Frederick National Laboratory for
Cancer Research, Frederick, MD

BPP

Biopharmaceutlcal Development Program

Standard Operating Procedure

Title: Origination, Implementation, and Maintenance of Stability Protocols

SOP Number: 22529

Revision Number: 05

Supersedes: Revision 04

Effective Date: FEB 06 2019

Originator/Date: [redacted]

Approval/Date:

Approval/Date:

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1.0 Purpose

Th is SOP describes the ful cycle of a stability protocol for Current Good Manufacturing Practice (CGMP) and selected Toxicology products produced in the Biopharmaceutical Development Program (BOP.)

2.0 Scope

This procedure applies to Process Analytics\Qualit.y Control (PA\QC) personnel, Biopharmaceutical Quality Assurance (BOA) personnel, Biopharmaceutical Regulatory Affa irs,

This **procedlJ'e** is made availablethrough federal funds from lhe National Cancer Institute, NIH, under contract [redacted]

and Project Scientists involved in stability studies for early Phase clinical products. Accelerated, inverted vial, administration compatibility, and excursion/adverse event studies are not specifically covered in this SOP due to their unique requirements.

3.0 Authority and Responsibility

3.1 The Director, Process Analytics\Quality Control (PA\QC) has the authority to define this procedure and initiate testing with an approved PA\QC Testing laboratory.

3.2 PA\QC, BQA, and the Project Scientist are responsible for originating and approving stability protocols.

3.3 The PA\QC Stability Program Manager is responsible for implementation, maintenance, and documentation of this procedure. This includes obtaining appropriate standards, communicating with contract laboratories, clinical sites, pharmacies, and investigators, maintaining experimental data pertaining to this procedure, reviewing PA/QC reports and conducting trend analyses, and preparing stability reports in conjunction with BQA Documentation.

3.4 BQA is responsible for quality oversight of this procedure.

3.5 BQA Documentation is responsible for assigning protocol numbers and assisting with the writing, distribution, and archival of official stability reports to the appropriate project and product recipients or locations.

4.0 Origination

4.1 The Project Scientist will notify the PA\QC Stability Manager of any new production campaign (R&D, GLP, or cGMP) that will result in a lot(s) requiring a real-time stability study.

4.2 Other studies may also require approved Stability Protocols, including accelerated and inverted vial stability programs.

4.3 The PA\QC Stability Manager will draft a Stability Protocol including:

4.3.1 Creation of a revision document to capture the reasons for generating the new protocol with its' associated testing and specifications.

4.3.2 A unique Stability Protocol ("SP") number is assigned by BQA Documentation.

4.3.3 An approved reference standard(s), as appropriate. Note that simple buffer, placebo, and diluent product lots may not have product-specific reference standards.

4.3.4 Testing based upon criteria outlined in Section 5.0.

5.0 Suggested Testing

5.1 The following are examples of recommended stability-indicating tests designed for final drug products, which are intended to support clinical studies. These tests are used where appropriate for each product.

A Appearance (including reconstitution time for lyophilized products).
B Bioassay (Product-Specific) – cell-based, binding (ELISA), or kinetic assay.

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P pH and if appropriate, osmolality and/or conductivity.
R Reverse Phase HPLC to detect impurities and/or degradation products.
H Size Exclusion Chromatography HPLC to monitor the presence of aggregates.
X HPLC-IEX or CE to monitor for the presence of charge variants.
E SDS-PAGE or CE-SDS to monitor molecular weight, impurities, and degradation.
G Agarose gel electrophoresis or native PAGE for nucleic acid or peptide products.
U UV absorbance (with extinction coefficient) or colorimetric/ELISA methods to measure product concentration.
S Sterility - may be substituted or augmented with container closure integrity testing. In some cases extended bioburden (Y) testing may be substituted.
M Mass Spectroscopy or other specialized methods to detect product changes.
I IEF Gel Electrophoresis or imaged cIEF to monitor charge variants.
T Virus Titer (plaque, $TCID_{50}$, and/or genomic copy number as appropriate).
V Virus Particle concentration (absorbance, EM, HPLC, qPCR copy number, or other methods as appropriate).
W Western blotting or transgene expression assays.
L LAL or other appropriate methods to quantitate Endotoxin.
Y Microbial Content (typically extended duration bioburden testing).
Z Viability and/or cell count determination.
O Other tests as determined appropriate, such as DLS, CD, SEC-MALS, etc.

