YEARLY BIOLOGIC PRODUCT REPORT TEMPLATE

CONTEXT

Yearly Biologic Product Report (YBPR) is a requirement that applies to Schedule D (biologic) drugs assigned to Evaluation Groups 2, 3, and 4, as defined in Health Canada guidance *Lot Release Program for Schedule D (Biologic) Drugs*. The content of YBPR is itemized in Section 5.1 of the guidance. However, these instructions are open to interpretation, resulting in inconsistent quality of the submitted documents. The iterative process currently used to prepare and review YBPR submissions is inefficient, challenging both the sponsor and the regulator.

PURPOSE

The intent is to facilitate both the preparation and the review of YBPR, primarily by minimizing superfluous information, information gaps, and time to locate specific information through consistent presentation.

OBJECTIVE

The goal is to develop a template (attached) that reflects the consensus by the BGTD reviewers on the interpretation of the YBPR guidance, focusing on the type of information required, the level of detail, preferred presentation of the data, and overall organization.

YEARLY BIOLOGIC PRODUCT REPORT (YBPR)

NOTE

1. All items in the template should be addressed. Items that do not apply should be clearly identified.

Proprietary/brand and non-proprietary name	ProductABC
Sponsor	SponsorXYZ
Reporting period	2012-2013
Number of volumes submitted	1
Contact information for this YBPR	

NOTE

2. Include in the report every (*i*) approved[5] product[4] associated with the above proprietary/brand name, (*ii*) facility involved in the manufacture or testing of each approved product, (*iii*) batch/lot of approved product, initiated during the current reporting period, whether intended for Canadian or international market, and (*iv*) test performed, during the current reporting period, for lot release, in-process, or stability assessment of each approved product.
3. Where a product is manufactured by multiple approved processes (*e.g.* drug substance at 5,000 L and 10,000 L scale, 100 mg in vial and pre-filled syringe) or at multiple facilities (*e.g.* 100 mg vial at ABC and XYZ), the information must be reported separately and clearly identified using the product type and/or facility name, respectively (*e.g.* "Drug product (100 mg vial / ABC)".
4. ***Product*** is drug substance (*i.e.* formulated or pre-formulated bulk drug), drug product units (*i.e.* formulated drug in primary packaging), and drug product kits (*i.e.* drug product units incorporated into secondary packaging containing *e.g.* packages comprising vials of lyophilized product and vials of diluent or packages containing multiple single-dose units).
5. Product is considered ***approved*** if every aspect of its manufacture (*e.g.* facility, equipment, manufacturing) and testing has been documented, submitted by the sponsor for review by Health Canada, and in response received before the end of the current reporting period a *No Objection Letter* (NOL) or a *Notice of Compliance* (NOC).

Section 1: FACILITIES INFORMATION

NOTE

6. For each facility provide the associated address and a brief description of responsibilities (*e.g.* manufacturing, analytical testing). This information serves to confirm the accuracy of Certified Product Information Document (CPID) currently on file at Health Canada, and to establish the scope for information to be provided in this report.

1.1. Drug substance

Facility	Address	Responsibility / Product type
Facility A	Street, City, Country	Manufacturing, analytical testing
Facility B	Street, City, Country	Manufacturing
Facility C	Street, City, Country	Analytical testing
Facility D	Street, City, Country	Analytical testing

1.2. Drug product

1.2.1. Drug product unit

Facility	Address	Responsibility / Product type
Facility A	Street, City, Country	Manufacturing, packaging, analytical testing
Facility B	Street, City, Country	Manufacturing

1.2.2. Drug product kit *(if applicable)*

Facility	Address	Responsibility / Product type
Facility G	Street, City, Country	• Manufacturing, packaging • Lyophilised Powder (100 mg/vial) in 3 mL vial • WFI diluent in 1 mL vial

Section 2: PRODUCTION INFORMATION ON DRUG SUBSTANCE AND DRUG PRODUCT LOTS

2.1 Drug product lots sold on Canadian market

Drug Identification Number (DIN)	Dosage form	Strength	Number of lots sold
00000000	Lyophilised powder	100 mg/vial	5
00000001	Solution for injection	100 mg/mL	9

2.2 Lot disposition

NOTE

7. For each manufacturing facility and product type, indicate on a separate line the number of aborted[11], quarantined[12], rejected[13], and released[14] lots.
8. For trending purposes, provide information concerning the current and previous (if available) reporting period.

