"Regulatory procedure of post approval changes and variation and comparative studies of European Union and United State"

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in Partial Fulfillment for the Award of the Degree of

MASTER OF PHARMACY

IN

REGULATORY AFFAIRS

BY

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May 2023

CERTIFICATE

This is to certify that the dissertation work entitled "REGULATORY PROCEDURE OF POST APPROVAL CHANGES AND VARIATION AND COMPARATIVE STUDIES OF EUROPEAN UNION AND UNITED STATE" submitted by Ms. Jahnavi Tailor with Regn. No. (21MPH803) in partial fulfillment for the award of Master of Pharmacy in "Regulatory Affairs" is a bonafide research work carried out by the candidate at the Department of Pharmaceutical Analysis, Institute of Pharmacy, Nirma University under our guidance. This work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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To whomsoever it may concern

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Duration of training 6 June-2022 to 23 December -2022

During her training, her performance was found to be satisfactory

We wish her all the best in future endeavors.

Sincerely

For Sun Pharmaceutical Inds Limited

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CERTIFICATE OF ORIGINALITY OF WORK

This is to certify that the dissertation work entitled "Regulatory procedure of post approval changes and variation and comparative studies of European Union and United States" submitted by Ms. Jahnavi Tailor with Regn. No (21MPH803) in partial fulfilment for the award of Master of Pharmacy in "Regulatory Affairs" is a bonafide research work carried out by the candidate at the Department of Pharmaceutical Analysis, Institute of Pharmacy, Nirma University under the guidance of "Dr. Hardik Bhatt". I am aware about the rules and regulations of Plagiarism Policy of Nirma University, Ahmedabad. According to that this work is original and has not been reported in part or full for any other degree or diploma to this or any other university or institution as per best of my knowledge.

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DECLARATION

I hereby declare that the dissertation entitled "REGULATORY PROCEDURE OF POST APPROVAL CHANGES AND VARIATION AND COMPARATIVE STUDIES OF EUROPEAN UNION AND UNITED STATE", is based on the original work carried out by me under the guidance of Dr. Hardik G. Bhatt, Associate Professor, Head of Department Pharmaceutical Chemistry, Institute of Pharmacy, Nirma University. I also affirm that this work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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Ms. Jahnavi Tailor

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LIST OF ABBREVATIONS

MAH	MARKETING AUTHORIZATION HOLDER
CCF	CHANGE CONTROL FORM
QA	QUALITY ASSURANCE
EC	EUROPEAN COMMUNITY
MRP	MUTUAL RECOGNITION PROCEDURE
EU	EUROPEAN UNION
EMEA	EUROPE, the MIDDLE EAST, AFRICA
RMS	REFERENCE MEMBER STATE
CMS	CONCERNED MEMBER STATES
EUCTD	EUROPEAN UNION COMMON TECHNICAL DOCUMENT
SmPC	SUMMARY OF PRODUCT CHARACTERISTICS
CMDH	CO-ORDINATION GROUP FOR MUTUAL RECOGNITION AND DECENTRALISED PROCEDURES-HUMAN
CTS	COMMON TECHNICAL SPECIFICATION
FUM	FOLLOW UP MEASURES
SO	SPECIFIC OBLIGATIONS
PSUR	PERIODIC SAFETY UPDATE REPORTS
PVAR	PRELIMINARY VARIABLE ASSESSMENT REPORT
DDPS	DETAILED DESCRIPTION OF THE PHARMACOVIGILANCE SYSTEMS
RSI	REQUEST FOR SUPPLEMENTARY INFORMATION
FVAR	FINAL VARIATION ASSESSMENT REPORT

PSRPH	POTENTIALLY SERIOUS PUBLIC HEALTH RISK
NDA	NEW DRUG APPLICATION
ANDA	ABBREVIATED NEW DRUG APPLICATION
USFDA	UNITED STATE FOOD AND DRUG ADMINISTRATION
CFR	CODE OF FEDERAL REGULATION
PAS	PRIOR APPROVAL SUPPLEMENT
CBE	CHANGES BEIMG EFFECTED
AR	ANNUAL REPORT
cGMP	current GOOD MANUFACTURING PRACTICE
MDI	METERED DOSE INHALER
DPI	DRY POWDER INHALER
CDER	CENTER FOR DRUG EVALUATION AND RESEARCH
HPLC	HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY
HDPE	HIGH DENSITY POLYETHYLENE
ICH	INTERNATIONAL COUNCIL FOR HARMONISATION
SUPAC	SCALE-UP AND POST-APPROVAL CHANGES
HCL	HYDROGEN CHLORIDE
USP	USA PHARMACOPEIA
q.s	quantum sufficiat
SOPs	STANDARD OPERATING PROCEDUREs
CHMP	COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
NTA	NOTICE TO APPLICANTS

ASMF	ACTIVE SUBSTANCE MASTER FILE
TSE	TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES
MRA	MUTUAL RECOGNITION AGREEMENT
VICH	VETERINARY INTERNATIONAL CONFERENCE ON HARMONIZATION
GC	GAS CHROMATOGRAPHY
LOD	LOSS ON DRYING
LOQ	LIMIT OF QUANTIFICATION
ppm	parts per million
CFU	COLONY FORMING UNIT

ABSTRACT

Examining the impact of post-approval alterations in the United States and Europe is the goal of this study. The study aims to identify the existing policies and comprehend the underlying concepts. The policies and procedures of regulatory authorities in both regions are compared and contrasted. The management of post-approval lifecycle activities is a significant responsibility of marketing authorization holders (MAHs). Real-time case studies have been conducted to enhance understanding and knowledge about the subject. Post-approval modifications are an essential part of pharmaceutical product life cycle management. These changes need to be carefully monitored and must follow the proper legal requirements for the relevant nation. Across the current work, after approval modifications are identified together with post approval change regulations, guidelines, and submission procedures across Europe. The European Medical Agency (EMA) has outlined the regulatory framework for post-approval adjustments, often known as variant filings in Europe, in a number of recommendations. The article goes on to discuss the different sorts of adjustments, classification, and application process for variation changes. Variations are categorised in Europe as Type-IA for modest changes, Type-IB for moderate alterations, and Type-II for significant changes. These little adjustments can be made without the agency's consent, however.

CHAPTER 1

INTRODUCTION

CHAPTER 1

INTRODUCTION

Changes is define as “A change to any aspect of a pharmaceutical product, including but not limited to a change to formulation, method and site of manufacture, specifications for the finished product and ingredients, container and container labelling and product information”.[1]

To ensure faster and more predictable implementation of changes after approval, corporations typically describe the specific changes they would like to make during a product's lifecycle, along with how these changes will be prepared and verified in a post-approval change management plan. This plan is developed after the Marketing Authorization Holder (MAH) obtains agreement from Regulatory Authorities on the proposed strategy and tests required to verify the impact of the changes on product quality.[2]

Post-Approval Change Management is a process that helps businesses make informed decisions to comply with ongoing regulatory guidelines during a product's lifecycle management. This process involves assessing and managing the risks associated with implementing changes to a product or its manufacturing processes. By doing so, companies can ensure that their products remain compliant with regulatory requirements while also being able to adapt to changes in the market and evolving consumer needs.

The existing post-market change management system varies across jurisdictions, with different methods for change management and reporting of proposed changes to relevant health authorities. This variability in approaches across countries can pose a challenge for manufacturers who need to ensure consistency in the supply of their products in different regions. Maintaining a consistent supply of the same product in different countries can be challenging due to the diversity of mechanisms employed by various regulatory authorities.

Post-Approval Change is an essential part of managing a product's lifecycle, and it can occur for various reasons, such as changes in regulatory requirements, improvements in manufacturing processes for greater efficiency and cost-effectiveness, changes in business requirements, alterations in product models, and updates in analytical and formulation

specifications. All of these changes aim to enhance the safety and quality of healthcare products available to consumers worldwide.

Some countries have their own regional product regulations for submitting post-marketing variations. This guidance provides post-approval change suggestions, recommended tests, and documentation on CMC changes regarding the use of new drugs or the use of new drugs that have been omitted. Implementation of this guideline has shortened the approval period and, where applicable, includes post-approval changes to products already on the market.[3, 4]

Appropriate review of the Change Control Form (CCF) is required to access the changes proposed by each department. The regulatory team is responsible for ensuring that any changes made to a product after it has been approved follow the proper change control procedures, which may involve completing a CCF. It must be filled out to meet the regulatory requirements of each country. The final copy of the CCF should include the tasks, actions, and target dates for completion for each department. It is a critical document that must be included in the audit scope as it captures important information about proposed changes and their completion timelines. The regulatory and quality assurance teams play a crucial role in ensuring that the CCF is appropriately reviewed and filled out to meet regulatory requirements. However, monitoring all CCF transactions and ensuring that all completed tasks are tracked can be a challenging task for the quality assurance department. Therefore, it is essential to have robust systems and processes in place to effectively manage and track changes throughout the product lifecycle.

It is essential to evaluate the impact of any changes made to approve products to ensure their quality, safety, and effectiveness. The assessment of these changes should be properly documented for future reference. Depending on the magnitude of the impact, it may be necessary to document the evaluation of changes. Different jurisdictions have different methods of reporting these changes, including annual reports, amendments, or new license applications. To comply with the regulations, manufacturers must refer to the guidance document specific to the jurisdiction in which they operate. This will enable them to follow the appropriate procedures and ensure compliance.

The various post approval changes are observed in:

- Components and composition
- Manufacturing sites
- Manufacturing process
- Specification
- Container closer system
- Labelling
- Miscellaneous

In USA and EU the post approval changes are designated as:

USA: SUPAC and Post Approval Changes

EU: Variation

CHAPTER 2

AIM & Objectives

CHAPTER 2

AIM AND OBJECTIVES

Aim:

To study the Regulatory procedure of post approval changes and comparative studies of European Union and United State

Objectives:

- To understand the type of variation and post approval changes
- To observe the challenges faced during filling the variation
- To know the comparison between the countries
- To have a better understanding of the filing process
- To learn the type of changes observed in industries

CHAPTER 3

EUROPE

CHAPTER 3

1 EUROPE

1.1 Introduction

The Commission Rule (EC) No. 1234/2008 was issued on November 24, 2008, for the revision of the marketing approval conditions for human and veterinary drugs. This rule is also known as the "Revised Rule" and was issued on December 12, 2008.[5] The main objective of the revised rules is to provide a legal framework that is simple, clear, and flexible for addressing changes in drug approval. This framework also aims to ensure the protection of human and animal health at a high level.

In addition to European law defining variations, the Directive uses classification codes to establish a harmonized list of expected variations. Since the introduction of Mutual Recognition Procedure (MRP) in 1998, a list of changes in MA in Europe has been defined. However, it should be noted that at the time of its issuance, the law regulating the amendment procedure for European Union member states was not fully implemented at the national level by many of these states. The law has since been updated regularly, with the most recent update in August 2013 requiring full implementation at the national level, and the change process is now fully harmonized across the EU.

The EMEA / EU has established regulatory standards for post-approval changes, known as variation notifications in Europe. These variations are classified into different types. Type 1A variations are minor and can be submitted annually without immediate reporting to the competent authority. Type IA IN changes, on the other hand, must be reported immediately. Type IB changes are moderate and require reporting to the competent authority. Type II variations are major and high-risk changes that require prior approval from the competent authority before implementation.[6]

1.2 Types of variation

- Type IA: These are minor changes that can be implemented immediately, but the competent authority must be informed of the change within 12 months of implementation. (Do and tell)

- Type IAIN: These changes are similar to Type IA but require immediate notification to the competent authority after implementation. (Do and tell)
- Type IB: These changes are moderate and require notification to the competent authority before implementation. The company must wait for 30 days after submission of the procedure before implementing the change. (Tell, wait and do)
- Type II: These changes are major and require prior approval from the competent authority before implementation. The review period is usually 60 days but can range from 30 to 90 days. (Tell and do)
- Extension applications: These are applications for additional strengths, pharmaceutical forms, or routes of administration and can take up to 210 days for review.[7]

VARIATION	TYPE	IMPLEMENTATION TIME
Admin	Type IA_{IN}	14 days before submission
	Type IA	Up to 1 year before submission
Minor	Type IB	Up to 3 months after submission
Major	Type II	Up to 6 months after submission

Table 1: Summary of variation in EU

1.2.1 Type IA variation[8]

1.2.1.1 Introduction

According to the rules, type IA changes are a change category that is explicitly identified in the Commission's guidance on classifying changes as type IA notices and meets all required conditions and data requirements.