A stability protocol not consistent with standard regulatory requirements for safety testing, including sterility, will be justified in the revision (i.e. creation) documentation. Any applicable documentation will be attached to the protocol or cross-referenced.

5.2 Suggested minimum stability testing guidelines for various classes of drug products are listed below. The tables pertain only to real-time stability studies for the first three lots of a clinical (CGMP) product manufactured by the BDP for early Phase studies. Individual products can be expected to have specific characteristics that may require additional or modified testing to ensure identity, content, potency, purity, or safety.

MONOCLONAL ANTIBODIES

Time Interval (Months)	# of Vials/Time Point	Methods
0, 3, 6, 9, 12, 18, 24	5	AUHEB
0, 12, 24	20	S
Each year (if still in clinic)	30	AUHEBS

RECOMBINANT PROTEINS

Time Interval (Months)	# of Vials/Time Point	Methods
0, 3, 6, 9, 12, 18, 24	5	A (R, X/I, or H) UEB
0, 12, 24	20	S
Each year (if still in clinic)	30	A (R, X/I, or H) UEBS

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NUCLEIC ACIDS

Time Interval (Months)	# of Vials/Time Point	Methods
0, 3, 6, 9, 12, 18, 24	5	AGXU(M/W)
0, 12, 24	20	S
Each year (if still in clinic)	30	AGXU(M/W)S

PEPTIDES

Time Interval (Months)	# of Vials/Time Point	Methods
0, 3, 6, 9, 12, 18, 24	5	AR(M)(X/I)(O)
0, 12, 24	20	S
Each year (if still in clinic)	30	AR(M)(X/I)(O)S

VIRUSES

Time Interval (Months)	# of Vials/Time Point	Methods
0, 3, 6, 9, 12, 18, 24	6	A(T/V)(W)LP
0, 12, 24	2	Y
Each year (if still in clinic)	12	A(T/V)(W)LPY

CELLS

Time Interval (Months)	# of Vials/Time Point	Methods
0, 3, 6, 9, 12, 18, 24	5	AZ(W)LP
0, 12, 24	2	Y or S
Each year (if still in clinic)	12	AZ(W)LPY or S

6.0 Approval

6.1 The protocol will be signed by the Project Scientist, PA\QC Representative, BQA Representative, and government representative or project officer. Other signatures may be required or added as needed.

7.0 Implementation

7.1 Time zero is defined as the production date (i.e., date the product was vialed).

7.2 Upon approval of the stability testing protocol, the PA\QC Stability Manager will initiate the appropriate testing at the specified times.

8.0 Documentation/Maintenance

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted]

8.1 A status spreadsheet is maintained of all outstanding stability testing and reports, including planned stability testing up to six months in advance of submission.

8.2 Revisions, amendments, and extensions to stability protocols may be generated, with justification, to reflect ongoing clinical trials, protocol changes, inclusion of additional test methods, or at the request of the BRB or the clinical investigator. Protocol revisions will follow the same origination, review and approval process as a new stability protocol. Revisions are noted on the Revision Justification Form 21419-02 and attached to the revised document.

8.3 Extended stability protocols are assigned a new Stability Protocol number by BQAD. A revision document is generated to capture the reasons for extending the protocol.

8.4 Revisions or amendments to an existing protocol are assigned a revision level and a revision document is generated to capture the justifications for the changes made.

8.5 Interim (or final, end of use (EOU)) stability reports will be prepared, analyzed for trends and out-of-specification / out-of-trend (OOS / OOT) results by PA/QC, reviewed by BQA, and approved upon the completion of each time point.

8.6 Stability reports will be distributed to the project principal investigator (PI), project scientist, IND sponsors, clinical sites and pharmacies as appropriate, involved government agencies (e.g. NCI/BRB, CTEP, NIAID, etc.), and to BDP staff (i.e. BQA/RA, BQAD, PA/QC) for archival purposes.

9.0 Protocol Holds, Closures, Stops, Terminations, and Completions

9.1 Stability programs and protocols may be placed on hold at the request of the PI and BRB or other client representative. Justifications for program holds include inactive clinical trials, clinical holds, and low vial inventories. An approved hold request is considered a stability protocol amendment and are documents as described above.

