BRDD Pre-Approval Group IB Consistency Testing

Industry Perspective of Submitting Samples within the 15-Day Clarifax Timeline

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Topics

- What can be expected for the sample request
- Case study example comparing between countries
- When to expect the sample request
- Logistical considerations
- Challenges and opportunities
- Testing risk assessment tool
- Opportunities for better predictability to prepare for timely delivery

References

- Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs - Canada.ca & Draft Lot Release Program for Schedule D (Biologic Drugs)
- Guidance Document: Post-Notice of Compliance (NOC) Changes: Quality Document
- Guidance Document: The Management of Drug Submissions and Applications - Canada.ca

Acknowledgement

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What Can be Expected For the Sample Request From Health Canada Guidance Documents

- **Group 1B: Consistency Testing (Lot Release Program for Schedule D Drugs)**
  This Evaluation Group is intended for consistency samples associated with an NDS or S/NDS. Generally, samples from 3 to 5 consecutively manufactured lots are tested by BGTD to ensure consistency of the manufacturing process. Upon request, consistency lots may be released for sale in Canada once an NOC is issued; a formal release letter is required from BGTD.

- **Consistency lot testing (Post-NOC Changes: Quality Document)**
  For Biologics (Schedule D drugs) and for Radiopharmaceuticals (Schedule C drugs) that have a biologic drug substance, Health Canada usually requests consistency samples to support the information provided in Level I or Level II Changes. The consistency samples should be representative of the revised process/proposed change(s) and should come from three to five consecutively manufactured lots. Sponsors are encouraged to discuss consistency lot testing requirements prior to the submission of Level I or Level II changes and this will be confirmed during the review process. Sponsors are also encouraged to consult the Health Canada guidance document “Lot release program for Schedule D (Biologic) drugs” for further guidance.

What Can be Expected For the Sample Request From Experience **varies by product and not an all-inclusive list**

- **Multi-strength products**
  Drug Product lots to bracket the high and low strengths

- **Lot genealogy**
  Drug Product lots should ideally be manufactured from different Drug Substance lots

- **Tests selected**
  Potency assay and potentially purity assay. Other tests may be selected by BRDD

- **Reagents and materials**
  Reference standard and any internally qualified standards/reagents/materials

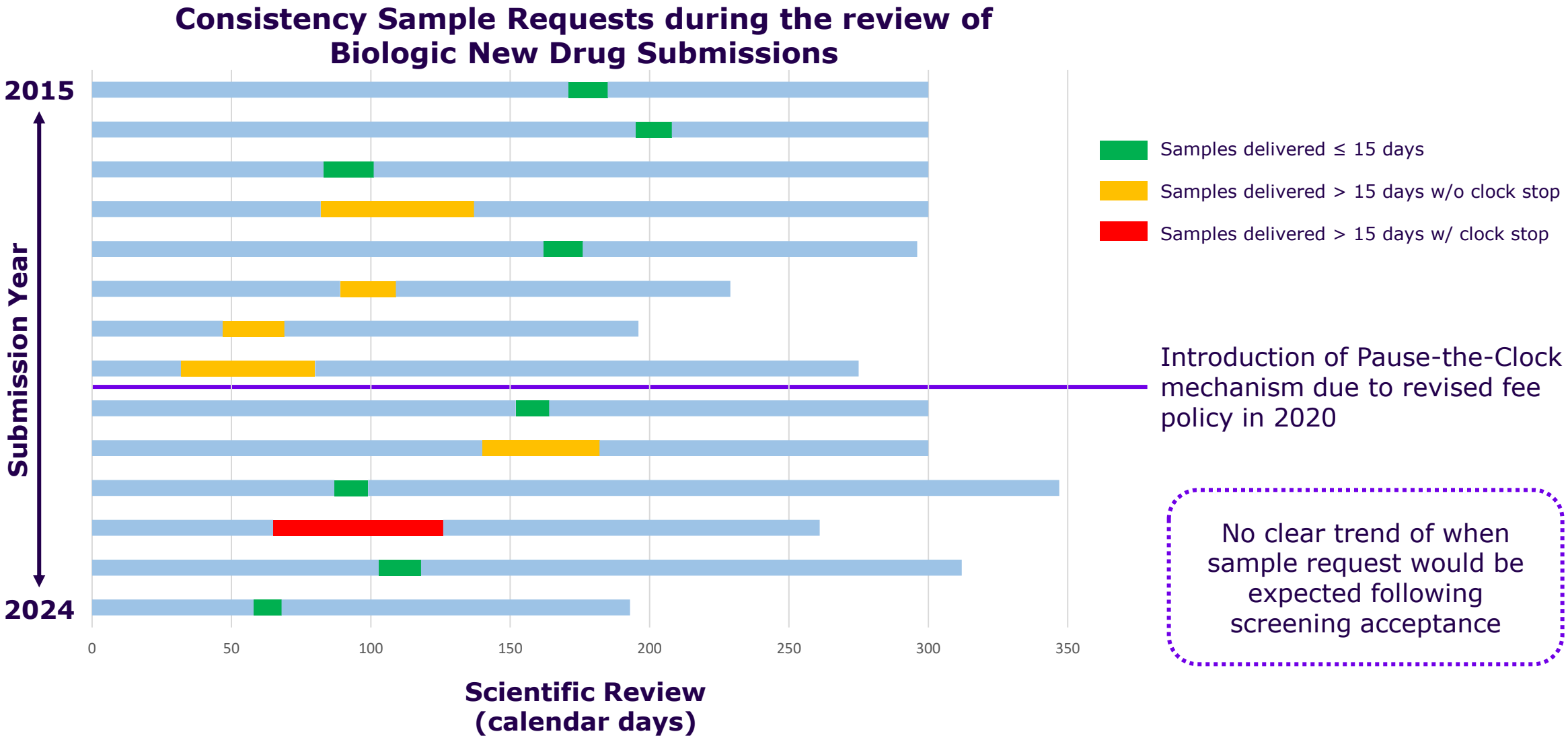
- **Documentation**
  - Method SOPs are often requested by clarifax just before the sample request
  - CoAs for the Drug Product lots provided as samples, and their corresponding Drug Substance lots
  - Raw data and data analyses for the Drug Product lots, including data analysis template