9. For each product lot that was aborted, quarantined, and/or rejected during the current reporting period provide a brief discussion, which includes (*i*) lot number, (*ii*) manufacturing step where event occurred, (*iii*) overview of the event, and (*iv*) reference to Section 2.5 of this template, which describes associated deviation(s) and corrective and preventive action(s).

10. For lots indicated as quarantined during the previous reporting period, discuss current status (*i.e.* disposition).

11. ***Aborted*** lot is a lot of process intermediate whose processing was not completed, *e.g.* due to a non-conforming in-process test result, equipment failure.

12. ***Quarantined*** lot is a product lot whose processing was completed but final recommendation regarding its disposition is pending, *e.g.* due to incomplete analytical testing, ongoing batch record review.

13. ***Rejected*** (failed) lot a product lot whose processing was completed but which was not deemed by competent quality assurance personnel as suitable for commercial distribution, *e.g.* due to non-conforming test result of analytical quality assessment, a critical deviation identified during batch record review.

14. ***Released*** (passed) lot is a product lot deemed by competent quality assurance personnel as suitable for commercial distribution.

2.2.1 Drug substance

Facility name / Product type	Current reporting period				Previous reporting period			
	Aborted	Completed			Aborted	Completed		
		Quarantined	Rejected	Released		Quarantined	Rejected	Released
Facility A	2	0	0	98	0	0	0	100
Facility B	1	1	0	98	0	0	1	99

Details on aborted, quarantined, and rejected lots:

2.2.2. Drug product

Facility name / Product type	Current reporting period				Previous reporting period			
	Aborted	Completed			Aborted	Completed		
		Quarantined	Rejected	Released		Quarantined	Rejected	Released

Details on aborted, quarantined, and rejected lots:

2.3 Reprocessed lots

NOTE

15. For each manufacturing facility and product type, list in a separate sub-section the corresponding lots of approved product initiated during the current reporting period and subjected to reprocessing[17].

16. For each affected lot provide *(i)* lot number, *(ii)* facility name, *(iii)* product type, *(iv)* reason for reprocessing, *(v)* overview of reprocessing steps, *(vi)* regulatory status in Canada, and *(vii)* whether lot sold in Canada.

17. ***Reprocessing*** is procedure, developed, validated, approved, and documented in a batch record for use under anticipated extraordinary circumstances, whereby a lot of process intermediate or finished product is re-introduced into the routine manufacturing process and subjected to one or several steps.

2.3.1 Drug substance

(a) [Facility name-product type]

(b) [Facility name-product type]

2.3.2. Drug product

(a) [Facility name-product type]

(b) [Facility name-product type]

2.4 Reworked lots

NOTE

18. For each manufacturing facility and product type, list in a separate sub-section the corresponding lots of approved product initiated during the current reporting period and subjected to reworking[20].

19. For each affected lot provide a *(i)* lot number, *(ii)* facility name, *(iii)* product type, *(iv)* reason for reworking, *(v)* overview of reworking steps, *(vi)* regulatory status in Canada, *(vii)* quality assessment of reworked lot, and *(viii)* whether lot sold in Canada.

20. ***Reworking*** is a procedure, developed in response to a specific unanticipated event, whereby a lot of process intermediate or finished product is subjected to one or several steps that may differ from the routine manufacturing process. If deemed appropriate, additional studies are performed to confirm that the quality of reworked material was not compromised (*e.g.* extended product characterization, stability studies).

2.4.1 Drug substance

(a) [Facility name-product type]

(b) [Facility name-product type]

2.4.2. Drug product

(a) [Facility name-product type]

(b) [Facility name-product type]

2.5. Critical deviations and non-conformances

NOTE

21. For each manufacturing facility and product type, provide in a separate sub-section a list of critical[25] deviations[23] and non-conformances[24].

22. For each event include an overview of associated investigations with root cause analysis, resolution with corrective and preventative actions (CAPA), and resulting product lot disposition.

23. ***Deviation*** is a failure to follow established procedures (*e.g.* manufacturing, analytical). A deviation may be deliberate (*i.e.* planned and pre-approved by quality assurance department) or inadvertent (*i.e.* unplanned).

24. ***Non-conformance*** is a failure of an analytical test result to meet established acceptance criteria.