Type IA changes are considered minor changes and can be implemented before notifying the competent authority. These changes only require a "do and tell" notification to the authority within 12 months of implementation. Grouping of changes is allowed for the purpose of submitting an annual report, which can reduce the administrative burden for the marketing authorization holder. However, if a Type IA change requires immediate

notification, it should be classified as Type IAIN and reported to the authority immediately after implementation.

Yes, that is correct. MAH may include Type IA variations in the submission of Type IAIN variations or other pending variations, rather than waiting to include them in the Annual Report. This is allowed as long as the Type IA variation meets the criteria for a Type IAIN variation, such as requiring immediate notification to the competent authority. It is important for the MAH to follow the guidelines for grouping changes and properly document all changes in the appropriate variation form.

1.2.1.2 Process

1. Start of notification process (0 day)

The MAH shall submit to RMS and CMS at the same time an application containing the elements presented as follows, according to the appropriate headings and numbering in EUCTD format.

- Cover letter.
- Application form, including the MR variation number, a description of the variation(s) submitted and the date(s) of implementation.
- A copy of the relevant published Article 5 Recommendation, if applicable.
- Supporting documentation as appropriate.

− The text states that mock-ups or specimens must be provided for variations that impact the SmPC and/or labeling or package leaflet. These mock-ups or specimens should be provided in accordance with the guidelines on Mock-ups, Specimens and Samples for variations and renewals issued by CMDh. Alternatively, they can be provided as discussed with the Reference Member State (RMS) on a case-by-case basis.

In addition, the RMS submission must include a list of shipping dates (all shipping dates to the CMS) and a declaration that the relevant domestic charges have been paid at the time of submission.

When a regulatory authority receives an application for a drug, they create an entry in their system called CTS. It is the responsibility of the CMS to check if they have received the application and the required fees. The RMS will confirm the acceptance of the application

after verifying the payment and notify all CMSs at the same time. The date of receipt of the application is considered as the start date of the notification process, and the RMS will update the CTS record accordingly. The CMS will only receive the notification through the CTS system, and no separate email will be sent.

2. Review Phase (0-30 day)

After receiving the application, the RMS will conduct a review of the report to ensure that all necessary supporting documentation has been included. The information provided by the MAH in the application form is valuable and should be reviewed to confirm that all required conditions have been met and all documents have been submitted. In cases where some documents are missing, the notification will be deemed unacceptable, and the MAH should cease implementation of any affected changes. Alternatively, the MAH may choose to submit a new change that will require a new change procedure number.

Both the RMS and CMS do not conduct a detailed evaluation of the support data. The RMS's responsibility is to conduct audits, which are broader than administrative audits, to determine the acceptance of notifications based on the submitted documents. The CMS should not provide any comment on the acceptance of content into the RMS or MAH. The CMS can only provide a comment if the document is not received or paid for. In the case of a Type IA notice related to product information, it is recognized that the changes have already been implemented before submission. It is the responsibility of the MAH to ensure that the updated text is correct, including any necessary translations. Therefore, updated product information, including translations, is not subject to individual assessment. For Type 1A variations, there are no requests for explanation, information, or documentation by the RMS to the MAH, and there are no specific time limits or delays in the process.

Notification process results The RMS decides whether to accept or reject the notification. The next action will be performed on the 30th day or earlier.

• When a Type 1A variation notice is deemed acceptable by the RMS, a "Confirm Acceptable Notice" letter will be sent to the MAH, and the CMS will also be notified of the result through an updated CTS record. This letter serves as confirmation that the changes have been accepted and can be implemented without further action needed from the MAH or CMS.

If the terms of approval are affected by the consequences of the change, the RMS will email the results to the CMS and explicitly point out by email that the respective terms are met and can be removed. If it is an approval, or a new condition for marketing approval, it must be included in the approval.

If changes have been made to the product information, the revised version will be marked with track changes and either emailed to the CMS at the end of the process or modified by the RMS. It is important to ensure that no further changes have been made since the submission.

• In case of unacceptable notice: RMS will notify MAH in writing that the change is unacceptable and provide simple justification and course of action. The CMS is notified of the updated CTS record. This should include the reason for disapproval.

For grouped changes, different results can occur for the various changes contained in the notification. Some changes may be accepted and others may be rejected.

Submission phase	The MAH submits the application and all necessary supporting documents to both the RMS and CMS. Additionally, the MAH must provide a list of dispatch dates to the RMS.
Day 0	The start of the procedure is initiated by the RMS who then updates the CTS record. The CMS will only be notified through the CTS system, and there will not be any additional email sent.
Until Day 30	The RMS is responsible for assessing the acceptability of the notification, including verifying that all required supporting documentation has been submitted. On the other hand, the CMS is only responsible for confirming the receipt of the notification and verifying that the appropriate fees have been paid..

Day 30	The RMS will communicate the results of the variation notification to the MAH, acting on behalf of the CMSs. The CMSs will be informed of the outcome through the updated CTS record. In some cases, the MAH will provide the RMS with highlighted and clean versions of the SmPC, labelling or package leaflet in electronic format during the notification process. The RMS will review the highlighted text and share these documents, along with a statement endorsing the changes, to the MAH and CMSs. Any changes made in the text, in comparison to the previously approved version of product information, should be marked with track-changes in the highlighted versions circulated at the end of the procedure or the RMS should confirm that the text is unchanged since submission. It is recommended to upload the clean documents to CTS for transfer to the MRI index. When changes to the marketing conditions are made as a result of a variation, the RMS will send an email to the CMSs to inform them of the outcome. The email will explicitly state that the affected condition has been fulfilled and can be removed from the marketing authorisation, or if a new condition has been added, it should be included in the marketing authorisation.
Within 6 months after acceptance	After a decision is made at the EU level, the national regulatory authorities of each member state should take the necessary steps to implement that decision within six months in their own country.

Table 2: Summary of TYPE IA

1.2.2 Type IB variation[8]

1.2.2.1 Introduction

Under the rule, changes that are not categorized under the rule's guidance, rather than extensions, are considered minor changes of type IB by default. In addition, any changes recommended as Type IB changes must be submitted as minor Type IB changes.

Type IB changes can be grouped with other changes in a single notification. If the highest priority change is a type IB change, it is classified as a type IB change. The

MAH can also submit multiple Type IB variations to multiple MAHs in a single application. This will be processed under the work sharing procedure unless the application relates only to a pure national authorization submitted to the same national jurisdiction. In this case, the procedure is classified as a Type IB bulk application (if the competent authority agrees). Such a one-time template).

1.2.2.2 Process

1. Validation of the application

The Marketing Authorization Holder (MAH) is required to submit an application containing the elements listed in Annex IV of the Variation Regulation to both the RMS and CMS simultaneously. The application should be presented in accordance with the appropriate headings and numbering of the EU-CTD format:

• Cover letter.

• The MAH needs to fill out an application form which should include the variation procedure number and the MRP variation number. Additionally, the form should provide a clear and detailed description of the variation(s) that are being submitted.

• If available, copy of the Art. 5 recommendation for the requested change.

• The MAH must provide supporting documentation as appropriate with the application. In the case of variations requested by a national competent authority, such as after the assessment of Follow-up Measures (FUMs), Specific Obligations (SOs), Periodic Safety Update Reports (PSURs), or class labelling, a copy of the request must be attached to the cover letter. The application form must include the variation procedure number and the MRP variation number, as well as a description of the variation(s) submitted.

• When variations affect the SmPC, labelling or package leaflet, mock-ups or specimens should be provided to the RMS and CMS along with the application. The mock-ups should be in line with the requirements specified in the CMDh “Mock-ups, Specimens and Samples for variations and renewals" guidance document. This includes providing both the English text and national translations of the mock-ups or specimens. The mock-ups or

specimens should be prepared according to Chapter 7 of the Notice to Applicants, or as discussed with the RMS on a case-by-case basis.

The MAH must provide a list of dispatch dates to the RMS as part of the submission. This list should include all dates of submission to the CMS, as well as a declaration that the relevant national charges have been paid at the time of submission. The RMS will use this information to track the progress of the submission and ensure that all necessary fees have been paid.

The RMS is responsible for creating a CTS record within 7 days of receiving the request.

If the change request is solely for a national administrative authority, it should also be submitted to the competent authority of the relevant Member State using the same document.

2. Start of notification process

After the validation period the RMS completes the CTS record as the means of informing the CMS of the start of the notification process and the timetable. The CMS are only informed via CTS, there will be no additional mail. The MAH is informed by the RMS about the start date (Day 0).

3. Evaluation process (0-30 day)

According to Rule (EC) No. 1234/2008, the time frame for validation and evaluation of requested changes is the responsibility of the RMS.

Within 30 days of starting the notification process, RMS will notify the sales authorization acquirer of the results of the process. In general, it is not intended to create an evaluation report to evaluate type IB changes. The only exception is the ASMF work sharing procedure.

If RMS does not submit a comment to MAH within 30 days, that is, H. Notifications are considered acceptable until the 30th day.

However, there are some specific variants that require input from the CMS for the RMS to make a decision. This situation can occur with changes in the following categories:

• Change in the name of the medicinal product (in a CMS);

• Change in pack size;

• All variations under heading C.I.z, C.I.1-C.I.3 and C.I.6.b-C.I.7;

In the case of the last bullet, if the classification policy is changed to the Caesarean section category, the RMS will position the requested change within 20 days of the start of the process. You need to notify the CMS. The CMS must submit a comment regarding the location of the RMS and update the CTS between the 20th and 27th days of the procedure.

If the product information is affected by the requested changes, the country translation can be checked and the CMS can comment by the 27th day. RMS will inform MAH and CMS of the reasons behind the refusal. Day 30 ("reason statement") CMS within 30 days. In addition, the sales authorization holder must send the RMS a list of shipping dates indicating the date the modified notification was sent to the CMS. After receiving the list of shipping dates, RMS restarts the process and notifies MAH accordingly. The RMS updates the CTS and notifies the CMS.

MHA have updated their national translations in accordance with the Reasonable Notice Change Requests so that if the product information is affected by the requested changes, they will be available for verification during this second 30 days. Please note that you must submit a correction notice.

Within 30 days of receiving the modified notification, RMS will use the Type IB Change Notification to notify MAH of the final approval / rejection of the change.

If MAH does not change the notification as requested within 30 days, the change will be rejected. The CMS will be notified accordingly by updating the CTS.

4. Outcome of the notification process

RMS decides whether to accept or reject the notification. The next action will be performed on the 30th day / new 30th day or earlier.

Approval: RMS will notify MAH with the date of approval that the variation application can be approved. The result is communicated to the CMS by the updated CTS record.

If the terms of approval are affected by the consequences of the change, the RMS will email the results to the CMS and explicitly point out by email that the respective terms are met

and can be removed. If it is an approval, or a new condition for marketing approval, it must be included in the approval.

If the product information is affected, at the end of the procedure, RMS will email the CMS a final approved text with all changes marked with track changes compared to the previously approved version of the product information.

Refusal: RMS informs the MAH and, if applicable, the CMS why the change request was rejected. RMS updates CTS. This should also include the reason for the refusal in the comment field on the result date.

Submission	The Marketing Authorization Holder (MAH) submits the variation request to both the Reference Member State (RMS) and Concerned Member States (CMS), along with a list of dispatch dates to the RMS. The RMS then creates a CTS record.
Day 0	After validating the variation submission from the MAH, the RMS initiates the procedure and records it in the CTS system. The RMS also sends an email to the MAH informing them of the start date of the procedure. On the other hand, the CMS is only notified of the procedure through the CTS system, and no further communication is sent via mail.
Until Day 20	The RMS is responsible for notifying the CMS of its position on changes to the product information, specifically those that fall under the C-section categories (i.e. changes to the quality, safety or efficacy of the product). This notification is typically made through the updated CTS record, which the CMS can access to stay informed of the status of the variation procedure.
Until Day 27	The RMS informs the CMS about their decision on changes to the product information according to the C-section categories. In turn, the CMS notifies the RMS of their comments for changes related to the product name, pack size, and C-section categories of the product information.