Sanofi Case Study Example:
Initial registration sample requirements for the same product compared

	Canada	China	Russia
Drug Product samples – quantity	3 lots x 2 vials/lot = 6 vials total	2 lots[1] x 210 vials/lot = 420 vials total	1 lot x 255 vials = 255 vials total
Drug Product samples – batch size	Commercial scale only	Commercial scale only	Commercial or pilot scale
Drug Product samples – labeling and packaging	Bulk drug product with manual labelling[2] is acceptable	In US commercial packaging + over-label applied at a GMP site	Commercial packaging is preferred
Drug Substance samples	None	2 lots[1] x 120 vials/lot, in 500 µL aliquots	None
Other samples	Reference standard	All test reagents/materials, including chromatography columns	Reference standard, placebo solution vials
Tests performed on Drug Product samples	Potency and purity tests	Full release specification testing	Full release specification testing
Timeline for sample delivery	Delivered to Health Canada within 15 calendar days upon request	Delivered to Chinese affiliate within 1 month of MAA submission	Delivered to Russian affiliate within 3 months of MAA submission
Health Authority guidance on sample requirements?	No	Yes, work procedure is available	Yes, memo is available

1. Regulation requires 3 batches, and number of sample per batch is 3 times the amount required for full specification testing.
2. Manual label to include information for identification such as: product name, strength/concentration, lot number, expiry.

Sanofi Biologic New Drug Submission Experiences 2015-2024:
When samples are requested and the duration to fulfillment



Logistical Considerations to Manage Consistency Sample Requests

- Identify product sample availability: lot numbers and genealogy, inventory, location(s), in bulk or finished goods stage, release status
- Availability of prepared reagents and materials, remaining shelf life, qualification status

- Prepare documentation for couriers, export and import prior to sample pick up
- Obtain requested SOPs, CoAs, raw data, data analysis template, etc
- Material Transfer Agreement (MTA) may be required to share commercial cell lines

- Customs broker contact information included on the ship to label
- Obtain waybill number, carrier and flight information to share with Health Canada prior to shipment of samples
- Maintaining samples at acceptable temperature

- Global cross-functional coordination across time zones and with external partners (CMOs, labs, couriers, etc)
- Clear accountability for each hand off

For international shipments anticipate at least 4-6 days from the time samples are ready for pick up to delivery at Health Canada

Challenges and Opportunities – AstraZeneca NDS Experiences

1. **The sample request timing can be variable**
   For 5 recent NDSs, sample requests were received 21, 48, 58, 128 and 175 days after screening acceptance. Submissions in red text had accelerated review.