25. ***Critical*** deviation or non-conformance is likely to compromise product quality with a potential impact on its safety and/or efficacy.

2.5.1 Drug substance

(a) Facility A – Drug Substance XYZ

Description of event	Date investigation initiated	Root cause	Resolution and corrective and preventative action (CAPA)	Product disposition
Microbiological contamination of 12,000L production bioreactor.	2009/12/02	Media used for 12,000L bioreactor was confirmed contaminated. A leak was discovered in the media hold tank.	Media hold tank was replaced. In addition, a 6 month review of media hold tank contaminations and maintenance activities was performed and did not reveal any trends.	Contaminated bioreactor batch was discarded.

(b) [Facility name-product type]

Description of event	Date investigation initiated	Root cause	Resolution and corrective and preventative action (CAPA)	Product disposition

2.5.2. Drug product

(a) Facility A – Dug Product XYZ

Description of event	Date investigation initiated	Root cause	Resolution and corrective and preventative action (CAPA)	Product disposition
Foreign matter (oil) was observed in in-process material at step B (pooling) during manufacture of lot 12345. (Quality Investigation #001)	2009/12/12	Inadequate preventative maintenance plan.	Corrective maintenance intervention on the tank and its parts were performed, and the preventative maintenance plan was updated.	500L of material was discarded (sub-pool A), resulting in a smaller batch size than routinely processed (3000L instead of 3500L), but still within licensed parameters.

(b) [Facility name-product type]

Description of event	Date investigation initiated	Root cause	Resolution and corrective and preventative action (CAPA)	Product disposition

Section 3: INFORMATION ON ANALYTICAL METHOD PERFORMANCE

3.1 Invalid lot release and stability tests

NOTE

26. For each test facility, provide in a separate sub-section a list of associated test methods.
27. For each test method provide (*i*) the total number of tests performed, (*ii*) the number or percentage of invalid tests, and (*iii*) a summary of causes resulting in invalid tests, including the associated corrective and preventative actions.
28. For trending purposes, provide information concerning the current and previous (if available) reporting period.
29. ***Invalid*** tests are test runs aborted due to events deemed to compromise the reliability of acquired test results (*e.g.* equipment failure, operator error, non-conforming analytical system suitability control).

(a) Facility A

Test name	Current reporting period			Previous reporting period	
	Total number of tests performed	Percentage of invalid tests	Explanation/cause and any corrective/preventive actions	Total number of tests performed	Percentage of invalid tests
Potency (ELISA)	67	6.0%	2 of the invalid assay are assignable to analyst error, the others were due to assay validity criteria failures	55	5.4%
Potency (Functional assay)	55	3.6%	Invalid assay were attributed to analyst error	55	14.5%
Molecular size distribution	135	2.5%	Invalid assay were due to system suitability failures	120	1.2%
pH	167	0.0%		155	0.0%
Protein	243	0.0%		250	0.0%

(b) [Facility name-product type]

Test name	Current reporting period			Previous reporting period	
	Total number of tests performed	Percentage of invalid tests	Explanation/cause and any corrective/preventive actions	Total number of tests performed	Percentage of invalid tests

3.2 Retesting due to out-of-specification (OOS) test results

NOTE

30. For each test facility, provide in a separate sub-section a list of associated test methods.

31. For each test method provide (*1*) the total number of tests performed, (*2*) the number of tests resulting in an out-of-specification (OOS) test result, (*3*) number of OOS results confirmed by retesting, and (*4*) a summary of causes resulting in unconfirmed (false) OOS test results, including the associated corrective and preventative actions.

32. For trending purposes, provide information concerning the current and previous (if available) reporting period.

(a) Facility A

Test name	Current reporting period				Previous reporting period		
	Total number of tests performed	Number of OOS	Number of confirmed OOS	Details	Total number of tests performed	Number of OOS	Number of confirmed OOS
SE-HPLC	5000	5	0	see footnote #1	1000	0	0
Footnote: (1) Root cause could not be confirmed.							

(b) [Facility name-product type]

Test name	Current reporting period				Previous reporting period		
	Total number of tests performed	Number of OOS	Number of confirmed OOS	Details	Total number of tests performed	Number of OOS	Number of confirmed OOS

Section 4: SUMMARY OF CHANGES

NOTE

33. For each manufacturing facility and product type, provide in a separate sub-section a list of changes implemented during the reporting period that have a potential impact on product quality (*i.e.* Level I, II, and III changes), including those to the manufacturing process and controls, raw material suppliers and non-compendial specifications, and to analytical methods. Duplicate subsections as necessary.

