National Institute of Biologicals

GUIDANCE DOCUMENT FOR INDUSTRY

SUBMISSION OF STABILITY DATA AND RELATED DOCUMENTS FOR REVIEW AND EXPERT OPINION FOR GRANTING POST APPROVAL CHANGES IN SHELF LIFE OF RECOMBINANT BIOTHERAPEUTIC PRODUCTS AND THERAPEUTIC MONOCLONAL ANTIBODIES

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Chronology of Events

S. No.	Activity	Process Time
1.	1st Meeting of Scientific Experts Committee for Recombinant Products and Therapeutic Monoclonal Antibodies at NIB	02.12.2015
2.	1st Sub-Committee meeting at DBT New Delhi	23.02.2016
3.	Meeting at CDSCO for PAC	25.04.2016
4.	Ist Draft Guidance Document placed on NIB Website for inviting comments from Industry Stakeholders	28.04.2016 to 23.06.2016
5.	• Incorporation of comments & opinion given by Industry Stakeholder, • Expert Review of Subcommittee members for PAC	30.06.2016
6.	Finalization of Guidance Document for Industry to be discussed in the subcommittee of PAC at NIB in Aug 2016	04.07.2016
7.	Guidance Document with few points of amendments (Annexed) discussed in the subcommittee meeting and Document is vetted.	23.08.2016
8.	Guidance document and PAC Checklist to be placed on NIB website	2016 Oct. – 2QTR.
9.	Date for coming into effect for the Industry	2016 Oct. – 2QTR.

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Guidelines published by National Institute of Biologicals (NIB) are intended to be scientific and advisory in nature. Each of the following sections constitutes guidance for manufacturers of rDNA Biotherapeutic Products & Therapeutic Monoclonal Antibodies. If an NRA so desires, these Guidelines may be adopted as definitive national requirements, or modifications may be justified and made by the NRA. It does not create or confer any rights for or on any person and does not operate to bind NIB or the public. You can use an alternative approach. If you want to discuss an alternative approach, contact the appropriate NIB staff.

1.0 Introduction

This guidance provides recommendations to holders of marketing authorization for recombinant technology based products including therapeutic monoclonal antibodies, who intend to make post approval changes in shelf –life of such product in accordance with CDSCO guidance Document No. - PAC/1108 Version – 1.1. The guidance covers recommended reporting categories, documents required, technical data requirements, data representation and interpretation to assess the compliance to various defined key points specified in the Guidance for Industry CDSCO for post approval changes with respect to shelf –life of such products and data requirements and analysis as given in ICH guidelines Q1A, Q1E and Q5C. The document also covers approval process at NIB along with turnaround time for each phase and also the procedures followed by NIB for handling non-compliances of the data provided by the manufacturer to the requirements mentioned in this document.

2.0 Background

The applications for post approval changes are submitted by the applicant to the Office of the Drugs Controller general of India for grant of approval for changes in the already approved shelf-life of the product. The applicants require to fulfill the conditions for the reporting category and submit the supporting data as per the para 4.1.7 & 4.2.7 as the case may be as given in the Guidance Document on Post approval changes in Biological Products: Quality Safety and Efficacy Documents Document No. - PAC/1108 Version – 1.1. The said document gives an overall requirement for submission of the application. The technical data with respect to stability testing for change in Shelf-life submitted by the applicants are forwarded by CDSCO to NIB, with a request for expert opinion before granting such post approval changes. Since the assessment requires detailed data inputs as per the requirements of ICH guidelines to assess its compliance to the recommendations given therein a more technically elaborate document is required. This guidance document enlists all the general and technical requirements expected by NIB to assess the compliance of the submitted documents to the national and international guidelines for post approval changes in shelf life of the product

3.0 Scope

This guidance is applicable to holders of marketing authorization for recombinant technology based products including therapeutic monoclonal antibodies, who have applied to CDSCO for grant of approval for post approval changes in shelf –life of the product in accordance with CDSCO guidance Document No. - PAC/1108 Version – 1.1. The document is applicable to only those applications forwarded by CDSCO to NIB for expert opinion before granting such post approval changes. This guidance document should be read in conjunction with CDSCO guidance Document No. - PAC/1108 Version – 1.1 and the assurance to the requirements mentioned therein are to be verified by CDSCO before forwarding the application to NIB for expert opinion.

