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1.0 Purpose

This procedure determines the sampling, testing, and review procedures by Process Analytics/Quality Control (PA/QC) of cGMP materials.

2.0 Scope

This Standard Operating Procedure applies to PA/QC personnel and designees who will be sampling, testing, and reviewing procedures for cGMP materials (raw materials and buffers) at the ATRF.

3.0 Authority and Responsibility

3.1 The Director, Technical Operations, PA/QC has the authority to define this procedure.

3.2 PA/QC and designated staff are responsible for performing this procedure.

3.3 Materials Management and Inventory Control (MMIC) are responsible for supplying the necessary documentation to perform this procedure.

3.4 PA/QC is responsible for final release of 'B' level raw materials, for sampling and testing 'C' and 'D' level raw materials, and for recommending the release disposition to Quality Assurance.

3.5 Biopharmaceutical Quality Assurance (BQA) is responsible for the final release of raw materials and components for "C" and "D" items.

3.6 BQA is responsible for quality oversight of this procedure

4.0 PA/QC Inspection Matrix for Raw Materials

Items that MMIC gives to Process Analytics/Quality Control			
	Level B Items	Level C Items	Level D Items
Inspection and Receipt of Materials Form	X	X	X
Certificate of Analysis	X	X	X
Master Specification Sheet	X	X	X
Test Request Form	**N/A**	X	X

X: Required

5.0 Certificate of Analysis (COA) Review – Inspection Levels B, C, and D for Raw Materials

5.1 Verify that the lot number on the manufacturer's COA is the same lot number as on the containers received from the lot as recorded on Form 20302-01, Inspection and Receipt of Materials - Inventoried Materials.

NOTE: The catalog number on the COA may be only part of the catalog number listed on the container. Container size and other indications may be added to the catalog number by the supplier.

5.2 Verify that a member of QC or QA department at the manufacturer has signed the COA.

NOTE: Some COAs are not provided by the supplier with a signature and will be indicated as such on the raw material specification sheet as acceptable without a signature. If the raw material specification sheet does not indicate that the COA is acceptable without a signature, contact the QA Manager to determine action to be taken.

5.3 Verify that the manufacturer's test results meet the specifications listed on the COA.

5.4 Verify that the test results performed by the manufacturer meet the approved Raw Material Master Specification Sheet (**Form 21903-02**).

5.5 After review, the analyst will sign and date the COA to signify his/her review and acceptance of the document.

5.6 Assign the shelf life per the approved Raw Material Part Number/Master Specification (RM/MS) Sheet (**Form 21903-2**) shelf life and the guidance below based on the terminology used.

5.6.1 **Vendor Assigned** – assign the same expiration date as listed by the manufacturer on either the product packaging or the accompanying Certificate of Analysis (COA).

NOTE: Commonly seen terms for this date could be: Expiration Date, Expiry, Expires, Use By, Use Before, Retest Date.

5.6.1.1 If the manufacturer's expiration is given as a month and year only (e.g., 07/21 or July 2021), the BDP-assigned expiration will be the last day of that month (e.g., 7/31/21).

5.6.1.2 If the manufacturer only provides a "shelf life" of "X" months or "X" years in addition to the date of manufacture, then "X" should be added to the date of manufacture to obtain the BDP expiration date.

5.6.2 **"X" years** – The RM/MS sheet states the shelf-life in years (e.g., 1, 2 3 years, etc.) BDP expiration is based on levels of information/dates as follows:

5.6.2.1 If the COA or product shows a date (see examples below), the BDP shelf life from the raw material part number/master specification will be added to that date to obtain the BDP expiration based on the following hierarchy:

5.6.2.1.1 Date of manufacture, production date, etc. - any date that indicates when the material/product was produced.

NOTE: Sometimes the date of manufacture is encoded in the lot number of the product.

5.6.2.1.2 Release date, certification date, etc. – any date that indicates when the quality group approved the material/product.

5.6.2.1.3 Date when the certificate was signed.

5.6.2.1.4 Date when the certificate was printed.

5.6.2.1.5 Packaging date.

5.6.2.2 Date of receipt at the BDP will be a last option for the basis of an expiration date. If no other means of determining an expiration date are available, then the shelf life is added to the date of receipt at the BDP to establish the expiration date.

5.6.3 **"X" years or manufacturer's expiration date, whichever is shorter, as stated on the PN/MS sheet.**

5.6.3.1 If the product is media, a biological, or chemical, the BDP expiration date will be assigned as directed, using the shorter of the two potential expiration dates.

5.6.3.2 For other consumables, the BDP expiration should be the manufacturer's expiration. This coincides with current BDP shelf life options per **SOP 21903 - *Using the Part Number/Master Specification Program to Establish Raw Material Part Numbers and Master Specifications***.

5.6.4 **"X" years or manufacturer's expiration date, not to exceed the manufacturer's assigned expiration date, as stated on the PN/MS sheet.**

5.6.4.1 If the manufacturer lists a date (see terminology in 5.6.1), that date will be used for the BDP expiration date.

5.6.4.2 If no expiration date is given, follow 5.6.2.1 to assign the BDP expiration date.

5.7 Level B inspection items will be released by PA/QC with a signature and date on **Form 20302-01**, Inspection and Receipt of Materials - Inventoried Materials.