Day 30	If the RMS determines that a variation cannot be accepted, after considering the comments of the CMS, a "Notification with Grounds" is circulated to the MAH and CMS and the clock stops. However, if the variation can be accepted, the RMS notifies the MAH with an acceptance notification and updates the CMS via CTS, thus concluding the procedure. During the procedure, the MAH may provide highlighted and clean versions of the SmPC, labelling and/or package leaflet in electronic format. The RMS checks the highlighted (changed) text and circulates these documents, along with a statement endorsing the changes made, to the MAH and CMS. If the outcome of the variation affects marketing conditions, the RMS communicates the outcome via email to the CMS and specifies whether a condition should be deleted from or added to the marketing authorization.
Clock stop	The MAH has 30 days to submit a revised notification to both the RMS and CMS after receiving the 'Notification with Grounds.' The RMS should be provided with a list of dispatch dates while national translations should be updated in accordance with the requests for modification raised in the 'Notification with Grounds.'
New Day 0	After the MAH submits an amended notification within 30 days of receipt of the 'Notification with Grounds', the RMS will restart the clock, update the CTS record, and notify the MAH by email that the procedure has restarted. The CMS will only be informed via CTS, and no additional mail will be sent to them.
Until New Day 20	The RMS will inform the CMS of its position regarding any changes to the product information that fall under the C-section categories.
Until New Day 27	The CMS notifies the RMS of their comments if there are changes to the product information related to the C-section categories, product name, and pack size.
New Day 30	If the RMS accepts the variation after considering the comments from the CMS, an acceptance notification is sent to the MAH and the procedure is completed.

	The RMS may request highlighted and clean versions of the SmPC, labelling, and package leaflet in electronic format from the MAH. The RMS checks the highlighted text for changes and circulates the documents with a statement endorsing the changes to the MAH and CMS. The RMS recommends uploading the clean documents to CTS for transfer to the MRI index. If the outcome of the variation affects marketing conditions, the RMS will inform the CMS via email that the condition has been fulfilled or needs to be included in the MA. However, if the RMS cannot accept the variation even after considering the CMS comments, a rejection notification is circulated to the CMS and MAH, and the procedure ends.
Within 6 months after acceptance	After a decision has been made, the competent authorities in each member state should take the necessary steps to implement the decision within a period of six months.

Table 3: Summary of Type IB

1.2.3 Type II variation[8]

1.2.3.1 Introduction

The submission of Type II variations is required for any changes to a drug that could have a substantial impact on its quality, safety, or effectiveness.

Type II variations require prior approval from regulatory authorities before implementation. They can be combined with other types of variations in a single application, but if a Type II change is the highest priority, then the entire application is classified as a Type II change. Additionally, the MAH may submit multiple Type II variations to multiple authorities in a single application, which is managed through the division of procedure.

1.2.3.2 Process

1. **Submission phase**

MAH submits application to RMS and CMS

Application includes:

- Cover letter with procedure number, application form with details of MA(s) concerned, and relevant supporting documentation
- If applicable, include published Article 5 Recommendation or recommendation for classification received from CMDh
- For variations requested by national competent authority, include copy of request for FUMs, SOs, PSURs, or class labelling
- If variation affects SmPC, labelling, or package leaflet, provide mock-ups or specimens
- RMS includes list of dispatch dates and declaration of payment of national fees in submission

RMS creates CTS record to inform CMSs of new procedure

2. Start of variation procedure (day 0)

At the end of the validation period, the RMS completes the CTS entry and informs the CMS that the procedure has started. RMS will also notify MAH of the start date (day 0).

3. Evaluation

Typically, the process for planned variations takes around 60 days. In some cases, the regulatory authority responsible for the Reference Member State (RMS) role will coordinate with the Marketing Approval Holder (MAH) to prevent duplicate steps and ensure synchronization between parallel or sequential variation processes. The aim is to avoid overlap whenever possible. However, the 60-day and 90-day timelines are flexible and can be shortened in exceptional situations. In such cases, the MAH should promptly contact the RMS, which will propose a faster schedule (such as a 30-day procedure) to the CMS. If the CMS rejects the simplified procedure, the RMS should propose an acceptable schedule. For simple changes in indications, a 60-day period is usually sufficient, but for more complex changes or additions that require a comprehensive assessment under Article 7, or for grouping, the deadline can be extended to 90 days. This agreed timetable is included in the CTS.The RMS must ensure that the Preliminary Variable Assessment Report (PVAR) is sent to the marketing authorization holder and CMS by the agreed date. MAH needs to understand that PVAR is used for informational and transparent purposes only at this stage of the process. In exceptional cases of delay, all CMS and MAH need to be notified. If the change involves the introduction of a new DDPS in one or more CMS

(after the change of marketing authorization holder to the CMS if there is already an approved DDPS for the drug in question), the RMS will be PVAR. Preparation requires this CMS.

The RMS has a responsibility to provide clear feedback on whether they support or reject proposed changes in the PVAR. If changes are needed, the RMS may request additional information from the marketing authorization holder. If the application is considered a serious defect, it should be rejected without the need for further information. If the RMS does not accept the proposed changes to the product summary, labeling, or package insert, they may suggest an alternative solution. The language used in the SmPC, labeling, or package insert should be consistent with that of other similar products approved through MR or DC procedures or as determined by the Commission under Article 30 procedures. Changes to the SmPC should only focus on items directly related to the requested changes. Revisions to the product summary, labeling, or other parts of the package insert are only accepted with RMS approval and must be minor editorial changes. These changes will be clearly indicated in the PVAR by the RMS.

Once the RMS receives the PVAR, it is the responsibility of the CMS to provide their opinion on whether to accept or reject the proposed changes by the agreed-upon date. The CMS must send their comments to the RMS through the MRVE mailbox. If the CMS fails to send their comments within the specified time frame, the RMS will assume that the CMS supports the proposed changes. However, the CMS is not allowed to comment on matters that are not related to the submitted changes. If the CMS approves the direct approval or rejection proposal from the RMS, the procedure can be completed at the end of the first phase, without needing to extend the agreed-upon timeline.

If the CMS does not accept the proposed changes or RMS proposals, the CMS must justify its opinion and clearly indicate the additional information requested by the MAH.

In addition, the CMS may suggest changes to product characteristic summaries, labels, or package inserts. Minimize the number of these suggestions and the suggestions should be directly related to the item you are changing. Other sections of product characteristics, labels, or package insert summaries can only be modified with individual modification steps. The CMS should avoid providing a summary of product characteristics and / or

significant revisions to other product documentation, and should focus on providing comments on proposals submitted by the RMS and marketing authorization holders.

In case the MAH's proposed changes are not approved by the RMS or any CMS, the RMS will ask the MAH for additional information through a request for supplementary information (RSI) and send a copy of the request to the CMS. The RMS should give a clear deadline to the MAH for providing a response to the RSI within the agreed timeframe. If needed, the MAH can contact the RMS during the deadline extension for any clarifications required. The CMS must always be informed of the reason for the extension and the new deadline.

In case the MAH fails to respond within a reasonable timeframe, it is recommended to withdraw the proposed variation. The MAH may submit new variations when new data is available. Upon receiving the supplementary information, the RMS will prepare a Final Change Assessment Report (FVAR) and revised SmPC, labelling, or package insert. The RMS will share this report with all CMSs for comments and with the MAH for information. The RMS must prepare the FVAR and restart the clock within the agreed time frame.

If there is a disagreement between the RMS and the CMS, a breakout session can be organized using tools such as Vitero.

4. Outcomes

When a variation is accepted, the RMS will notify the Marketing Authorization Holder (MAH) and all relevant CMSs that the variation has been accepted, along with the date of acceptance. This notification will be sent via email.

Once the MAH proposes a change that affects the SmPC/PL/labeling, they must provide the RMS with both a clean and highlighted version of the electronic format of the text. It is then the RMS's responsibility to review the highlighted (modified) text. Once RMS approves the changes, it will distribute the documents along with a statement of approval.

If any of the terms of the marketing authorization are affected by the consequences of the change, RMS will specifically indicate in an email that the relevant terms are currently being met and may be disqualified. , If it is a new condition for sales approval, it must be included in the approval.

If applicable, MAH must submit a national translation within 7 days of completing the procedure.

These translations can be performed within 30 days of submission, unless comments have been received from the relevant competent authority.

The competent authority must make a decision at the national level within two months of completing the procedure.

Rejection: If the proposed change is rejected by both the RMS and the CMS, the MAH will be informed of the rejection via email along with an explanation for the decision. The RMS will also update the CTS records to reflect the rejection and include the reason for the refusal.

Disagreement: To clarify, the process for escalation to CMDh for a potentially serious public health risk (PSRPH) is as follows:

If a CMS determines that a variation may pose a PSRPH, it should immediately inform the RMS and other CMSs. If the RMS and all CMSs agree that the variation poses a PSRPH, the RMS will escalate the issue to CMDh, along with a formal transfer request from the CMS that identified the risk. The transfer request must include a detailed explanation of the issue, including the nature and extent of the potential risk to public health, and any relevant data or information. The RMS must forward the transfer request to CMDh within two days of receiving it. CMDh will then review the transfer request and may request additional information from the MAH or RMS. If CMDh determines that the variation poses a PSRPH, it may take a range of actions, including suspending or revoking the MAH's marketing authorization, issuing a safety warning, or requiring additional measures to manage the risk. It is important to note that if the MAH believes that the PSRPH issue can be resolved, it may choose to withdraw the application for the variation from all CMSs and RMS, not just those who disagree. This can help avoid the need for arbitration and may allow the MAH to resubmit the variation at a later time.

Recommended reduced (30-day) procedure for type II variations

Day 0	At the beginning of the procedure, the RMS informs the CMSs of the timeline through the CTS system and sends an email to the MAH.
Day 15	The PVAR is distributed by the RMS to both the CMSs and the MAH.
Day 20	The CMS's send any comments they may have on the PVAR to the RMS.
Day 21	The RMS sends a request for supplementary information (RSI) to both the MAH and the CMSs, and the clock stops.
Clock off period	The duration of the RSI process should not exceed a total of 20 days, consisting of 10 days for the MAH to provide the required information and another 10 days for the RMS to prepare the Final Change Assessment Report (FVAR).
Day 22	Yes, that is correct. After receiving the supplementary information from the MAH, the RMS prepares the Final Change Assessment Report (FVAR) and circulates it to the CMSs and the MAH for their review and comment.
Day 25	After the RMS circulates the FVAR, the CMS's have the opportunity to review and provide comments on it to the RMS.
Day 30	At the end of the variation procedure, the RMS informs all parties involved and shares the final endorsed version of the SmPC/PL/labelling, both in highlighted and clean formats, if applicable. If the variation affects any conditions related to the marketing authorization, the RMS explicitly

	mentions in the email that those conditions have been fulfilled or new ones need to be included in the MA. An example text for this is provided in Annex I.
60-day procedure for type II variations	
Day 0	At the beginning of the variation procedure, the RMS informs the CMSs about the timeline via the Common Timetable Service (CTS) and sends an email to the MAH to notify them about the start of the procedure.
Day 40	This means that the RMS shares the proposed variation (PVAR) with both the CMSs and the MAH for their review and feedback.
Day 55	After the RMS circulates the PVAR to the CMSs and MAH, the CMSs have the opportunity to review and provide any possible comments on the proposed variation to the RMS.
Day 59	The RMS sends the request for supplementary information (RSI) to both the MAH and the CMSs, and the clock stops at this point. The MAH has a certain amount of time to respond to the RSI, and the clock restarts once the RMS receives the response from the MAH.
Clock off period	The correct time frame for responding to a request for supplementary information is usually 60 + 60 days (60 days for the MAH to provide the responses and 60 days for the RMS to prepare the FVAR), unless otherwise agreed upon by the parties involved.