4.0. Guidance for Implementation

4.1 Reporting Categories for change in retest period of Drug substances/ Drug product as per the CDSCO guidance Document No. - PAC/1108 Version – 1.1

4.1.1 Notifiable Change-Level-II

Level II - Notifiable Changes (Moderate Quality Changes) are changes that have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the biological product as these factors may relate to the safety or effectiveness of the product. The changes included in this reporting category should be filed, along with the recommended supporting data, to DCGI as a Notifiable Change (NC). The applicant shall implement changes upon receipt of DCG (I) approval or acceptance letter for the changes submitted. The Change in the re-test period (or shelf life) for the drug substance or Drug product should be reported as Level-II Notifiable changes if:

4.1.1.1 Extension of re-test period/shelf-life: when Full long term stability data are not available covering the changed shelf life or are not based on stability data generated on at least three production scale batches. If the proposed shelf life is beyond the available long term data, the extrapolation is in accordance with ICH's Q1E guideline.

However, in this case also Stability data should comply the following conditions:

a) Stability data should have been generated in accordance with the approved stability protocol.

b) Significant changes (as defined in ICH's Q1A guideline) were not observed in the stability data.

c) No change to the container closure system in direct contact with the drug substance or to the recommended storage conditions of the drug substance.

d) **Supporting Data:** The supporting data for extension of retest period under the Level-II reporting category should include the following:

i. Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).

ii. Proposed storage conditions and re-test period (or shelf life, as appropriate).

iii. Updated post-approval stability protocol and stability commitment.

iv. Justification of the change to the post-approval stability protocol or stability commitment.

v. Results of stability testing (i.e., less than full real time/real temperature stability data covering the changed re-test period (or shelf life) and/or not generated on at least three (3) production scale batches) and a commitment to submit the stability report when completed and to notify DCGI of any failures in the ongoing stability studies.

4.1.1.2 Reduction of re-test period: The study design should comply with the conditions that Stability data are generated in accordance with the approved stability protocol. And there is No change to the container closure system in direct contact with the drug substance or to the recommended storage conditions of the drug substance/ drug product

The supporting data for Reduction of retest period under the Level-II reporting category of should be as mentioned in section **4.1.1.1 d (i - v).**

4.1.1.3 Addition of storage condition for drug substance /Drug product: The study design should comply with the conditions that there is no change to the container closure system in direct contact with the drug substance or to the recommended storage conditions of the drug substance.

The supporting data for Addition of storage condition for drug substance /Drug product under the Level-II reporting category should be as mentioned in section **4.1.1.1 d (i - v).**

4.1.2 Level-III Annual Notification

Level III - Annual Notification (Minor Quality Changes) are changes that have minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the biological product as these factors may relate to the safety or effectiveness of the product. The changes included in this reporting category may be implemented by the sponsor without the prior review by DCGI of the data supporting such a change. Supporting data for the Level III changes recommended in this guidance documents should be submitted on annual basis; however, the data on such changes should be available to DCGI within fifteen (15) calendar days, if requested at any time.

Extension of re-test period are allowed as a level-III Notification if Full long term stability data are available covering the changed shelf life and are based on stability data generated on at least three production scale batches.

However, in this case also Stability data should comply the following requirements:

a) No change to the container closure system in direct contact with the drug substance or to the recommended storage conditions of the drug substance.

b) The approved shelf life is at least 24 months.

c) Stability data were generated in accordance with the approved stability protocol.

d) Significant changes (as defined in ICH's Q1A guideline) were not observed in the stability data.

The supporting data for Addition of storage condition for drug substance /Drug product under the Level-III reporting category should include the following

a) Summary of stability testing and results (e.g., studies conducted, protocols used, results obtained).

b) Proposed storage conditions and re-test period (or shelf life, as appropriate).

c) Results of stability testing (i.e. full real time/real temperature stability data covering the changed re-test period (or shelf life) generated on at least three (3) production scale batches).

4.2 General Documents required by NIB to review the stability data submitted by the applicants

i) Forwarding letter from the Office of the drug controller General of India for review and comments on the application for change in retest period.

ii) The documents both general and technical have to be page numbered consecutively and each page of the document authorized with the seal and signature of the authorized signatory on behalf of the applicant or an undertaking that that the sender is taking the responsibility of the authenticity of the document.

iii) Covering letter from the applicant with the following statements :

a) Purpose should be clearly mentioned along with whether change in Drug substance or Drug product and description of Statement on Proposed storage conditions and retest period (or shelf life, as appropriate).

b) The approved shelf-life and the recommended storage temperature should also be clearly mentioned.

c) Statement on Change category: Notifiable/Annual Notification as per CDSCO Guidance for Industry.

d) If the product is a similar Biologic, the approved shelf –life of the corresponding innovator product and the evidences to substantiate this should be furnished. For imported products copy of approval from NRA of country of origin and/or from EMEA, USFDA. Etc. if available, along with list of countries where proposed variation is approved.