6.0 Sampling Procedure - Inspection Levels C, and D Procedure for Raw Materials

6.1 Requests to sample and test cGMP materials are made by Materials Management and Inventory Control staff on the PA/QC Test Request Form per **SOP 22002 - *Request for Quality Control Testing.***

6.2 The lot is sampled as follows:

6.2.1 The number of containers sampled is determined by the ANSI/ASQC Z1.4 Table Requirements for General Inspection Level II (Attachment I).

Example: If there are six containers in the lot and they are tested at ANSI/ASQC Z1.4 Inspection Level II, two containers are randomly selected, sampled, and tested. (A sample is pulled from each container and tested independently from the other samples.) ANSI/ASQC Z1.4 will not be used to determine sample size in certain cases due to the sterility claim of the product and/or the material is not product contact. These cases of exception will be noted on the master specification sheet in the sample size section.

6.2.2 Each manufacturer unit sampled is labeled indicating a sample was removed from the container, with the initials of the person who removed the sample, the date the sample was taken, and a container ID number for when multiple sample containers in the lot are sampled. For example, 1, 2, 3, etc. (Attachment 2).

6.2.3 The number of containers sampled and amount removed is recorded on the Raw Material Test Report **Form 22714-01**.

6.2.4 Any multi-component material (i.e., – dehydrated culture media) must be mixed by multiple (minimum of five inversions) inversions prior to sampling to ensure a uniform mixture and representative sample.

6.2.4.1 Containers larger than 15kg require the use of a sample thief because adequate mixing may not be possible. In this case, each sample from the thief must be treated as an individual sample. They should not be combined into a single sample. All samples should pass release criteria. In the case that a sample fails release criteria, an attempt to mix the material again followed by retesting could be made before the material is deemed to be outside specifications.

6.2.5 Sample Quantities

6.2.5.1 Sampling for Release Testing: The sample quantities taken from each unit sampled must be adequate for specified tests to be performed. Reference the raw material specification sheet for the specific sample size to be taken.

6.2.5.2 Sampling for Retention: From the first container sampled, in addition to collecting a volume sufficient to perform all required release testing, collect a separate retention sample at a volume sufficient to perform all required release testing in duplicate, except the volume required for testing of sterility or rabbit pyrogen need not be retained. Reference the raw material specification sheet for the specific retention sample volume. Retention samples will not be taken for media plates. Stoppers, vials, crimps, and any other components will be retained at a sample size of 20.

6.2.6 Each sample taken for release testing will be identified with a label indicating it is a test sample. The label will have the following information: Name, BDP Part Number, BDP Lot Number, QC Test Request Form Number, Manufacturer's Lot Number, Container ID Number, the initials of the person sampling the material, and the date the sample was taken. The samples will be taken in appropriate containers.

6.2.7 Each sample taken for retention will be identified with a label indicating it is a retention sample. The label will have the following information: Name, BDP Part Number, BDP Lot Number, QC Test Request Form Number, Manufacturer's Lot Number, Container ID Number, Retain Discard Date, initials of the person sampling the material, and the date the sample was taken. The retention sample must be placed and stored in a container comparable in construct to the received raw material container construct. For example, if the raw material was received in a brown glass bottle, the retention sample will be collected and stored in a brown glass container.

6.2.8 Samples will be taken in the QC Sampling Lab, ATRF, [redacted]. Gowning should be performed in accordance to **SOP 19406 - *Gowning Requirements for Personnel and Visitors: ATRF Manufacturing and Support Areas***. All raw materials must be aseptically sampled using new/clean utensils for each sampling. Only one raw material may be opened and sampled at a time. Should the QC Sampling Lab, [redacted], not be available, the Telstar Recirculating Downflow Booth 3001DFBH003B (located in [redacted]) will be used. **SOP 11152 - *Operation and Maintenance of the Telstar Recirculating Downflow Booths*** should be followed while sampling material in the alternate area.

7.0 Testing Procedure – Raw Material Inspection Levels C and D

7.1 Document testing on the Raw Material Test Report, **Form 22714-01**.

7.2 Attach all raw data, graphs, charts, standard curves or reference their location, etc. All attached documents must be signed and dated by the analyst and include the QC Test Request form number.

7.3 If applicable, show all calculations used in determining the final results.

8.0 Retention Samples

8.1 Raw material retention samples will be stored at the same temperature as the bulk raw material.

8.2 Retention duration will be defined on the master specification sheet.

8.2.1 Critical raw materials will be retained for 10 years.

8.2.2 Cell culture media that contains a degrading form of glutamine will not be retained.

8.2.3 Media plates will not be retained.

8.2.4 All other raw materials will be retained for 1 year after their labeled expiration.

9.0 Buffer Testing

9.1 Buffers made by Technical Operations will be tested to specifications listed on the Reagent Preparation Batch Production Record.

9.2 The sample volume submitted for testing must be adequate for the specified tests to be performed. Separate containers must be submitted for microbiology testing and chemistry testing.