34. For each Level I and Level II change provide the control number of the relevant Canadian submission and its regulatory status. For each Level III change provide the date of the relevant Annual Notification.

4.1 Manufacturing process and controls

4.1.1 Drug substance

(a) Facility A – Drug Substance XYZ

Brief description	Rationale	Change level	Regulatory status
Scale-up at the fermentation and purification stage.	In order to meet increased product demand.	I	To be filed Q1 2010.

(b) [Facility name-product type]

Brief description	Rationale	Change level	Regulatory status

4.1.2 Drug product

(a) Facility A – Drug Product XYZ

Brief description	Rationale	Change level	Regulatory status
Change in the concentration of the active ingredient (e.g. 20 unit/mL *vs* 10 unit/mL).	To accommodate new indication.	I	Approved by Health Canada (S/NDS Ctrl# 456789)

(b) [Facility name-product type]

Brief description	Rationale	Change level	Regulatory status

4.2 Raw material suppliers and non-compendial specifications

4.2.1 Drug substance

(a) Facility A – Drug Substance XYZ

Brief description	Rationale	Change level	Regulatory status
Generation of a new master cell bank	Adaptation to a new fermentation medium with no raw materials derived from animal, human or recombinant origin	I	Under review (S/NDS Ctrl # 456789).
Solvent A specifications changed from USP to supplier limits	Supplier cannot guarantee the material will meet USP specification.	III	MECS# 000-000-0001 (Annual Notification filed December 1, 2009).

(b) [Facility name-product type]

Brief description	Rationale	Change level	Regulatory status

4.2.2 Drug product

(a) Facility A – Drug Product XYZ

Brief description	Rationale	Change level	Regulatory status
Change in the source of an excipient from an animal source to a vegetable source.	TSE risk mitigation.	II	Approved by Health Canada (S/NDS Ctrl# 456789)

(b) [Facility name-product type]

Brief description	Rationale	Change level	Regulatory status

4.3 Analytical methods

(a) Facility A

Brief description	Rationale	Change level	Regulatory status
Replacement of the Rabbit Pyrogen Test with the LAL test for Bacterial Endotoxins.	Replace animal testing with an in vitro method.	II	Not filed yet.
Revision of the potency specification.	Tightening of the acceptance criterion.	III	MECS# 000-000-0001 (Annual Notification filed December 1, 2009).

(b) [Facility name-product type]

Brief description	Rationale	Change level	Regulatory status

Section 5: TEST RESULTS

NOTE

35. For each manufacturing facility and product type, provide in a separate sub-section a list of critical in-process control tests (as defined in CPID) and lot release tests.

36. For each test provide associated acceptance criteria, the range of result values, and identify any overall shifts or trends.

37. For each test provide in the Appendix control charts (indicating acceptance limits, mean, and standard deviation) representing all lots manufactured during the current reporting period. If fewer than ten lots were manufactured during the current reporting period, provide data on the last 30 lots (including lots from previous reporting periods) or all available lot data, whichever is less.

38. If trend or shift is detected, provide in the Appendix tabulated summary of the data, including the status of relevant investigations.

5.1 In-process test results

5.1.1 Drug substance

(a) Facility A – Drug Substance XYZ

Process step	In-process control	Acceptance criteria / Action limits	Range of results (n)	Observed shifts or trends
Pre-harvest cell culture fluid	Bioburden	≤1 CFU/mL	≤1 CFU/mL (n=25)	No trends or shifts.
Concentration/ diafiltration	Conductivity	≤1.25 mS/cm	0.75-1.23 mS/cm (n=25)	No trends or shifts.

(b) [Facility name-product type]

Process step	In-process control	Acceptance criteria / Action limits	Range of results (n)	Observed shifts or trends

5.1.2 Drug product

(a) [Facility name-product type]

Process step	In-process control	Acceptance criteria / Action limits	Range of results (n)	Observed shifts or trends

(b) [Facility name-product type]

Process step	In-process control	Acceptance criteria / Action limits	Range of results (n)	Observed shifts or trends

5.2 Lot release test results

5.2.1 Drug substance

(a) Facility A – Drug Substance XYZ

Lot release test	Acceptance criteria	Range of results (n)	Observed shifts or trends
Potency	80-120%	82-95 (n=45)	No trends or shifts.
SE-HPLC	Monomer ≥98 %	98.5-99.5 (n=45)	No trends or shifts.