e) Whether information is submitted as per CDSCO Guidance for Industry for proposed post approval change in the shelf life of the product to be stated

f) Statement that there is no change to the container closure system in direct contact with the drug substance /drug product or to the recommended storage conditions of the drug substance/Drug product.

g) Total number of pages including general and technical documents to be stated in the covering letter with the number of Annexure enclosed

iv) Copy of marketing authorization and other permissions/approvals for subject's product for which approval is sought

4.3 Technical requirements

4.3.1 The dossier accompanying the application for post approval change in the shelf –life should include a detailed protocol for the assessment of the stability of both drug substance and drug product in support of the proposed storage conditions and expiration dating periods as submitted during the grant of marketing authorization. The protocol should include all necessary information which demonstrates the stability of the biotechnological/biological product throughout the proposed change of expiration dating period including, for example, well-defined specifications and test intervals and data interpreted using appropriate statistical methods

4.3.2 Common Technical Document approved by the regulatory authorities for the product. The CTD module section - 3.2.S.4, 3.2.S.5, 3.2.S.6 & 3.2.S.7 for Drug Substance or 3.2.P.5, 3.2.P.6, 3.2.P.7 & 3.2.P.8 for Drug product may be forwarded by CDSCO to NIB along with the application. If submitted by manufacturer an undertaking by authorized signatory of the manufacturer stating that the CTD is the same as approved by the regulatory authorities (CDSCO) should be furnished.

4.3.3 Results of stability testing (i.e. full real time/real temperature stability data covering the changed re-test period (or shelf life) generated on at least three (3) production scale batches complying the following recommendations:

4.3.3.1 Selection of batches: stability data should be provided on at least 3 batches for which manufacture and storage are representative of the manufacturing scale of production. If data for less than three production batches are submitted for grant of approval, the change will be reviewed under a level –II notifiable change subject to the condition that data requirements are complete and complies with ICH Q1A R2 and Q1E guideline. Stability studies should be performed on each individual strength and container size of the drug product unless bracketing or matrixing is applied

4.3.3.2 Specifications: Shelf-life acceptance criteria should be derived from consideration of all available stability information. It may be appropriate to have justifiable differences

between the shelf-life and release acceptance criteria based on the stability evaluation and the changes observed on storage. The use of different specifications for release and expiration should be supported by sufficient data to demonstrate that clinical performance is not affected as discussed in the tripartite guideline on stability.

4.3.3.3 Testing parameters: Stability studies should include testing of those attributes of the drug product that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological and microbiological attributes, and functionality tests. These tests should be properly validated as per ICH Q1D guideline and statement regarding this has to be incorporated in the stability protocol.

a) Potency studies should be performed at appropriate intervals as defined in the stability protocol including the proposed change in shelf-life and the results should be reported in units of biological activity calibrated, whenever possible, against nationally or internationally recognized standard. Where no national or international reference standards exist, the assay results may be reported in in-house derived units using a characterized reference material. The software printouts of the calculation of potency value for each batch and the compliance to system suitability criteria and validation criteria have to be submitted

b) Purity and degradation: The degree of purity, as well as individual and total amounts of degradation products of the biotechnological/biological product entered into the stability studies, should be reported and documented whenever possible. Limits of acceptable degradation should be derived from the analytical profiles of batches of the drug substance and drug product used in the preclinical and clinical studies. The necessary chromotragrams, electropherograms and SDS-PAGE images should be submitted for the data points at approved shelf-life and proposed change in shelf-life period. The values of quantitative attributes at all time points should be reported as measured values.

c) The following product characteristics should be monitored and reported for the drug product in its final container: Visual appearance of the product (colour and opacity for solutions/suspensions; color, texture and dissolution time for powders), visible particulates in solutions or after the reconstitution of powders or lyophilized cakes,

pH, and moisture level of powders and lyophilized products. The data should be provided for all the testing points as mentioned in the stability protocol including the proposed change in shelf life

d) For Drug products Sterility testing or alternatives (e.g., container/closure integrity testing) should be performed at a minimum initially and at the end of the proposed shelf-life.

e) If there is any indication during preliminary stability studies that reaction or degradation of additives or excipient materials adversely affect the quality of the drug product, these items may need to be monitored during the stability program.

f) The stability of freeze-dried products after their reconstitution should be demonstrated for the conditions and the maximum storage period specified on containers, packages, and/or package inserts. Such labelling should be in accordance with relevant national/regional requirements.

g) **Accelerated Stability studies:** It is strongly suggested that stability studies be conducted on the drug substance and drug product under accelerated condition. The related declaration regarding the study and the data generated should be submitted.

