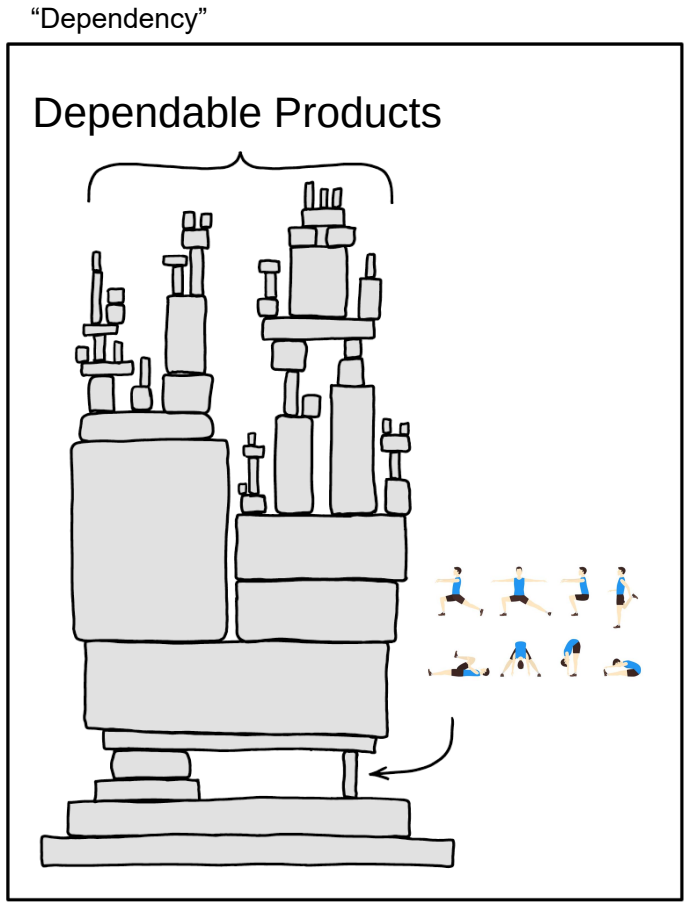
Pandemic development challenges scrutiny

- Limited experience
- Validation gaps
- Limited stability data
- Lack of consistency data
- Container closures
- Fewer opportunities for input

As a regulator, you have all the tools to ensure quality of new products but prioritizing issues is the key.

USE YOUR TOOLS WISELY!

Build Quality In Early!



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

Thank you!

Extra slide 1: Outside the box CMC issues

- In a pandemic, fill/finish capacity can easily be saturated

- Unique supply chain solutions may be sought out but these bring their own questions:
  - Contract fill/finish – who's responsible for testing? Who is the "sponsor?"
  - May be more relevant for smaller manufacturers
  - GMP/Establishment compliance verification

- For products entirely manufactured by CMOs: Who is responsible for validation activities? How can this be enforced from a regulatory perspective, especially when licensure is granted prior to completion of validation?

- Final container shortages – MDVs support widespread dosing but are in short supply.
  - May change during development, at which point stability/CC compatibility become crucial