Day 60	The RMS distributes the FVAR document to both the CMS's and the MAH.
Day 75	The possible break-out meeting
Day 80	The CMS's have the opportunity to provide comments on the FVAR, which is circulated by the RMS to both the CMS's and the MAH.
Day 90	At the end of the procedure, the RMS will inform all parties involved about the completion of the variation process. If there are any changes to the SmPC/PL/labelling as a result of the variation, the RMS will provide both highlighted and clean versions of the final text to the CMS's and the MAH. If any conditions of the marketing authorization are affected, the RMS will indicate in the email that the relevant condition(s) have been fulfilled and can be removed or if new conditions have been added, they need to be included in the marketing authorization.
90-day procedure for type II variations	
Day 0	At the beginning of the procedure, the RMS will inform the CMS's of the timeline through the CTS and notify the MAH of the same via email.
Day 70	RMS distributes the PVAR to both the CMS's and the MAH.
Day 85	After receiving the PVAR, the CMS's review it and send any potential comments to the RMS for further consideration.
Day 89	When the RMS requires additional information related to a variation, it will send a request for

	supplementary information to both the MAH and CMS's involved in the procedure. The clock is stopped during this time, which means that the timeframe for completing the procedure is put on hold until the requested information is received.
Clock off period	This means that the duration of time between when the RMS sends a request for supplementary information to the MAH and the CMS's, and when the RMS prepares the FVAR should not exceed 90+60 days. Specifically, the MAH has 90 days to provide the responses, and the RMS has 60 days to prepare the FVAR.
Day 90	The "Re-start of the procedure" refers to the situation where the variation procedure needs to be restarted after the RMS requested supplementary information from the MAH and the CMSs. Once the requested information has been provided, the procedure resumes with the RMS circulating the FVAR (final variation assessment report) to the CMSs and the MAH.
Day 105	The possible break-out meeting
Day 110	After the RMS has circulated the FVAR to the CMSs and the MAH, the CMSs can send their possible comments on the FVAR to the RMS.
Day 120	At the end of the procedure, the RMS informs the completion of the procedure and provides the final SmPC/PL/labelling in both highlighted and clean versions to the CMSs and the MAH, if applicable. If the outcome of the variation affects any condition(s) to the marketing authorization, the

	RMS will clearly state in the email that the respective condition(s) can now be deleted from the MA or needs to be added to the MA as a new condition.

Table 4: Summary of Type II

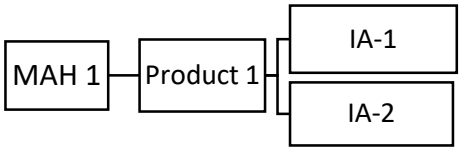
1.2.4 Grouping

1.2.4.1 Introduction

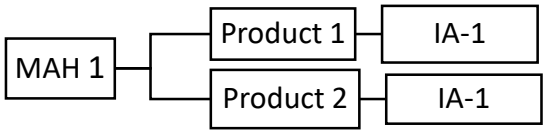
Article 7 of the Commission Regulations (EU) No. 1234/2008 specifies the requirements for submitting variations to the marketing authorization of a medicinal product. According to this regulation, if any amendments are required, a separate application must be submitted for each variation that requires an application. This means that if multiple variations are needed, each variation should be submitted as a separate application.[16]

1.2.4.2 Types of grouping

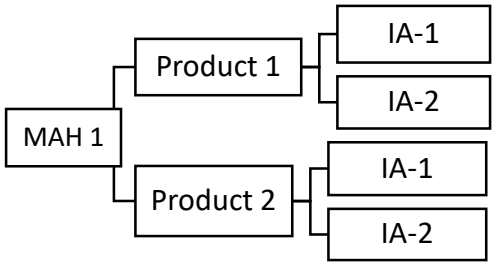
Situations where there are several Type IA or Type IAIN variations related to a single medicinal product.



Situation where a single Type IA or IAIN variation impacts multiple medicinal products that belong to the same MAH



Multiple Type IA and/or IAIN variations can be applied to multiple medicinal products belonging to the same MAH, as long as the variations are identical for all the products and are submitted to the same relevant authority.[17]



1.2.4.3 Acceptable grouping of variation

There is no obligation to group Type IA / IAIN changes for medicinal products.

However, if a group submission is made, the MAH must adhere to the statutory deadline for each variation. Type IAINs should be submitted immediately regardless of whether they are grouped with other variations, and Type IA variations should be submitted within 12 months of implementation. If merging one or more Type IA / IAIN variations that impact multiple centrally approved drugs from the same MAH, the variation or group of variations must be the same for all related drugs.

Grouping of other types of variations is only permissible when falling under one of the cases outlined in section 2.2.4.4, or when agreed upon by the Agency and the MAH before submission if it does not fit within the aforementioned cases.[17]

1.2.4.4 Cases for grouping variations[15]

There are specific cases where grouping of variations is allowed. These cases include:

- One of the variations in the group is an extension of the marketing authorisation, such as a new strength or pharmaceutical form, combined with a Type II variation for a new therapeutic indication related to already authorised strengths or forms.
- One of the variations in the group is a major Type II variation, and all other variations in the group are consequential to this major variation.
- One of the variations in the group is a minor Type IB variation, and all other variations in the group are consequential to this minor variation.
- All variations in the group are administrative changes to the summary of product characteristics, labelling, and package leaflet or insert.

- All variations in the group are changes to an Active Substance Master File, Vaccine Antigen Master File, or Plasma Master File.
- All variations in the group are intended to improve the manufacturing process, quality of the medicinal product or its active substance(s).
- All variations in the group are changes affecting the quality of a human pandemic influenza vaccine.
- All variations in the group are changes to the pharmacovigilance system referred to in Article 8(3)(ia) and (n) of Directive 2001/83/EC or Article 12(3)(k) and (o) of Directive 2001/82/EC.
- All variations in the group are consequential to a given urgent safety restriction and submitted in accordance with Article 22.
- All variations in the group relate to the implementation of a given class labelling.
- All variations in the group are consequential to the assessment of a given periodic safety update report.
- All variations in the group are consequential to a given post-authorisation study conducted under the supervision of the holder.
- All variations in the group are consequential to a specific obligation carried out pursuant to Article 14(7) of Regulation (EC) No 726/2004.
- All variations in the group are consequential to a specific procedure or condition carried out pursuant to Articles 14(8) or 39(7) of Regulation (EC) No 726/2004, Article 22 of Directive 2001/83/EC or Article 26(3) of Directive 2001/82/EC.

1.2.4.5 Timelines[17]

When grouping different types of variations, the statutory deadline for submission and the review timetable will be determined by the highest variation type in the group.

For example, if a group consists of a Type II variation and three Type IB variations, the group will follow the review timetable of the Type II variation. Similarly, if a group consists of an extension and a Type II variation, the group will follow the review timetable of the extension. This ensures that the review process is efficient and timely.

When a group of Type IA/IAIN variations is submitted, the agency will issue a notification indicating which variations have been approved and which have been rejected. If a variation

has been rejected, the MAH must discontinue the associated variation without delay. This means that the MAH must take the necessary steps to ensure that the rejected variation is no longer implemented and must update the relevant documentation accordingly. It is important for the MAH to act promptly in discontinuing the rejected variation to ensure compliance with regulatory requirements and patient safety.

Once the review of the grouped changes is completed, the regulatory agency issues an opinion or notification that reflects the final outcome of the process and lists all the changes that are considered acceptable. This notification also includes any changes that were not accepted, unless they were removed from the group by the MAH during the review process. The MAH should take immediate action to implement the approved variations and discontinue any rejected variations without delay.

As an example,

if there is an extension and a type II variation grouped together, the evaluation process will follow the extension evaluation procedure. If the extension receives a negative assessment outcome, such as quality issues, but the type II variation is positive, the MAH can choose to withdraw the extension from the group. In this case, the CHMP will only adopt a positive opinion on the type II variation.

1.2.4.6 Examples[17]

There are several ways in which variations can be grouped, including:

- Grouping of variations that relate to either the active substance or the finished product (but not both). For example, a type IB variation to extend the re-test period of the active substance may be grouped with a type IB variation to change the storage conditions of the active substance.
- Grouping of variations that relate to both the active substance and the finished product. For example, a type IB variation to change a test procedure of the active substance may be linked with a type IA variation to delete a nonsignificant in-process control of the finished product.
- Grouping of quality and administrative variations. For example, a type IB variation to extend the shelf life of the finished product may be grouped with a type IAIN variation to

change the name of a manufacturer responsible for batch release and a type IA variation to change the ATC code.

- Grouping of several non-clinical studies.

- Grouping of several drug-drug interaction studies. For example, a type II variation for an interaction study with Rifampicin may be grouped with a type II variation for an interaction study with an oral contraceptive.
- Grouping of several safety changes with similar implementation timelines.

1.2.5 Examples[7]

1.2.5.1 Administrative changes

1.Change in the (invented) name of the medicinal product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) for Centrally Authorised products	1	1,2	IAIN
b) for Nationally Authorised Products		2	IB
Conditions 1. The check by the EMA on the acceptability of the new name has been finalised and was positive.			
Documentation 1. Copy of the EMA letter of acceptance of the new (invented) name. 2. Revised product information.			
2.Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) The activities for which the manufacturer/importer is	1	1,2	IAIN

responsible include batch release			
b) The activities for which the manufacturer/importer is responsible do not include batch release	1	1,2	IA
Conditions 1. The manufacturing site undergoing the name and/or address change and all manufacturing operations must remain the same.			
Documentation 1. Copy of the modified manufacturing authorisation, if available; or a formal document from a relevant official body (e.g. Chamber of Commerce, or if not available, from a Regulatory Agency) in which the new name and/or address is mentioned. 2. If applicable, amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including revised product information as appropriate.			

1.2.5.2 Quality changes

ACTIVE SUBSTANCE

- Manufacture

Change in the manufacturer of a starting material/ reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	1,2,3	1,2,3,4,5,6,7	IAIN
b) Introduction of a manufacturer of the active substance supported by an ASMF			II

c) The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions, which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability			II
d) New manufacturer of material for which an assessment is required of viral safety and/or TSE risk			II
e) The change relates to a biological active substance or a starting material/reagent/intermediate used in the manufacture of a biological/immunological product			II
f) Changes to quality control testing arrangements for the active substance-replacement or addition of a site where batch control/testing takes place	2,4	1,5	IA
g) Introduction of a new manufacturer of the active substance that is not supported by an ASMF and requires significant update to the relevant active substance section of the dossier			II
h) Addition of an alternative sterilisation site for the active substance using a Ph.Eur. method		1,2,4,5,8	IB
i) Introduction of a new site of micronisation	2,5	1,4,5,6	IA
j) Changes to quality control testing arrangements for a biological active substance: replacement or addition of a site where batch control/testing including a biological/immunological/immunochemical method takes place			II
k) New storage site of Master Cell Bank and/or Working Cell Banks		1,5	IB
Conditions			

1. For starting materials and reagents the specifications (including in process controls, methods of analysis of all materials), are identical to those already approved. For intermediates and active substances the specifications (including in process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed route of synthesis are identical to those already approved. 2. The active substance is not a biological/immunological substance or sterile. 3. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with the current Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products. 4. Method transfer from the old to the new site has been successfully completed. 5. The particle size specification of the active substance and the corresponding analytical method remain the same.
Documentation 1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), if applicable. 2. A declaration from the marketing authorisation holder or the ASMF holder, where applicable, that the synthetic route (or in case of herbal medicinal products, where appropriate the method of preparation, geographical source, production of herbal drug and manufacturing route) quality control procedures and specifications of the active substance and of the starting material/reagent/intermediate in the manufacturing process of the active substance (if applicable) are the same as those already approved. 3. Either a TSE Ph. Eur. Certificate of Suitability for any new source of material or, where applicable, documentary evidence that the specific source of the TSE risk material has previously been assessed by the competent authority and shown to comply with the current Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products. The information should include the following: Name of manufacturer, species and tissues from which the

material is a derivative, country of origin of the source animals, its use and previous acceptance. For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant).

4. Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the active substance from the current and proposed manufacturers/sites.

5. The variation application form should clearly outline the 'present' and 'proposed' manufacturers as listed in section 2.5 of the application form for marketing authorisation.

6. A declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application where the active substance is used as a starting material and a declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application as responsible for batch release. These declarations should state that the active substance manufacturer(s) referred to in the application operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances — see the note under variation No B.II.b.1.

7. Where relevant, a commitment of the manufacturer of the active substance to inform the MA holder of any changes to the manufacturing process, specifications and test procedures of the active substance.

8. Proof that the proposed site is appropriately authorised for the pharmaceutical form or product or manufacturing operation concerned, i.e.: For a manufacturing site within the EU/EEA: a copy of the current manufacturing authorisation. A reference to the EudraGMP database will suffice. For a manufacturing site outside the EU/EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a GMP certificate issued within the last 3 years by the relevant competent authority. For a manufacturing site outside the EU/EEA where no such mutual recognition agreement exists: a GMP certificate issued within the last 3 years by an inspection service of one of the Member States of the EU/EEA. A reference to the EudraGMP database will suffice.

- Control of active substance

Change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Tightening of specification limits for medicinal products subject to Official Control Authority Batch Release	1,2,3,4	1,2	IAIN
b) Tightening of specification limits	1,2,3,4	1,2	IA
c) Addition of a new specification parameter to the specification with its corresponding test method	1,2,5,6,7	1,2,3,4,5,7	IA
d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	1,2,8	1,2,6	IA
e) Deletion of a specification parameter which may have a significant effect on the overall quality of the active substance and/or the finished product			II
f) Change outside the approved specifications limits range for the active substance			II
g) Widening of the approved specifications limits for starting materials/intermediates, which may have a significant effect on the overall quality of the active substance and/or the finished product			II
h) Addition or replacement (excluding biological or immunological substance) of a specification parameter with its		1,2,3,4,5,7	IB

corresponding test method as a result of a safety or quality issue			
i) Where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State for the active substance, a change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country		1,2,3,4,5,7	IB

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).

2. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.

3. Any change should be within the range of currently approved limits.

4. The test procedure remains the same, or changes in the test procedure are minor.

5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

6. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeia microbiological methods).

7. For any material, the change does not concern a genotoxic impurity. If it involves the final active substance, other than for residual solvents which must be in line with ICH/VICH limits, any new impurity control should be in line with the Ph. Eur. or National Pharmacopoeia of a Member State.

8. The specification parameter does not concern a critical parameter, for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the

manufacture of the active substance), any critical physical characteristics, e.g. particle size, bulk or tapped density, identity test, water, any request for skip testing.
Documentation 1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate). 2. Comparative table of current and proposed specifications. 3. Details of any new analytical method and validation data, where relevant. 4. Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the relevant substance for all specification parameters. 5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the active substance complying with the current and proposed specification. For herbal medicinal products, comparative disintegration data may be acceptable. 6. Justification/risk assessment from the marketing authorisation holder or the ASMF Holder, as appropriate, that the in-process parameter is non-significant, or that the in-process parameter is obsolete. 7. Justification from the MAH or ASMF Holder as appropriate of the new specification parameter and the limits.

- Container closure system

Change in immediate packaging of the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Qualitative and/or quantitative composition	1,2,3	1,2,3,4,6	IA
b) Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological active substances			II

c) Liquid active substances (non-sterile)		1,2,3,5,6	IB

Conditions

The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.
Relevant stability studies have been started under ICH/VICH conditions and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least 3 months satisfactory stability data are at the disposal of the applicant at time of implementation. However, if the proposed packaging is more resistant than the existing packaging, the 3 months' stability data do not yet have to be available. These studies must be finalised and the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the shelf-life/retest period (with proposed action).
Sterile, liquid and biological/immunological active substances are excluded.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

2. Appropriate data on the new packaging (e.g. comparative data on permeability, e.g. for O_2, CO_2 moisture), including a confirmation that the material complies with relevant pharmacopoeial requirements or legislation of the Union on plastic materials and objects in contact with foodstuffs.

3. Where appropriate, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack), including confirmation that the material complies with relevant pharmacopoeia requirements or legislation of the Union on plastic material and objects in contact with foodstuffs.

4. A declaration from the marketing authorisation holder or the ASMF holder as appropriate that the required stability studies have been started under ICH/VICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided

immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). 5. The results of stability studies that have been carried out under ICH/VICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved retest period (with proposed action). 6. Comparison of the current and proposed immediate packaging specifications, if applicable.

- Stability

Change in the retest period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Retest period/storage period			
1. Reduction	1	1,2,3	IA
2. Extension of the retest period based on extrapolation of stability data not in accordance with ICH/VICH guidelines (*)			II
3. Extension of storage period of a biological/immunological active substance not in accordance with an approved stability protocol			II
4. Extension or introduction of a retest		1,2,3	IB

period/ storage period supported by real time data			
b) Storage conditions			
1. Change to more restrictive storage conditions of the active substance	1	1,2,3	IA
2. Change in storage conditions of biological/immunological active substances, when the stability studies have not been performed in accordance with a currently approved stability protocol			II
3. Change in storage conditions of the active substance		1,2,3	IB
c) Change to an approved stability protocol	1,2	1,4	IB

Conditions

1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.

2. The changes do not concern a widening of the acceptance criteria in the parameters tested, a removal of stability indicating parameters or a reduction in the frequency of testing.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate). This must contain results of appropriate real time stability studies, conducted in accordance with the relevant stability guidelines on at least two (three for biological medicinal products) pilot or production scale batches of the active substance in the authorised packaging material and covering the duration of the requested retest period or requested storage conditions.

2. Confirmation that stability studies have been done to the currently approved protocol. The studies must show that the agreed relevant specifications are still met. 3. Copy of approved specifications of the active substance. 4. Justification for the proposed changes.

- Design Space and post-approval change management protocols

Changes to an approved change management protocol	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Major changes to an approved change management protocol			II
b) Minor changes to an approved change management protocol that do not change the strategy defined in the protocol		1	IB
Documentation 1. Declaration that any change should be within the range of currently approved limits. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.			

FINISHED PRODUCT

- Description and composition

Changes in the composition (excipients) of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Changes in components of the flavouring or colouring system			

1. Addition, deletion or replacement	1,2,3,4,5,6,7,9,11	1,2,4,5,6	IAIN
2. Increase or reduction	1,2,3,4,11	1,2,4	IA
3. Biological veterinary medicinal products for oral use for which the colouring or flavouring agent is important for the uptake by target animal species			II
b) Other excipients			
1. Any minor adjustment of the quantitative composition of the finished product with respect to excipients	1,2,4,8,9,10	1,2,7	IA
2. Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the medicinal product			II
3. Change that relates to a biological/immunological product			II
4. Any new excipient that includes the use of materials of human or animal origin for which assessment is required of viral safety data or TSE risk			II
5. Change that is supported by a bioequivalence study			II
6. Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level		1,3,4,5,6,7,8,9,10	IB

Conditions

1. No change in functional characteristics of the pharmaceutical form, e.g. disintegration time, dissolution profile.

2. Any minor adjustment to the formulation to maintain the total weight should be made by an excipient which currently makes up a major part of the finished product formulation.

3. The finished product specification has only been updated in respect of appearance/odour/taste and if relevant, deletion of an identification test.

4. Stability studies have been started under ICH/VICH conditions (with indication of batch numbers) and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least 3 months satisfactory stability data are at the disposal of the applicant (at time of implementation for Type IAs and at time of notification for Type IBs) and that the stability profile is similar to the currently registered situation. Assurance is given that these studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action). In addition, where relevant, photo-stability testing should be performed.

5. Any new proposed components must comply with the relevant Directives (e.g. Directive 94/36/EC of the European Parliament and of the Council (1) and Commission Directive 2008/128/EC (2) for colours for use in foodstuffs and Council Directive 88/388/EEC (3) for flavours).

6. Any new component does not include the use of materials of human or animal origin for which assessment is required of viral safety data or compliance with the current Note For Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.

7. Where applicable, the change does not affect the differentiation between strengths and does not have a negative impact on taste acceptability for paediatric formulations.

8. The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one (no significant differences regarding comparability, see the relevant (Human or Veterinary) guidance on Bioavailability). For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one.

9. The change is not the result of stability issues and/or should not result in potential safety concerns, i.e. differentiation between strengths.

10. The product concerned is not a biological/immunological medicinal product.

11. For veterinary medicinal products for oral use, the change does not affect the uptake by target animal species.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including identification method for any new colorant, where relevant, and including revised product information as appropriate.

2. A declaration that the required stability studies have been started under ICH/VICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

3. The results of stability studies that have been carried out under ICH/VICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

4. Sample of the new product, where applicable (see Notice to Applicants Requirements for samples in the Member States).

5. Either a Ph. Eur. Certificate of Suitability for any new component of animal susceptible to TSE risk or where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by the competent authority and shown to comply with the scope of the current Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathies via Human and Veterinary Medicinal Products. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use. For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant).

6. Data to demonstrate that the new excipient does not interfere with the finished product specification test methods, if appropriate. 7 Justification for the change/choice of excipients etc. must be given by appropriate development pharmaceutics (including stability aspects and antimicrobial preservation where appropriate). 8. For solid dosage forms, comparative dissolution profile data of at least two pilot scale batches of the finished product in the new and old composition. For herbal medicinal products, comparative disintegration data may be acceptable. 9. Justification for not submitting a new bioequivalence study according to the current Note for Guidance on The Investigation of Bioavailability and Bioequivalence. 10. For veterinary medicines intended for use in food producing animal species, proof that the excipient is classified according to Article 14(2) (c) of Regulation (EC) No 470/2009 or, if not, justification that the excipient does not have pharmacological activity at the dose at which it is administered to the target animal.

- Manufacture

Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Secondary packaging site	1,2	1,3,8	IAIN
b) Primary packaging site			IAIN
c) Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products, or for pharmaceutical forms manufactured by complex manufacturing processes			II

d) Site which requires an initial or product specific inspection			II
e) Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products		1,2,3,4,5,6,7,8,9	IB
f) Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/immunological medicinal products		1,2,3,4,5,6,7,8	IB

Conditions

1. Satisfactory inspection in the last 3 years by an inspection service of one of the Member States of the EU/EEA or of a country where an operational Good Manufacturing Practice (GMP) mutual recognition agreement (MRA) exists between the country concerned and the EU.

2. Site appropriately authorised (to manufacture the pharmaceutical form or product concerned).

3. Product concerned is not a sterile product.

4. Where relevant, for instance for suspensions and emulsions, validation scheme is available or validation of the manufacture at the new site has been successfully carried out according to the current protocol with at least three production scale batches.

5. Product concerned is not a biological/immunological medicinal product.

Documentation

1. Proof that the proposed site is appropriately authorised for the pharmaceutical form or product concerned, i.e.: For a manufacturing site within the EU/EEA: a copy of the current manufacturing authorisation. A reference to the EudraGMP database will suffice; For a manufacturing site outside the EU/EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a GMP certificate issued within the last 3 years by the relevant competent authority; For a manufacturing site outside the EU/EEA where no such mutual recognition agreement exists: a GMP certificate issued within the last 3 years by an inspection service of one of the Member States of the EU/EEA. A reference to the EudraGMP database will suffice.

2. Where relevant, the batch numbers, corresponding batch size and the manufacturing date of batches (≥ 3) used in the validation study should be indicated and the validation data presented, or validation protocol (scheme) to be submitted.

3. The variation application form should clearly outline the 'present' and 'proposed' finished product manufacturers as listed in section 2.5 of the application form.

4. Copy of approved release and end-of-shelf life specifications if relevant.

5. Batch analysis data on one production batch and two pilot-scale batches simulating the production process (or two production batches) and comparative data on the last three batches from the previous site; batch data on the next two production batches should be available on request or reported if outside specifications (with proposed action).

6. For semisolid and liquid formulations in which the active substance is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology or any other appropriate imaging technique.