4.3.3.4 Testing Frequency:

For long term studies, frequency of testing should be sufficient to establish the stability profile of the drug product. When shelf-lives of 1 year or less are proposed, the real-time stability studies should be conducted monthly for the first 3 months and at 3 month intervals thereafter. For products with proposed shelf-lives of greater than 1 year, the studies should be conducted every 3 months during the first year of storage, every 6 months during the second year, and annually thereafter.

4.3.3.5 Labelling:

The label with approved shelf –life depicted on it should be submitted along with the application which is authenticated by the authorized signatory of the firm.

4.3.3.6 Data presentation

Data for all attributes should be presented in an appropriate format (e.g., tabular, graphical, narrative) and an evaluation of such data should be included in the application.

The values of quantitative attributes at all time points should be reported as measured (e.g., assay as percent of label claim/relative to reference standard, molecular aggregates as percentage of HMW, LMW and monomers, IEX as % Monomer, % basic and % acidic variants, Glycan as %GU units of each glycoforms set etc). If a statistical analysis is performed, the procedure used and the assumptions underlying the model should be stated and justified. A tabulated summary of the outcome of statistical analysis and/or graphical presentation of the long-term real-time stability data should be included.

4.3.3.7 Data Interpretation

Data interpretation to be submitted by the applicant: wherever applicable, in addition to the numerical measured value of the results, except for sterility testing, BET and physical characteristics, compliance to acceptance criteria needs to be specified.

4.3.3.8 Data Evaluation

Data Evaluation Wherever applicable, an appropriate statistical method should be employed to analyze the long-term primary stability data in an original application. The purpose of this analysis is to establish, with a high degree of confidence, a retest period or shelf life during which a quantitative attribute will remain within acceptance criteria for all future batches manufactured, packaged, and stored under similar circumstances. Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient. Any deviation to the acceptance criteria at any time point of the study should be sufficiently justified with corrective and preventive actions taken. This is permissible only for one of the three batches charged for stability studies. If more than one batch shows such non-compliance to the specified acceptance criteria of any test parameters at the time point of the proposed shelf-life, the product will be considered as unstable for the said parameter at the proposed shelf-life

4.3.3.9 Compliance to specifications: Each product should retain its specifications within established limits (as per respective Pharmacopoeial monograph for Pharmocopoeial products; for non-pharmacopoeial products as per the drug products/ Drug substance specifications as approved by the National regulatory authority) for safety, purity, and potency throughout its proposed shelf-life.

General statement on the effect of change in shelf –life on quality, safety and efficacy of the product: The applicant has to submit a summarized Statement and evidences about effect of change in shelf –life on quality, safety and efficacy of the product. The summary should include all necessary information which demonstrates the stability of the biotechnological/biological product throughout the proposed change of expiration dating period including, for example, well-defined specifications and test intervals and data interpreted using appropriate statistical methods

4.3.3.10 Stability Commitment:

i) If the submission includes real-time stability data from studies covering the proposed change in shelf –life period but on a fewer than three production batches, a commitment should be made to continue the long term studies through the proposed shelf life and the accelerated studies for 6 months or alternative justified period , and to place additional production batches, to a total of at least three, on long term stability studies through the proposed shelf life and on accelerated studies for 6 months or alternative justified period.

ii) If the submission includes real-time stability data from studies covering the proposed change in shelf –life period on batches other than production batches or at least 3 batches for which manufacture and storage are representative of the manufacturing scale of production,, a commitment should be made to place the first three production batches on long term stability studies through the proposed shelf life and on accelerated studies for 6 months or alternative justified period.

iii) For cases when a manufacturer asks for approval of a duration for which they do not have stability data (say approval for 2 years of shelf life with 1 year stability data), a stability commitment should be given by the manufacturer to submit the actual stability data when the study is over. The approval is deemed to be contingent till then

iv) The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.

4.4 Checklist to be filled by the applicant to full fill the criteria as per general documents and technical requirements are given in Annexure1

4.5 Template for data representation for side by side Side by side comparison of results obtained for test parameters of the product with reference to previously approved shelf-life data point and proposed Change in shelf-life in Tabular form is give at Annexure-II or in other format which covers all the elements/information as mentioned in Annexure-II

4.6 All the documents as mentioned in general requirements and technical requirements along with the checklist and data analysis sheet submitted to NIB has to be authenticated with the seal of the authorized signatory along with signature and date

5.0 The approval process of PAC application at NIB

5.1 The approval process of PAC application will be carried out at NIB as per the following three phase strategy:

a) Phase I: Desktop Review: This is case-by-case to accomplish the compliance to the information submitted by the Manufacturer as per the checklist annexed.