(b) [Facility name-product type]

Lot release test	Acceptance criteria	Range of results (n)	Observed shifts or trends

5.2.2 Drug product

(a) [Facility name-product type]

Lot release test	Acceptance criteria	Range of results (n)	Observed shifts or trends

(b) [Facility name-product type]

Lot release test	Acceptance criteria	Range of results (n)	Observed shifts or trends

Section 6: STABILITY STUDIES

NOTE

39. For each manufacturing facility and product type, provide in a separate sub-section a list of lots assessed in stability studies (due to *e.g.* annual commitments, manufacturing process changes, reworking), whether initiated, ongoing, or completed during the current reporting period.

40. For each lot provide in the Appendix a graphical representation of available stability data (one figure for each test), including acceptance criteria, the regression line, and suitable confidence intervals.

41. If a trend is detected, provide in the Appendix tabulated summary of the data.

42. Where appropriate, provide a statement regarding current stability program commitments, and changes to shelf-life, cross-referencing relevant submission control number.

6.1 Stability lots

6.1.1 Drug substance

(a) Facility A – Drug Substance XYZ

Lot number	Batch size	Enrolment date	Storage condition	Completed (and proposed) test intervals	Study type / purpose
1001	10 Kg	2008/06/25	2-8°C	3, 6, 9, 12, (18, 24, 36, 48, 60) months	Annual GMP
1002	10 Kg	2009/06/25	2-8°C	3, (6, 9, 12, 18, 24, 36, 48, 60) months	Annual GMP

(b) [Facility name-product type]

Lot number	Batch size	Enrolment date	Storage condition	Completed (and proposed) test intervals	Study type / purpose

6.1.2 Drug product

(a) Facility A – Drug Product XYZ

Lot number	Dosage form & strength	Enrolment date	Storage condition	Completed (and proposed) test intervals	Study type / purpose
09001	Lyophilised Powder 100 mg/vial	2009/06/25	2-8°C	3, (6, 9, 12, 18, 24, 36, 48, 60) months	Annual GMP

Lot number	Dosage form & strength	Enrolment date	Storage condition	Completed (and proposed) test intervals	Study type / purpose
09002	Solution for injection 100 mg/mL	2009/01/15	2-8°C	6, (18, 36, 60) months	Confirmatory study – new filling site (S/NDS Ctrl # 987654)

(b) [Facility name-product type]

Lot number	Dosage form & strength	Enrolment date	Storage condition	Completed (and proposed) test intervals	Study type / purpose

6.2 Stability test results

6.2.1 Drug substance

(a) [Facility name-product type]

(b) [Facility name-product type]

6.2.2 Drug product

(a) [Facility name-product type]

(b) [Facility name-product type]

Section 7: ANALYSIS OF ADVERSE DRUG REACTION REPORTS ATTRIBUTABLE TO PRODUCT QUALITY

NOTE
43. Provide a list and an assessment of Canadian and international adverse drug reaction (ADR) reports received by the sponsor during the current reporting period and deemed to be linked or potentially linked to product quality; or provide a clear statement confirming that no ADR reports related to product quality were received during the reporting period.

Section 8: PRODUCT RECALL AND CORRECTIVE ACTIONS

NOTE
44. Provide a list of product recalls issued during the current reporting period, including for each (*1*) the cause, (*2*) the issue date, (*3*) the list of implicated product lot numbers identifying those distributed in Canada, and (*4*) a summary of resulting corrective actions; or provide a clear statement confirming that no product recalls were issued during the current reporting period.

Section 9: CERTIFIED PRODUCT INFORMATION DOCUMENT (CPID)

NOTE

45. Provide a confirmation that changes implemented during the current reporting period are captured in CPID that is currently on file at Health Canada, cross-referencing the version number and relevant submission control number; or provide an annotated and a clean copy of the revised CPID; or provide a commitment to providing the revised CPID at a future date (*e.g.* upon the completion of scheduled annual CPID revision cycle).