2. **Shipments are coordinated from all over the world**
   Different components of the request (samples, reference standards, reagents) likely come from different sources. These sources are typically in different countries.

3. **Determining if samples are required is difficult**
   For industry it's difficult to tell if samples will be requested and what will be requested. We try to prepare for any situation that could *potentially* require samples.

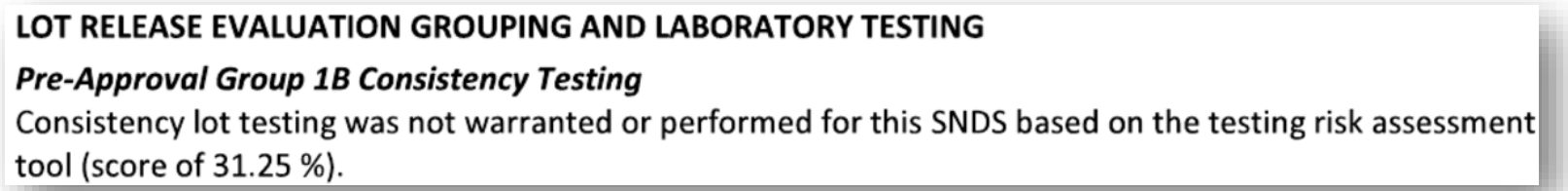
4. **Shipping addresses for delivery change**
   To start the export process from many countries an exact "ship to" address is required for the final sample destination. This address changes between requests.

5. **Contents of sample request are unknown until it's received**
   This includes what will be requested and how many samples are needed. Recent requests asked for 30 – 54 samples. Most samples are not readily available and have to be prepared well in advance.

Testing Risk Assessment Tool – Sanofi Experiences

Reasons for consistency testing selection gleaned from reviewer reports

- **NDS examples where consistency testing were waived**
  - Testing risk assessment tool recommends testing for the drug product (**score of 68.75%**). However, due to the Covid-19 pandemic it was not possible to complete the planned in-house laboratory testing. Instead, paper-based assessment of the recommended SE-HPLC and RP-HPLC methods was conducted.
  - Testing risk assessment tool recommends testing for the drug product (**score of 62.5%**). However, Health Canada has significant experience for similar products, and SOPs for stability-indicating methods are found to be clear, consistent, and aligned with similar methods submitted for similar products.
- **SNDS example where consistency testing was recommended by the review team**
  - Testing risk assessment tool does not recommend testing for the drug product (**score of 56.25%**). However, given that substantial changes to the drug substance manufacturing process are being proposed along with revised control strategy for several methods, the review team recommended that testing be performed.
- **SNDS example where consistency testing was not warranted**
  - Testing risk assessment tool (**score of 31.25%**)



LOT RELEASE EVALUATION GROUPING AND LABORATORY TESTING

Pre-Approval Group 1B Consistency Testing

Consistency lot testing was not warranted or performed for this SNDS based on the testing risk assessment tool (score of 31.25 %).

Opportunities for Better Predictability to prepare for timely delivery of samples

- **Long Term**
  - Defined window of time during the scientific review when BRDD will inform Sponsors whether consistency samples are required - *e.g. courtesy email to Sponsors within 30 calendar days after screening acceptance*
  - Establish a longer timeline for delivering consistency samples than the response to clarification request service standard of 15 calendar days to accommodate sample preparation and shipping logistics - *e.g. 30 calendar days from the date of request*
  - Testing Risk Assessment Tool scoring parameters and threshold is shared with industry to limit the number of surprises, especially for post-NOC changes

- **Short Term**
  - BRDD to consistently request for SOP(s) to the method(s) selected for testing consistency samples 1 month prior to issuing the request for samples. This would serve as a signal to Sponsors to prepare for the sample request to come
  - BRDD to use a consistent ship to address for samples to help streamline supply chain operations for booking the shipment(s) - *e.g. consistently use C/O 251 Sir Frederick Banting Driveway as the delivery location, with specific laboratory building/floor/room numbers to be provided in the sample request*

Thank you!

Questions?

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