b) Phase II: Verification with additional data: If the applicant cannot substantiate their claim by desktop review, additional data to be verified including validation data for each test parameter, stability indicating profile (chemical & biological), matrix for charging of samples and quantity of containers for stability studies, statistical significance of variations found in the test results, images of gels, chromatograms, details of molecular weight markers and internal reference standard or reference product used, formulation buffer etc.

c) Phase III: Wet verification: This is to clarify any deficiencies noted in phase II verification. The wet verification may be done for any of test parameters specified in the stability protocol for which compliance to the acceptance criteria needs to be verified. In the event of a particular testing facility for verification is not available within NIB, then NIB will jointly conduct that particular test at identified Government Laboratories with whom NIB has signed its MOU.

5.2 Turnaround time for each Phase

i. Phase I: Desktop Review: The Desktop Review shall be completed within 15 days of the receipt of the application at NIB. The communications regarding clarifications on key points and other technical requirements will be communicated by NIB directly to the applicant. The response from the applicant is expected to be submitted within 15 days

from the date of communication to the applicant. The email Id of the authorized signatory of the applicant has to be mentioned in the covering letter to facilitate the processes in a speedy manner. If the response is not received at NIB within the stipulated time, the PAC application will not be recommended due to the incomplete data submission. The matter will be communicated to CDSCO and the applicant will be declared non-responsive. The clarification submitted by the applicant shall be reviewed by NIB and the report will be submitted to CDSCO within 15 days of receipt of the said documents at NIB.

Note: *For Imported products the response from the applicant is expected to be submitted within eight weeks from the date of communication to the applicant. The final turn around time for these products will be 86 days*

a) **Turnaround time, if all the requirements are complied = 15 days from receipt of the complete document**

b) Clarification, if any to be submitted by applicant- within 15 days from the date of communication to the applicant.

c) Response from NIB and final decision on compliance to requirements or further decision for next phase of verification- 15 days of receipt of the said documents at NIB

Total turnaround time = 15 days + 15 days + 15 days = 45 days

ii. Phase II: Verification with additional data: In case of the need of Phase-II verification, the matter will be communicated to the applicant directly by NIB and a copy of the communication will be marked to CDSCO for information. The requirements mentioned in the letter from NIB regarding the Phase-II verification have to be furnished within 15 days from the date of communication of this to the applicant. The Phase-II verification at NIB will start only once all the requirements mentioned in the letter is furnished by the applicant. Once all the documents are received then an acknowledgement will be sent to the applicant in this regard. The review and verification process at NIB shall be completed within 15 days of receipt of all the documents and the required data. If the response is not received at NIB within the stipulated time, the PAC application will not be recommended due to the incomplete data submission. Non-responsiveness of the applicant will be communicated to CDSCO for further perusal at their end. The verification documents

submitted by the applicant shall be reviewed by NIB and the report will be submitted to CDSCO within 15 days of receipt of the said documents at NIB.

45 days (Phase-I) +15 Days + 15 Days = 75 days

Note: For Imported products the response from the applicant is expected to be submitted within eight weeks from the date of communication to the applicant. The final turn around time for these products will be 127 days

iii. Phase III: Wet verification: In case there is a further need of wet Verification, the applicant will be intimated in this regard directly by NIB and a copy of the communication will be marked to CDSCO for their information. The applicants will be intimated regarding the testing requirements and other additional documents required during a formal meeting with the technical representatives of the applicant along with the representatives from CDSCO. On concurrence to the testing strategies finalized at the said meeting and the strategy approved and signed by both the parties, the applicants are to submit these within a period of 15 days. The duration of testing of the product shall be estimated case by case and will be updated accordingly after the receipt of samples and other additional requirements at NIB. The sample quantity required for testing will also be estimated case by case and informed accordingly.

Note: *For Imported products the response from the applicant is expected to be submitted within eight weeks from the date of communication to the applicant*

6.0 Handling non-compliances to the requirements as specified in this guidance document

The verification of the stability data & related documents will be performed as per the process given at point No.5.0 of this document. Even after the three phase verification the satisfactory conclusion is not possible regarding compliance of the data to the acceptance criteria specified in the approved stability protocol or if the study process is not compliant to the technical requirements mentioned in this document, the matter will be communicated to the applicant for necessary clarifications and justifications. The response from the applicant thus submitted will be deliberated by the Experts of the NIB- Scientific Committee for recombinant Products and therapeutic Monoclonal antibodies along with the representatives from the applicant, representatives from CDSCO and NIB representatives. The final

decision on the matter will be taken by NIB- Scientific Expert Committee for recombinant Products and therapeutic Monoclonal antibodies as per the conclusions derived in the meeting.