7. i) If the new manufacturing site uses the active substance as a starting material — A declaration by the Qualified Person (QP) at the site responsible for batch release that the active substance is manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the Union. ii) In addition, if the new manufacturing site is located within the EU/EEA and uses the active substance as a starting material — A declaration by the Qualified Person (QP) of the new

manufacturing site that the active substance used is manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the Union.

8. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

9. If the manufacturing site and the primary packaging site are different, conditions of transport and bulk storage should be specified and validated.

- Control of excipients

Change in the specification parameters and/or limits of an excipient	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Tightening of specification limits	1,2,3,4	1,2	IA
b) Addition of a new specification parameter to the specification with its corresponding test method	1,2,5,6,7	1,2,3,4,6,8	IA
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	1,2,8	1,2,7	IA
d) Change outside the approved specifications limits range			II
e) Deletion of a specification parameter which may have a significant effect on			II

the overall quality of the finished product			
f) Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method, as a result of a safety or quality issue		1,2,3,4,5,6,8	IB
g) Where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State for the excipient, a change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country		1,2,3,4,5,6,8	IB

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).

2. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.

3. Any change should be within the range of currently approved limits.

4. The test procedure remains the same, or changes in the test procedure are minor.

5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

6. The test method is not a biological/immunological/immunochemical method, or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods)

7. The change does not concern a genotoxic impurity. 8. The specification parameter does not concern the control of a critical parameter, e.g.: impurities (unless a particular solvent is definitely not used in the manufacture of the excipient) any critical physical characteristics (particle size, bulk, tapped density, etc.) identity test (unless there is a suitable alternative control already present) microbiological control (unless not required for the particular dosage form)
Documentation 1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate). 2. Comparative table of current and proposed specifications. 3. Details of any new analytical method and validation data, where relevant. 4. Batch analysis data on two production batches (3 production batches for biological excipients) of the excipient for all specification parameters. 5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the excipient complying with the current and proposed specification. For herbal medicinal products comparative disintegration data may be acceptable. 6. Justification for not submitting a new bioequivalence study according to the relevant (Human, Veterinary) Guideline on Bioavailability, if appropriate. 7. Justification/risk assessment showing that the parameter is non-significant or that it is obsolete. 8. Justification of the new specification parameter and the limits.

- Control of finished product

Change in the specification parameters and/or limits of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**

a) Tightening of specification limits	1,2,3,4	1,2	IA
b) Tightening of specification limits for medicinal products subject to Official Control Authority Batch Release	1,2,3,4	1,2	IAIN
c) Addition of a new specification parameter to the specification with its corresponding test method	1,2,5,6,7	1,2,3,4,5,7	IA
d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter such as odour and taste or identification test for a colouring or flavouring material)	1,2,9	1,2,6	IA
e) Change outside the approved specifications limits range			II
f) Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product			II
g) Addition or replacement (excluding biological or immunological product) of a specification		1,2,3,4,5,7	IB

parameter with its corresponding test method as a result of a safety or quality issue			
h) Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur for the finished product	1,2,3,4,5,7,8	1,8	IAIN
i) Ph. Eur. 2.9.40 Uniformity of dosage units is introduced to replace the currently registered method, either Ph. Eur. 2.9.5 (Uniformity of mass) or Ph. Eur. 2.9.6 (Uniformity of content)	1,2,10	1,2,4	IA

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure), unless the supporting documentation has been already assessed and approved within another procedure.

2. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.

3. Any change should be within the range of currently approved limits.

4. The test procedure remains the same, or changes in the test procedure are minor.

5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

6. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance.

7. The change does not concern any impurities (including genotoxic) or dissolution.

8. The change concerns the updating of the microbial control limits to be in line with the current Pharmacopoeia, and the currently registered microbial control limits (present situation) are in line with the pre January 2008 (non-harmonised) situation and does not include any additional specified controls over the Pharmacopoeia requirements for the particular dosage form and the proposed controls are in line with the harmonised monograph.

9. The specification parameter or proposal for the specific dosage form does not concern a critical parameter for example: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the finished product) any critical physical characteristics (hardness or friability for uncoated tablets, dimensions, etc.) a test that is required for the particular dosage form in accordance with the general notices of the Ph. Eur.; any request for skip testing.

10. The proposed control is fully in line with the Table 2.9.40.-1 of Ph. Eur. 2.9.40 monograph, and does not include the alternative proposal for testing uniformity of dosage units by Mass Variation instead of Content Uniformity when the latter is specified in Table 2.9.40.-1.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

2. Comparative table of current and proposed specifications.

3. Details of any new analytical method and validation data, where relevant.

4. Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the finished product for all specification parameters

5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch complying with the current and proposed specification. For herbal medicinal products, comparative disintegration data may be acceptable.

6 Justification/risk assessment showing that the parameter is non-significant or that it is obsolete. 7. Justification of the new specification parameter and the limits

- Container closure system

Change in immediate packaging of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Qualitative and quantitative composition			
1. Solid pharmaceutical forms	1,2,3	1,2,3,4,6	IA
2. Semi-solid and non-sterile liquid pharmaceutical forms		1,2,3,5,6	IB
3. Sterile medicinal products and biological/immunological medicinal products.			II
4. The change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life.			II
b) Change in type of container or addition of a new container			
1. Solid, semi-solid and non-sterile liquid pharmaceutical forms		1,2,3,5,6	IIB
2. Sterile medicinal products and biological/immunological medicinal products			II
3. Deletion of an immediate packaging container that does not	4	1,8	IA

lead to the complete deletion of a strength or pharmaceutical form			

Conditions

1. The change only concerns the same packaging/container type (e.g. blister to blister).

2. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.

3. Relevant stability studies have been started under ICH/VICH conditions and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least 3 months satisfactory stability data are at the disposal of the applicant at time of implementation. However, if the proposed packaging is more resistant than the existing packaging, e.g. thicker blister packaging, the 3 months' stability data do not yet have to be available. These studies must be finalised and the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

4. The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including revised product information as appropriate.

2. Appropriate data on the new packaging (comparative data on permeability, e.g. for O_2, CO_2 moisture).

3. Where appropriate, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack), including confirmation that the material complies with relevant pharmacopoeial requirements or legislation of the Union on plastic material and objects in contact with foodstuffs.

4. A declaration that the required stability studies have been started under ICH/VICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

5. The results of stability studies that have been carried out under ICH/VICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

6. Comparative table of the current and proposed immediate packaging specifications, if applicable.

7. Samples of the new container/closure where applicable (see NTA, Requirements for samples in the Member States/EMA).

8. Declaration that the remaining pack-size(s) is/are consistent with the dosage regimen and duration of treatment and adequate for the dosing instructions as approved in the summary of product characteristics.

- Stability

Change in the shelf-life or storage conditions of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Reduction of the shelf life of the finished product			
1. As packaged for sale	1	1,2,3	IAIN
2. After first opening	1	1,2,3	IAIN

3. After dilution or reconstitution	1	1,2,3	IAIN
b) Extension of the shelf life of the finished product			
1. As packaged for sale (supported by real time data)		1,2,3	IB
2. After first opening (supported by real time data)		1,2,3	IB
3. After dilution or reconstitution (supported by real time data)		1,2,3	IB
4. Extension of the shelf-life based on extrapolation of stability data not in accordance with ICH/VICH guidelines			II
5. Extension of the shelf-life of a biological/immunological medicinal product in accordance with an approved stability protocol.		1,2,3	IB
c) Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol			II
d) Change in storage conditions of the finished product or the diluted/reconstituted product		1,2,3	IB
e) Change to an approved stability protocol	1,2	1,4	IA

Conditions
1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 2. The change does not concern a widening of the acceptance criteria in the parameters tested, a removal of stability indicating parameters or a reduction in the frequency of testing.
Documentation
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate). This must contain results of appropriate real time stability studies (covering the entire shelf life) conducted in accordance with the relevant stability guidelines on at least two pilot scale batches (1) of the finished product in the authorised packaging material and/or after first opening or reconstitution, as appropriate; where applicable, results of appropriate microbiological testing should be included. 2. Revised product information 3. Copy of approved end of shelf life finished product specification and where applicable, specifications after dilution/reconstitution or first opening. 4. Justification for the proposed change(s).

- Design Space and post approval change management protocol

Implementation of changes foreseen in an approved change management protocol	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) The implementation of the change requires no further supportive data	1	1,2,4	IAIN

b) The implementation of the change requires further supportive data		1,2,3,4	IB
c) Implementation of a change for a biological/immunological medicinal product		1,2,3,4,5	IB

Conditions

1. The proposed change has been performed fully in line with the approved change management protocol, which requires its immediate notification following implementation.

Documentation

1. Reference to the approved change management protocol.

2. Declaration that the change is in accordance with the approved change management and that the study results meet the acceptance criteria specified in the protocol. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.

3. Results of the studies performed in accordance with the approved change management protocol.

4. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

5. Copy of approved specifications of the finished product.

Introduction of a post approval change management protocol related to the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
		1,2,3	II

Documentation

1. Detailed description for the proposed change.

2. Change management protocol related to the finished product.

3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

- Adventitious Agents Safety

Update to the 'Adventitious Agents Safety Evaluation' information	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Studies related to manufacturing steps investigated for the first time for one or more adventitious agents			II
b) Replacement of obsolete studies related to manufacturing steps and adventitious agents already reported in the dossier			
1) with modification of risk assessment			II
2) without modification of risk assessment		1,2,3	IB
Documentation 1. Amendment of the relevant section(s) of the dossiers including the introduction of the new studies to investigate the capability of manufacturing steps to inactivate/reduce adventitious agents. 2. Justification that the studies do not modify the risk assessment. 3. Amendment of product information (where applicable).			

CHAPTER 4

USA

2 USA

2.1 Introduction

According to the Federal Food, Drug, and Cosmetic Act (Act) and Section 314.70 (21 CFR 314.70), any modifications made to a previously approved NDA/ANDA must be reported to the USFDA under Section 506A. Applicants are required to inform the FDA of any changes made to the approved NDA/ANDA beyond those already stated in the application. The notification provided must explain the change in detail. Depending on the nature of the modification, applicants must submit a supplement to notify the FDA of the change.

For USA post approval changes the covered documents are

- Changes to an Approved NDA or ANDA
- SUPAC
  - SUPAC IR
  - SUPAC MR
  - SUPAC SS

The detail description are covered further.

2.2 Changes to an Approved NDA or ANDA

2.2.1 Introduction

After the approval of an NDA / ANDA, any changes to it must be reported to the USFDA as per Section 506A and Section 314.70 (21 CFR 314.70) of the Federal Food, Drug, and Cosmetic Act (Act).

The guidance provides recommendations for reporting post-approval changes to the USFDA in various categories, including components and composition, manufacturing sites, manufacturing process, specifications, container closure system, labelling, miscellaneous changes, and multiple related changes. This guidance was published in April 2014.

Section 506A outlines the criteria for reporting changes in the manufacturing and distribution of drugs that have been approved in an application. In accordance with Section 506A of the Federal Food, Drug, and Cosmetic Act (Act), the FDA has updated its

regulations concerning submitting supplements and making other changes to approved applications (21 CFR 314.70) to align with these criteria..[10]

2.2.2 Types of changes

There are three types of changes: Major, Moderate, and Minor.

- Major Changes: These changes require a Prior Approval Supplement (PAS) and include modifications that may significantly affect the safety, efficacy, or labeling of the product.
- Moderate Changes: These changes can be made through a Changes Being Effected (CBE)-0 or CBE-30 supplement. CBE-0 supplements require FDA notification at the time of distribution, while CBE-30 supplements require FDA review and approval before distribution.
- Minor Changes: These changes can be made through an Annual Report (AR) and include modifications that have no significant impact on the safety, efficacy, or labeling of the product.

TYPE	**ANTICIPATED IMPLEMENTATION TIME**
AR	Up to 1 year before submission
CBE-0	On receipt of submission by FDA
CBE-30	30 days after receipt of submission
PAS	Up to 6 months after submission

Table 5: Summary of post approval changes in USA

Major Changes

Major changes are those that have a significant or high potential impact on the identity, strength, quality, purity, or potency of a drug product, and may affect its safety and efficacy. PAS is the type of supplement required for major changes. Before distributing the drug product manufactured with proposed changes into the market, the PAS needs to be submitted to the FDA for approval.