9.3 All results will be written on the Buffer Test Report, **Form 22714-02**. Attach the supporting assay form(s) (for example, pH, Conductivity, Endotoxin, LAL and Bioburden from the specific assay SOPs).

9.4 The requestor will submit to PA/QC a completed test request form, a copy of the page of the Reagent Preparation Batch Production Record with the specifications, required tests, a label attached to the form, and samples of the buffer.

10.0 Pass/Fail Determination

10.1 A member of PA/QC or designee, other than the analyst, will review all the test data and attached documentation and, based upon the total information, recommend release or reject of the material by signature on either the Raw Material Test Report, Form 22714-01 or **Form 22714-02** . This individual verifies the following prior to signing.

10.1.1 Confirms that all tests required for release per the Component/Raw Materials Master Specification Sheet (**Form 21903-02**) or the Reagent Preparation Batch Production Record has been performed

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10.1.2 For each test, confirm proper standards, standard curves, calibrations, and/or controls were performed and that all system suitability requirements are acceptable as per the specific assay SOP. Assess the testing data for data integrity - attributable, legible, contemporaneously recorded, original or true copy and accurate (reference FDA Guidance: Data Integrity and Compliance with CGMP April 2018).

10.1.3 All entries to **Form 22714-01** or **Form 22714-02** are properly made, and corrections are acceptable.

10.1.4 All test values meet the specifications stated on the Component/Raw Material Master Specification Sheet (**Form 21903-02**) or the Reagent Preparation Batch Production Record.

10.2 The documentation including **Form 22714-01** and test data are forwarded to BQA to release or reject the component per **SOP 21708 - *QA Disposition of CGMP Raw Materials.***

10.3 The documentation for buffer testing (Form 22714-02) is submitted to QA for review and approval per **SOP 22002 - *Request for Quality Control Testing.***

11.0 Definitions

11.1 **COA –** In this document, any reference to a COA includes the Certificate of Analysis, Certificate of Conformance, Certificate of Compliance, Certificate of Quality, or Certificate of Sterilization.

11.2 **ANSI/ASQC Z1.4 – 2003: Sampling Procedure and Tables for Inspection by Variables for Percent Nonconforming–** Standards for choosing sample size according to the receiving lot size.

11.3 **A, B, C, and D Inspection Levels –** Refer to **SOP 21902 - *Requirements for Establishing Part Numbers and Specifications for BDP Components and Materials***, for the definitions of A, B, C, and D inspection levels.

12.0 References and Related Documents

12.1 **BDP SOP 11152** *Operation and Maintenance of the Telstar Recirculating Downflow Booths*

12.2 **BDP SOP 20302** *Receipt and Inspection of Materials*

12.3 **BDP SOP 21409** *Good Documentation Practices*

12.4 **BDP SOP 21708** *QA Disposition of CGMP Raw Materials*

12.5 **BDP SOP 21902** *Requirements for Establishing Part Numbers and Specifications for BDP Components and Materials*

12.6 **BDP SOP 21903** *Using the Part Number/Master Specification Program to Establish Raw Material Part Numbers and Master Specifications*

12.7 **BDP SOP 22002** *Request for Quality Control Testing*

12.8	**BDP SOP 19406**	*Gowning Requirements for Personnel and Visitors: ATRF Manufacturing and Support Areas*
12.9	**BDP SOP 19102**	*Routine Use and Disinfection of Biological Safety Cabinets, Incubators, Shakers, and Centrifuges*
12.10	**FDA Guidance**	FDA Guidance: Data Integrity and Compliance with CGMP, April 2018)

13.0 Attachments

13.1	**Attachment 1**	ANSI/ASQC Z1.4 – 2003: Sampling Procedure and Tables for Inspection by Variables for Percent Non-conforming
13.2	**Attachment 2**	CGMP Labels

Attachment 1

ANSI/ASQC Z1.4.2003: Sampling Procedure and Tables for Inspection by Variables for Percent Non-conforming.

Lot or Batch size			Special Inspection Levels				General Inspection Levels			Sample Size code letter	Sample size
			S-1	S-2	S-3	S-4	I	II	III		
2	to	8	A	A	A	A	A	A	B	A	2
9	to	15	A	A	A	A	A	B	C	B	3
16	to	25	A	A	B	B	B	C	D	C	5
26	to	50	A	B	B	C	C	D	E	D	8
51	to	90	B	B	C	C	C	E	F	E	13
91	to	150	B	B	C	D	D	F	G	F	20
151	to	280	B	C	D	E	E	G	H	G	32
281	to	500	B	C	D	E	F	H	J	H	50
501	to	1200	C	C	E	F	G	J	K	J	80
1201	to	3200	C	D	E	G	H	K	L	K	125
3201	to	10000	C	D	F	G	J	L	M	L	200
10001	to	35000	C	D	F	H	K	M	N	M	315
35001	to	150000	D	E	G	J	L	N	P	N	500
150001	to	50000	D	E	G	J	M	P	Q	P	800
500001	and	over	D	E	H	K	N	Q	R	Q	1250
										R	2000

Attachment 2
CGMP Labels