7.0 Chronology of compilation

S. No.	Name	Designation	Resource Organization
A. Contributors – Document Compilation			
1.	Dr. G. R. Soni	Deputy Director (Quality Control)	National Institute of Biologicals, Noida, INDIA
2.	Dr. Renu Jain	Scientist Grade – I & Head Recombinant Product Laboratory	
3.	Ms. Sudha V. Gopinath	Scientist Grade – III, Therapeutic Monoclonal Antibody Laboratory	
4.	Dr. Meena Kumari	Scientist Grade – III, Recombinant Product Laboratory	
5.	Mr. Subhash Chand	Scientist Grade – III, Therapeutic Monoclonal Antibody Laboratory	
6.	Dr. Gaurav Pratap Singh	Junior Scientist, Recombinant Product Laboratory	
7.	Mr. P. S. Chandranand	Junior Scientist, Therapeutic Monoclonal Antibody Laboratory	
B. Reviewers- Industry stakeholders of rDNA Biotherapeutic Products & Therapeutic Monoclonal Antibodies			
C. Reviewers- Expert Committee Member of Post Approval Changes (PAC) in rDNA Biotherapeutic Products & Therapeutic Monoclonal Antibodies			
1.	Dr. Anurag S. Rathore	Professor, Department of Chemical Engineering	Indian Institute of Technology-New Delhi Delhi, INDIA
2.	Dr. V. S. Reddy	Chief Scientific Officer - Expert	Biosafety Support Unit, New Delhi, INDIA
3.	Dr. Anand Kumar Kondapi	Professor, Department of Biotechnology	University of Hyderabad Telangana, INDIA

8.0 References

1. CDSCO Guidance Document on Website *"Post approval changes in Biological Products: Quality, Safety and Efficacy Id - PAC/1108 Version – 1.1"*.
2. ICH Harmonised Tripartite Guideline Stability Testing of New Drug Substances and Products Q1A(R2)
3. ICH Harmonised Tripartite Guideline Evaluation for Stability Data Q1E
4. ICH Harmonised Tripartite Guideline Quality of Biotechnological Products: Stability Testing of Biotechnological/ Biological Products Q5C.

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NATIONAL INSTITUTE OF BIOLOGICALS
CHECK LIST FOR POST APPROVAL CHANGE APPLICATIONS DOCUMENTATION
Doc Id – NIB/QMU/PAC-2014-B (R1), Dated: 04/07/2016
rDNA Products & Therapeutic Monoclonal Antibody

Name of the Firm: Product Name:
Reference: F. No.
Description of Change:

ANNEXURE I

S. No.	Particulars	Information required to be submitted	Status (Yes/No) Reference page of submitted document
1.	Covering letter –	purpose should be clearly mentioned with page number and index	
	Total number of pages including general and technical documents	to be stated in the covering letter with the number of Annexure enclosed	
2.	Whether change in Drug substance or Drug product	e.g. In Drug Substance/ Drug product; Extension/ reduction of retest period	
3.	Change category: Notifiable/Annual Notification as per CDSCO Guidance for Industry	Mention the change category	
4.	Copy of marketing authorization and other permissions/approvals for subject's products	Should be submitted with the application and annexed.	
5.	Undertaking or satisfactory statement to fulfil conditions of proposed shelf –life change as per CDSCO Guidance for Industry	Undertaking should be given	
6.	Side by Side comparison of previously approved and changed shelf-life as given in the annex –II of the NIB guidance document	annex –II of the NIB guidance document to be filled and submitted	
7.	If the product is a similar Biologic, the approved shelf –life of the corresponding innovator product and	Name of the innovator Product Brand name and current approved shelf –life of the product	

All information should be typed in this format. Please read the information carefully. Where not applicable write NA or strike off and where asked for submission follow the same. Refer Guidance Document (**Doc Id – NIB/QMU/PAC-2014-B (R1), Date: 04/07/2016)**

		Compiled By	Verified By	Approved By
Manufacturer Review	Signature			
	Name			
	Designation			
	Date (dd/mm/yyyy)			
NCL/ Regulators Review	Signature			
	Name			
	Designation			
	Date (dd/mm/yyyy)			

Name of the Firm: Product Name:
Reference: F. No.
Description of Change:

S. No.	Particulars	Information required to be submitted	Status (Yes/No) Reference page of submitted document
	the evidences to substantiate this should be furnished	along with evidences	
8.	For imported products certified copy of approval from NRA of country of origin and from EMEA, USFDA. Etc. along with list of countries where proposed variation is approved	Should be preferably from Regulated and developed countries. May mention the Non-Regulated countries	
9.	Declaration that no other information is changed or no variation in the product as a result of proposed change. (Mention clearly if there is any variation)	Declaration should be given	
10.	No change to the container closure system in direct contact with the drug substance/product or to the recommended storage conditions of the drug substance/product.	Declaration should be submitted	
11.	Name of the product & nature for which the stability data is submitted for the proposed change in Shelf-life	Brand name of the product along with the batch numbers and details whether the batches are of R& D scale/ laboratory scale/ clinical trial/ process validation/ commercial production	
12.	Stability protocol and release test specification	stability protocol and release test specification submitted to CDSCO during marketing authorization to be	

All information should be typed in this format. Please read the information carefully. Where not applicable write NA or strike off and where asked for submission follow the same. Refer Guidance Document (**Doc Id – NIB/QMU/PAC-2014-B (R1), Date: 04/07/2016)**

		Compiled By	Verified By	Approved By
Manufacturer Review	Signature			
	Name			
	Designation			
	Date (dd/mm/yyyy)			
NCL/ Regulators Review	Signature			
	Name			
	Designation			
	Date (dd/mm/yyyy)			

Name of the Firm: Product Name:
Reference: F. No.
Description of Change:

S. No.	Particulars	Information required to be submitted	Status (Yes/No) Reference page of submitted document
		submitted	
13.	Approved storage temperature & shelf Life	Mention the Approved storage temperature & shelf Life	
14.	Proposed storage temperature & shelf Life	Mention the proposed storage temperature & shelf Life	
15.	Stability data	Page Numbers of the stability data for proposed change in shelf life	
SELECTION OF BATCHES			
16.	stability data should be provided on at least 3 batches for which manufacture and storage are representative of the manufacturing scale of production	Any deviation must be declared	
	Stability commitment	To be submitted in case stability data from studies covering the proposed change in shelf –life period are on a fewer than three production batches or on batches other than production batches or at least 3 batches and also for For cases when a manufacturer asks for approval of a duration for which they do not have stability data	

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		Compiled By	Verified By	Approved By
Manufacturer Review	Signature			
	Name			
	Designation			
	Date (dd/mm/yyyy)			
NCL/ Regulators Review	Signature			
	Name			
	Designation			
	Date (dd/mm/yyyy)			

Name of the Firm: Product Name:
Reference: F. No.
Description of Change:

S. No.	Particulars	Information required to be submitted	Status (Yes/No) Reference page of submitted document
17.	Stability Protocol	should include a detailed protocol for the assessment of the stability of drug substance / drug product in support of the proposed storage conditions and expiration dating periods	
18.	Potency	Reference material used for stability study along with traceability to innovator / or working Primary Reference standard used by the manufacturer to be given along with the data The software printouts of the calculation of potency value for each batch and the compliance to system suitability criteria and validation criteria have to be submitted	
19.	Purity and Molecular Characterisation: For the purpose of stability testing, tests for purity should focus on methods for determination of degradation products.	The related chromotragrams, electropherograms and SDS-PAGE images should be submitted for the data points at approved shelf-life and proposed change in shelf-life period. The values of quantitative attributes at these time points should be reported as measured values	

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Reference: F. No.
Description of Change:

S. No.	Particulars	Information required to be submitted	Status (Yes/No) Reference page of submitted document
20.	**Other Product Characteristics**	Visual appearance of the product (colour and opacity for solutions/suspensions; colour, texture and dissolution time for powders), visible particulates in solutions or after the reconstitution of powders or lyophilised cakes, pH, and moisture level of powders and lyophilised products	
		Sterility testing or alternatives (e.g., container/closure integrity testing) should be performed at a minimum initially and at the end of the proposed shelf-life	
STORAGE CONDITIONS			
21.	**Temperature**	the storage conditions for the real-time/real-temperature stability studies may be confined to the proposed storage temperature	
22.	**Humidity**	Where humidity-protecting containers are not used, appropriate stability data should be provided.	