9.2 Stability programs for products not in active clinical use may be stopped prior to the end of planned protocol at the request of the PI and/or BRB or the Client Representative. A stop request is treated the same as a protocol amendment as described above.

9.3 Protocol stops may also be implemented in case an inadequate number of accessible vials remain to conduct the study as originally planned. In such cases the PI and BRB are notified of the stop requirement prior to the final executable time point. A ‘forced stop’ notification is treated the same as a protocol amendment as described above.

9.4 Once a stability study has been fulfilled (i.e. reached the final time point and/or a notice of clinical end of use has been received from the PI), the Project Scientist, BRB or Client Representative, BQA Regulatory Affairs, and PA/QC Director will be notified of pending completion.

9.5 If the stability study has been fulfilled and a decision has been made not to extend the protocol (or no additional product vials remain to extend), a final report will be written and provided to all appropriate parties.

9.6 Based on a review of stability data and in consultation with the government sponsor, project scientist, and BQA/RA, the PA\QC Director has the authority to terminate or place on hold a study at any time. Clinical sites and IND sponsors must be notified of

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protocol termination, stoppage, and hold notices immediately to halt further investigational use of the affected product lot. A memorandum will be written to the project file detailing the termination or hold notice and a Material Review Board meeting may be convened.

10.0 References and Related Documents

10.1 SOP 21419 Origination, Modification, and Approval of Documents

10.2 ICH Guidance for Industry Q1A (R2) “Stability Testing of New Drug Substances and Products. November 2003.

10.3 ICH Guidance for Industry Q1E “Evaluation of Stability Data.” June 2004.

11.0 Attachments

11.1 Attachment 1 Sample Stability Protocol

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Attachment 1

Form 22529-01, Stability Testing of ABC

FNLCR, BDP
Form No.: 22529-01
SOP No.: 22529
Revision 05: FEB 06 2019

Production Date: **XX/XX/XX**
Reference Std: **123456**
Protocol No.: **SP-0XX**
Effective:
Project: XXXX

Stability Testing of ABC
Final Vialed Product, Lot LXXXXXX

OBJECTIVE

This protocol provides for the assessment of the real time stability of the Final Vialed ABC Product in specific time intervals for two years.

Attribute	Test	SOP	Specifications	Time Pts (Months)	Vials
VISUAL	Appearance	22925	Clear, colorless, no foreign matter or visible particulates	0,3,6,9,12,18,24	1
CONTENT	A_{280}	22180	5.0 ± 1.0 mg/mL (ext. coeff = 1.4)	0,3,6,9,12,18,24	
IDENTITY	SDS-PAGE: Reduced and Non-reduced	22175, 22176, 22161, 22906	Report Major Bands; Conforms to Standard	0,3,6,9,12,18,24	
PURITY	HPLC-SEC	22178	≥ 95% Total Protein, ≥ 90% Monomer	0,3,6,9,12,18,24	
POTENCY	Cell based ELISA -Binding to 32DB cells	16101	Binding reactivity within 50-150% of Standard	0,3,6,9,12,18,24	1
SAFETY	Sterility	21 CFR 610.12	No Growth	0, 12, 24	10

FILLED VIAL STORAGE AND TESTING

A. Containers:

X mL vial / X mL fill volume

B. Filled Product Temperature Storage Conditions and Withdrawal for Testing:

1. Storage at ≤ -70°C
2. Vial Requirements: 32 plus 8 retains, 40 vials total.

Time (Months)	3	6	9	12	18	24
Requirement (# Vials)	2	2	2	12	2	12

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Attachment 1 (Continued)

Form 22529-01, Stability Testing of ABC

FNLCR, BDP
Form No.: 22529-01
SOP No.: 22529
Revision 05: FEB 06 2019

Production Date: **XX/XX/XX**
Reference Std: **123456**
Protocol No.: **SP-0XX**
Effective:
Project: XXXX

Stability Testing of ABC
Final Vialed Product, Lot LXXXXXX

DOCUMENTATION

A BQC Request Form (22002-01) will be completed for each time point. Termination of study will be at the request of the Director, PA/QC Assay results and a final report will be compiled by PA/QC.

APPROVALS

Project Scientist: _____ Date: _____
Printed name / Title

PA/QC Review: _____ Date: _____
Printed name / Title

BQA Review: _____ Date: _____
Printed name / Title

NCI/BRB Review: _____ Date: _____
Printed name / Title

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