Moderate Changes

Moderate changes are those that have a moderate potential to affect the identity, strength, quality, purity, or potency of a drug product and may impact its safety and efficacy. There are two types of moderate changes:

- CBE-30: This type of change requires submission to the FDA at least 30 days before the distribution of the drug product made using the change.
- CBE-0: These changes are minor and do not require prior FDA approval. The drug product can be distributed when the FDA receives the supplement.

Minor changes

These changes are considered to have minimal impact on the identity, strength, quality, purity, or potency of a drug product, and are unlikely to significantly affect its safety and effectiveness. Such changes are typically described in the next Annual Report, which is submitted up to one year prior to the anniversary date of the original NDA/ANDA submission.

2.2.3 General requirement

When submitting a change to an approved application, a detailed description of the proposed change must be included. This should be accompanied by a cover letter and a summary section in the annual report. The applicant should also ensure that the proposed change is compliant with current good manufacturing practice (cGMP) requirements.

For moderate changes, such as a CBE, the applicant should provide 12 copies of the final printed labeling. Additionally, a certifying statement should be included to confirm that the information submitted is accurate and complete to the best of their knowledge.

2.2.4 Post approval changes

The following list covers the post approval changes of component and composition, manufacturing site and process, specification, container closure system, labelling and miscellaneous with examples of major, moderate and minor changes.

Changes	Major	Moderate	Minor
Component and composition	Changes in the qualitative or quantitative formulation, including inactive ingredients (specified in SUPAC)		The deletion or reduction of an ingredient intended to affect only the colour of the drug product
Manufacturing sites	. A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site has never been inspected by FDA for the type of operation that is being moved or the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than two years. A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site does not have a satisfactory cGMP inspection for the type of operation being moved. A move to a different manufacturing site for (1) the manufacture, processing, or primary packaging of drug products when the	**CBE-30:** A move to a different manufacturing site for the manufacture or processing of any drug product, in-process material, or drug substance that is not otherwise provided for in this guidance. A move to a different manufacturing site for the primary packaging of (1) any drug product that is not otherwise listed as a major change and (2) modified-release solid oral dosage form drug products. A move to a different manufacturing site for testing if (1) the test procedures approved in the application or procedures that have been implemented	A move to a different manufacturing site for secondary packaging. A move to a different manufacturing site for labelling. A move to a different manufacturing site for the manufacture or processing of drug substance intermediates other than the final intermediate. A change in the contract sterilization site for packaging components when

	primary packaging components control the dose delivered to the patient or the formulation modifies the rate or extent of availability of the drug, or (2) the manufacture or processing of in-process materials with modified-release characteristics. Examples of these types of drug products include modified-release solid oral dosage forms, transdermal systems, liposomal drug products, depot drug products, oral and nasal metered-dose inhalers (MDIs), dry powder inhalers (DPIs), and nasal spray pumps.	via an annual report are used, (2) all post approval commitments made by the applicant relating to the test procedures have been fulfilled (e.g., providing methods validation samples), and (3) the new testing facility has the capability to perform the intended testing. **CBE-0:** A move to a different manufacturing site for the manufacture or processing of the final intermediate	the process is not materially different from that provided for in the approved application A transfer of the manufacture of a finished product sterilized by terminal processes to a newly constructed building or existing building at the same manufacturing site. A move to a different manufacturing site for the ink imprinting of solid oral dosage form drug products.
Manufacturing process	Changes that may affect the controlled (or modified) release, metering or other characteristics (e.g., particle size) of the dose delivered to the patient, including the addition or deletion of	**CBE-30:** For drug products, any change in the process, process parameters, and/or equipment For drug substances, any change in	For drug products, changes to equipment of the same design and operating principle and/or changes in scale

	a code imprint by embossing, debossing, or engraving on a modified-release solid oral dosage form. Changes that may affect drug product sterility assurance including, where appropriate, process changes for sterile drug substances and sterile packaging components. These include: •Changes in the sterilization method (e.g., gas, dry heat, irradiation). These include changes from sterile filtered or aseptic processing to terminal sterilization, or vice versa. •Addition, deletion, or substitution of sterilization steps or procedures for handling sterile	process and/or process parameters For natural protein drug substances and natural protein drug products: •Any change in the process, process parameters, and/or equipment •An increase or decrease in production scale during finishing steps that involves different equipment. •Replacement of equipment with equipment of different design that does not affect the process methodology or process operating parameters. For sterile drug products, drug substances, and components, as appropriate:	A minor change in an existing code imprint for a dosage form. For example, changing from a numeric to alphanumeric code. Addition of an ink code imprint or a change in the ink used in an existing code imprint for a solid oral dosage form drug product when the ink is currently used on CDER-approved drug products. Addition or deletion of a code imprint by embossing, debossing, or engraving on a solid dosage form drug product other than a modified-release dosage form. A change in the order of addition of ingredients for

	materials in an aseptic processing operation. •Replacing sterilizers that operate by one set of principles with sterilizers that operate by another principle (e.g., substituting a gravity displacement steam process with a process using superheated water spray). •Addition to an aseptic processing line of new equipment made of different materials (e.g., stainless steel versus glass, changes between plastics) that will come in contact with sterilized bulk solution or sterile drug components, or deletion of equipment from an aseptic processing line. •Replacing a Class 100 aseptic fill area with a barrier system or isolator for aseptic	•Changes in dry heat depyrogenation processes for glass container systems for drug substances and drug products that are produced by terminal sterilization processes or aseptic processing. •Changes to filtration parameters for aseptic processing (including flow rate, pressure, time, or volume, but not filter materials or pore size rating) when additional validation studies for the new parameters should be performed. •Filtration process changes that provide for a change from single to dual sterilizing filters in series, or for repeated filtration of a bulk.	solution dosage forms or solutions used in unit operations (e.g., granulation solutions). Changes in scale of manufacturing for terminally sterilized drug products that increase the bulk solution storage time by no more than 50 percent beyond the validated limits in the approved application when bioburden limits are unchanged. For natural protein drug products and natural protein drug substances: •An increase or decrease in production scale during finishing steps that does not

	filling. Once this change has been approved, subsequent process changes for similar product types in the same barrier system or isolator may be submitted as a changes-being-effected-in-30-days supplement. •Replacement or addition of lyophilisation equipment of a different size that uses different operating parameters or lengthens the overall process time. •Changes from bioburden-based terminal sterilization to the use of an overkill process, and vice versa. •Changes to aseptic processing methods, including scale, that extend the total processing, including bulk storage time, by more than 50 percent	•Changes from one qualified sterilization chamber to another for in-process or terminal sterilization that result in changes to validated operating parameters (time, temperature, F0, and others). •Changes in scale of manufacturing for terminally sterilized drug products that increase the bulk solution storage time by more than 50 percent beyond the validated limits in the approved application when bioburden limits are unchanged. For drug substances, redefinition of an intermediate, excluding the final intermediate, as a starting material.	involve an equipment change. •Replacement of equipment with equipment of the same design, operating principle, and capacity with no change in production scale.

	beyond the validated limits in the approved application. •Changes in sterilizer load configurations that are outside the range of previously validated loads. •Changes in materials or pore size rating of filters used in aseptic processing. The following changes for a natural product: •Changes in the virus or adventitious agent removal or inactivation methods. This applies to any material where such procedures are necessary, including drug substance, drug product, reagents, and excipients. •For drug substance and drug product, changes in the source material (e.g., microorganism, plant) or cell line.	**CBE-0:** A change in methods or controls that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess. 2. For sterile drug products, elimination of in-process filtration performed as part of the manufacture of a terminally sterilized drug product.	

	•For drug substance and drug product, establishment of a new master cell bank or seed. Addition of an ink code imprint or change to or in the ink used for an existing imprint code for a solid oral dosage form drug product when the ink as changed is not currently used on CDER-approved drug products Establishing a new procedure for reprocessing a batch of drug substance or drug product that fails to meet the approved specification.		
Specification	Relaxing an acceptance criterion Deleting any part of a specification Establishing a new regulatory analytical procedure including	**CBE-30:** .Any change in a regulatory analytical procedure other than those identified as major changes or editorial changes.	.Any change in a specification made to comply with an official compendium, For drug substance and drug product,

	designation of an alternative analytical procedure as a regulatory procedure. A change in a regulatory analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the regulatory analytical procedure described in the approved application. A change in an analytical procedure used for testing components, packaging components, the final intermediate, in-process materials after the final intermediate, or starting materials introduced after the final intermediate that does not provide the same or increased	.Relaxing an acceptance criterion or deleting a test for raw materials used in drug substance manufacturing, in-process materials prior to the final intermediate, starting materials introduced prior to the final drug substance intermediate, or drug substance intermediates (excluding final intermediate) .A change in an analytical procedure used for testing raw materials used in drug substance manufacturing, in-process materials prior to the intermediate, starting materials introduced prior to the final drug substance intermediate, or drug substance intermediates	the addition or revision of an alternative analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application or deletion of an alternative analytical procedure. Tightening of acceptance criteria. A change in an analytical procedure used for testing raw materials used in drug substance synthesis, starting

	assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application except as otherwise noted. For example, a change from an HPLC procedure that distinguishes impurities to (1) an HPLC procedure that does not, (2) another type of analytical procedure (e.g., titrimetric) that does not, or (3) an HPLC procedure that distinguishes impurities but the limit of detection and/or limit of quantitation is higher. Relating to testing of raw materials for viruses or adventitious agents:	(excluding final intermediate) that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application . Relaxing an in-process acceptance criterion associated with microbiological monitoring of the production environment, materials, and components that are included in NDA and ANDA submissions. For example, increasing the microbiological alert or action limits for critical processing environments in an aseptic fill facility or increasing the	materials introduced prior to the final drug substance intermediate, in-process materials prior to the final intermediate, or drug substance intermediates (excluding final intermediate) that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

	(1) relaxing an acceptance criterion, (2) deleting a test, or (3) a change in the analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.	acceptance limit for bioburden in bulk solution intended for filtration and aseptic filling. .Relaxing an acceptance criterion or deleting a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements **CBE-0:** An addition to a specification that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess. For example, adding a new test and	

		associated analytical procedure and acceptance criterion. A change in an analytical procedure used for testing components, packaging components, the final intermediate, in-process materials after the final intermediate, or starting materials introduced after the final intermediate that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.	
Container closure system	For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams,	**CBE-30:** A change to or in a container closure system, except as	. A change in the container closure system for a nonsterile drug

	ointments) dosage forms, a change to or in polymeric materials (e.g., plastic, rubber) of primary packaging components, when the composition of the component as changed has never been used in a CDER-approved drug product of the same dosage form and same route of administration. For example, a polymeric material that has been used in a CDER-approved topical ointment would not be considered CDER-approved for an ophthalmic ointment. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms in permeable or semipermeable container closure systems, a change from an ink and/or adhesive	otherwise provided for in this guidance, that does not affect the quality of the drug product. Changes in the size or shape of a container for a sterile drug substance. A change in the number of units (e.g., tablets, capsules) or labelled amount (e.g., grams, millilitres) of a nonsterile drug product in a unit-of-use container **CBE-0:** A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change from one container closure system to another	product, based on a showing of equivalency to the approved system . A change in the size and/or shape of a container for a nonsterile solid dosage form . A change in the number of units (e.g., tablets, capsules) or labelled amount (e.g., grams) of nonsterile solid dosage form in a multiple-unit container. . The following changes in the container closure system of solid oral dosage form drug products as long as the new package provides the same or better protective properties (e.g., light, moisture) and any new primary

	used on the permeable or semipermeable packaging component to an ink or adhesive that has never been used in a CDER-approved drug product of the same dosage form and same route of administration and with the same type of permeable or semipermeable packaging component (e.g., low density polyethylene, polyvinyl chloride). A change in the primary packaging components for any drug product when the primary packaging components control20 the dose delivered to the patient (e.g., the valve or actuator of a metered-dose inhaler). For sterile drug products, any change that may affect drug	A change in the labelled amount (e.g., grams, millilitres) of drug product for a nonsterile drug product in a multiple-unit container A change in or addition or deletion of a desiccant.	packaging component materials have been used in and been in contact with CDER-approved solid oral dosage form drug products: . Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap. •Changing from one plastic container to another of the same type of plastic (e.g., high density polyethylene (HDPE) container to another HDPE container). •Changes in packaging materials used to control

	product sterility assurance, such as: •A change from a glass ampule to a glass vial with an elastomeric closure. •A change to a flexible container system (bag) from another container system. •A change to a prefilled syringe dosage form from another container system. •A change from a single unit dose container to a multiple dose container system. •Changes that add or delete silicone treatments to container closure systems (such as elastomeric closures or syringe barrels). •Changes in the size and/or shape of a container for a sterile drug product.		odour (e.g., charcoal packets). •Changes in bottle filler (e.g., change in weight of cotton or amount used) without changes in the type of filler (e.g., cotton to rayon). •Increasing the wall thickness of the container. •A change in or addition of a cap liner. •A change in or addition of a seal (e.g., heat induction seal). •A change in an antioxidant, colorant, stabilizer, or mold releasing agent for production of the container and/or closure to one that is used at similar levels in the