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Name of the Firm: Product Name:
Reference: F. No.
Description of Change:

S. No.	Particulars	Information required to be submitted	Status (Yes/No) Reference page of submitted document
ACCELERATED AND STRESS CONDITIONS			
23.	It is strongly suggested that studies be conducted on the drug substance and drug product under accelerated and stress conditions.	It is strongly suggested that studies be conducted on the drug substance and drug product under accelerated condition. the related declaration regarding the study may be submitted	
STABILITY AFTER RECONSTITUTION			
24.	**Stability after Reconstitution of Freeze-Dried Product**	The stability of freeze-dried products after their reconstitution should be demonstrated for the conditions and the maximum storage period specified on containers, packages, and/or package inserts	
TESTING FREQUENCY			
25.	**TESTING FREQUENCY**.	For products with proposed shelf-lives of greater than 1 year, the studies should be conducted every 3 months during the first year of storage, every 6 months during the second year, and annually thereafter	
SPECIFICATIONS			
26.	Each product should retain its specifications within established limits	The use of different specifications for release and expiration should be	

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Reference: F. No.
Description of Change:

S. No.	Particulars	Information required to be submitted	Status (Yes/No) Reference page of submitted document
	for safety, purity, and potency throughout its proposed shelf-life. These specifications and limits should be derived from all available information using the appropriate statistical methods.	supported by sufficient data to demonstrate that clinical performance is not affected as discussed in the tripartite guideline on stability	
COMPLIANCE TO SPECIFICATIONS			
27.	Compliance to specifications: Each product should retain its specifications within established limits for safety, purity, and potency throughout its proposed shelf-life.	For pharmacopoeial products compliance to the pharmacopoeia should be mentioned (IP/BP/EP/USP/others) In case of non- pharmacopoeial specification, basis of specifications to be justified by submitting the approved specification in MA. This should be for release and shelf life specifications.	

Signature of the authorized personnel of manufacturer:

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ANNEXURE-II

SIDE BY SIDE COMPARISON OF DATA FOR APPROVED AND PROPOSED SHELF LIFE

Batches tested			
Mfg. date			
Stability Start date			
Intended study period			
Stability period completed			
Testing frequency			
Testing frequency for sterility			
Storage condition			

S. No.	Proposed essential tests for assessing stability of the biotechnological product *	Specification as in the stability protocol	Results of THREE batches as stated in the stability data document submitted by the manufacturer						Release Test Specification	Remarks
			Batch No.1		Batch No.2		Batch No.3			
			Approved Shelf-life	Proposed shelf life	Approved Shelf-life	Proposed shelf life	Approved Shelf-life	Proposed shelf life		
1.	**Colour & clarity**									
2.	**Reconstitution time (if freeze dried)**									
3.	**pH**									
4.	**Purity by HPLC (SEC) Degree of IgG aggregation.**									
5.	**Protein concentration (UV spectrophotometry)**									

S. No.	Proposed essential tests for assessing stability of the biotechnological product *	Specification as in the stability protocol	Results of THREE batches as stated in the stability data document submitted by the manufacturer						Release Test Specification	Remarks
			Batch No.1		Batch No.2		Batch No.3			
			Approved Shelf-life	Proposed shelf life	Approved Shelf-life	Proposed shelf life	Approved Shelf-life	Proposed shelf life		
6.	**Biological Activity**									
7.	**Purity by Gel Electrophoresis SDS-PAGE/CE-SDS (REDUCING & Non-reducing)**									
8.	**Isoelectric focusing (IEF)/ IEX Chromatography**									
9.	**Bacterial Endotoxin**									
10.	**Sterility**									
11.	**Any other**									

*** Note:** The proposed essential tests should be as per the Pharmacopoeial requirement or in case of non – pharmacopoeial products the test should be as per the NRA approved marketing authorization specification.

Analyzed by: **Verified By:** **Approved By:**

Amendments dated: Aug 23, 2016

S. No	Section & Page No.	Changes
1.	4.1.1.2 & 4.1.1.3 Page 5 - 7	Deletion: repetition of the information on supporting data required for submission and referred as section 4.1.1.1d (i-v)
2.	4.3.3.3 (g) Page 11	Addition: data to be submitted for Accelerated stability studies'
3	5.2 Page 14 - 16	Edited as below; a) Phase I: Desktop Review: TAT = 15 days (NIB Review) + 15 days (Clarification from Manufacturer) + 15 days (NIB Review) = 45 days b) Phase II: Verification of additional data: TAT = 45 days (Phase I) + 15 days (Clarification from Manufacturer) + 15 days (NIB Review) = 75 days c) Phase III: 15 days for submission of test requirements and STPs by Manufacturers and TAT for testing and report release by NIB will be estimated case to case and informed accordingly.
4	5.2 Page 14 - 16	Addition; If the response is not received at NIB within the stipulated time, the PAC application will not be recommended due to the incomplete data submission.
5	Annexure –II	Edited: The proposed minimum tests in annexure –II of Guidance document should be as per the Pharmacopoeial requirement or in case of non – pharmacopoeial products the test should be as per the NRA approved marketing authorization specification.