	Deletion of a secondary packaging component intended to provide additional protection to the drug product (e.g., carton to protect from light, overwrap to limit transmission of moisture or gases) or a change in the composition of, or the addition of, a secondary packaging component that may affect the impurity profile of the drug product. A change to a new container closure system if the new container closure system does not provide the same or better protective properties than the approved container closure system.		packaging of CDER-approved solid oral dosage form drug products. •A change to a new container closure system when the container closure system is already approved in the NDA or ANDA for other strengths of the drug product. . The following changes in the container closure system of nonsterile liquid drug products as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved liquid drug

			products with the same route of administration (i.e., the material in contact with a liquid topical should already have been used with other CDER-approved liquid topical drug products): •Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap. •Increasing the wall thickness of the container. •A change in or addition of a cap liner. •A change in or addition of a seal (e.g., heat

			induction).A change in the container closure system of unit dose packaging (e.g., blister packs) for nonsterile solid dosage form drug products as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved drug products of the same type (e.g., solid oral dosage form, rectal suppository). . The following changes in the container closure system of nonsterile semisolid drug products as long as the new package

			provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved semisolid drug products: •Changes in the closure or cap. •Increasing the wall thickness of the container. •A change in or addition of a cap liner. •A change in or addition of a seal. •A change in the crimp sealant. . A change in the flip seal cap colour as long as the cap colour is consistent with any established colour

			coding system for that class of drug products.
Labelling	. Changes based on post marketing study results, including, but not limited to, labelling changes associated with new indications and usage. . Change in, or addition of, pharmacoeconomic claims based on clinical studies. . Changes to the clinical pharmacology or the clinical study section reflecting new or modified data. . Changes based on data from preclinical studies. . Revision (expansion or contraction) of population based on data. . Claims of superiority to another drug product.	Revision (expansion or contraction) of population based on data. Claims of superiority to another drug product. Change in the labelled storage conditions, unless exempted by regulation or guidance.	Changes in the layout of the package or container label that are consistent with FDA regulations without a change in the content of the labelling. Editorial changes, such as adding a distributor's name. Foreign language versions of the labelling if no change is made to the content of the approved labelling and a certified translation is included. Labelling changes made to comply with an official compendium.

	. Change in the labelled storage conditions, unless exempted by regulation or guidance.		
Miscellaneous	. Changes requiring completion of studies in accordance with 21 CFR part 320 to demonstrate equivalence of the drug product to the drug product as manufactured without the change . Addition of a stability protocol or comparability protocol. . Changes to an approved stability protocol or comparability protocol . An extension of an expiration dating period based on (1) data obtained under a new or revised stability testing protocol that has not been approved in the application or (2) full shelf life data on	**CBE-30:** Reduction of an expiration dating period to provide increased assurance of the identity, strength, quality, purity, or potency of the drug product. Extension of an expiration date that has previously been reduced under this provision should be submitted in a changes-being-effected-in-30-days supplement even if the extension is based on data obtained under a protocol approved in the application. **CBE-0:** No changes have been identified.	An extension of an expiration dating period based on full shelf life data on production batches Addition of time points to the stability protocol or deletion of time points beyond the approved expiration dating period. A change from previously approved stability storage conditions to storage conditions recommended in International Conference on Harmonisation (ICH) guidances. Non-USP reference standards:

	pilot scale batches using an approved protocol. . Changes to a drug product under an application that is subject to a validity assessment because of significant questions regarding the integrity of the data supporting that application		•Replacement of an in-house reference standard or reference panel (or panel member) according to procedures in an approved application. •Tightening of acceptance criteria for existing reference standards to provide greater assurance of drug product purity and potency.

2.3 SUPAC

2.3.1 Introduction

The term SUPAC refers to the process of scaling up a drug manufacturing process and the changes that are made to the composition, manufacturing process, manufacturing equipment, and site after the drug has been approved.

After approval, changes will be made to the manufacturing process and composition of the drug, and will continue throughout its life. Changes in raw materials, processes, equipment or manufacturing locations, and batch sizes can ultimately affect the quality attributes of the drug or finished product. Hence, it is important to anticipate and thoroughly evaluate the impact of any change on the quality of the drug or final product. The strength of the adverse effect produced by a particular change depends on the type of dosage form.[25]

It provides recommendation to sponsor to NDA and ANDA and AADA's to change[11]

- The components or composition
- The site of manufacture
- The scale-up/scale-down of manufacture
- The manufacturing (process and equipment) of an immediate release oral formulation.

The SUPAC guidelines consist of three different guidelines, which are SUPAC-IR, SUPAC-MR, and SUPAC-SS. These guidelines provide instructions for making changes to manufacturing processes and chemistry of drugs after approval, which may affect the quality attributes of the drug or finished product. It is important to anticipate and fully evaluate the impact of any type of change on the quality of the drug or final product to avoid unwanted effects.[11,26,27]

2.3.2 Level of changes

The three main types of changes are related to chemistry, manufacturing, and control tests, and they involve in vitro dissolution and bioequivalence tests for each level.

These changes are classified into three levels,

- Level 1 being changes that are not expected to have any noticeable effect on the formulation, quality, or performance.

- Level 2 changes may have an impact on the formulation, quality, or performance
- Level 3 changes are likely to have a significant impact on the formulation, quality, or performance.

According to the guidelines, changes specified from section 3.3.4 to 3.3.7 are different for SUPAC-IR, SUPAC-MR, and SUPAC-SS only in terms of component and composition. For all other changes, the guidelines are the same for all three types of dosage forms.

2.3.3 General stability considerations

When implementing SUPAC changes, it is important to evaluate the effect on drug product stability. The following considerations should be taken into account:

- Stability data from pilot scale batches are generally acceptable.
- If there is a loss of potency or an increase in degradation products under accelerated conditions, it is recommended to compare the historical accelerated stability data with the changes, and long-term stability data may need to be provided as a supplement.
- For the first or first three batches, a commitment to conduct long-term stability studies throughout the expiration dating period should be included, and the results should be reported in the annual report.

2.3.4 Component and composition

2.3.4.1 Immediate release solid dosage form

It focuses on the changes in the excipients in the drug products.

Tests and filing documentation depends on 3 factors:

- Therapeutic range
- Solubility
- Permeability

LEVEL 1 changes

<table>
<tr><td>Definition of level</td><td>Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.
Examples:
a. Deletion or partial deletion of an ingredient intended to affect the colour or flavour of the drug product; or change in the ingredient of the printing ink to another approved ingredient.
b. Changes in excipients, expressed as percentage (w/w) of total formulation, less than or equal to the following percent ranges:
<table>
<tr><th>EXCIPIENT</th><th>PERCENT EXCIPIENT (w/w) OUT OF TOTAL TARGET DOSAGE FORM WEIGHT</th></tr>
<tr><td>Filler</td><td>±5</td></tr>
<tr><td>Disintegrant
Starch
Others</td><td>
±3
±1</td></tr>
<tr><td>Binder</td><td>±0.5</td></tr>
<tr><td>Lubricant
Calcium (Ca) or Magnesium (Mg) Stearate
Other</td><td>
±0.25
±1</td></tr>
<tr><td>Glidant
Talc
Other</td><td>
±1
±0.1</td></tr>
<tr><td>Film Coat</td><td>±1</td></tr>
</table></td></tr>
<tr><td>Test documentation</td><td></td></tr>
<tr><td>Chemistry documentation</td><td>Application/compendial release requirements and stability testing.
Stability testing: one batch on long-term stability data reported in annual report.</td></tr>
</table>

Dissolution documentation	None beyond application/compendial requirements.
In Vivo Bioequivalence Documentation	None
Filing documentation	Annual report (all information including long-term stability data).

LEVEL 2 changes

Definition of level	Level 2 changes are those that could have a significant impact on formulation quality and performance Examples: a. Change in the technical grade of an excipient. (Example: Avicel PH102 vs. Avicel PH200.) b. Changes in excipients, expressed as percent (w/w) of total formulation, greater than those listed above for a Level 1 change but less than or equal to the following percent ranges (which represent a two fold increase over Level 1 changes):

EXCIPIENT	**PERCENT EXCIPIENT (w/w) OUT OF TOTAL TARGET DOSAGE FORM WEIGHT**
Filler	±10
Disintegrant Starch Others	 ±6 ±2
Binder	±1
Lubricant Calcium (Ca) or	 ±0.5

	<table><tr><td>Magnesium (Mg) Stearate Other</td><td> ±2</td></tr><tr><td>Glidant Talc Other</td><td> ±2 ±0.2</td></tr><tr><td>Film Coat</td><td>±2</td></tr></table>
Test documentation	
Chemistry documentation	Application/compendial release requirements and batch records. Stability testing: 1 batch with 3 months accelerated stability data in supplement and 1 batch on long-term stability.
Dissolution documentation	Case A: High Permeability, High Solubility Drugs Dissolution of 85% in 15 minutes in 900 mL of 0.1N HCl. If a drug product fails to meet this criterion, the applicant should perform the tests described for Case B or C (below). Case B: Low Permeability, High Solubility Drugs Multi-point dissolution profile should be performed in the application/compendial medium at 15, 30, 45, 60 and 120 minutes or until an asymptote is reached. The dissolution profile of the proposed and currently used product formulations should be similar.

	Case C: High Permeability, Low Solubility Drugs Multi-point dissolution profiles should be performed in water, 0.1 N HCl, and USP buffer media at pH 4.5, 6.5, and 7.5 (five separate profiles) for the proposed and currently accepted formulations. Adequate sampling should be performed at 15, 30, 45, 60, and 120 minutes until either 90% of drug from the drug product is dissolved or an asymptote is reached. A surfactant may be used, but only with appropriate justification. The dissolution profile of the proposed and currently used product formulations should be similar.
In Vivo Bioequivalence Documentation	None: if the situation does not meet the description in Case A, Case B or Case C, refer to Level 3 changes.
Filing documentation	Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

LEVEL 3 changes

Definition of level	Level 3 changes are those that are likely to have a significant impact on formulation quality and performance. Examples: a. Any qualitative and quantitative excipient changes to a narrow therapeutic drug beyond the ranges in Example 2 of level 1 change b. All other drugs not meeting the dissolution criteria under Dissolution document. c. Changes in the excipient ranges of low solubility, low permeability drugs beyond those listed in Example 2 of level 1 change d. Changes in the excipient ranges of all drugs beyond those listed in Example 2 of level 2 change
Test documentation	
Chemistry documentation	Application/compendial release requirements and batch records. Significant body of information available:

	One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report. Significant body of information not available: Up to three batches with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report.
Dissolution documentation	Case B dissolution profile
In Vivo Bioequivalence Documentation	Full bioequivalence study. The bioequivalence study may be waived with an acceptable in vivo/in vitro correlation has been verified.
Filing documentation	Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

2.3.4.2 Modified release

Nonrelease controlling excipients

LEVEL 1 changes

<table>
<tr><td>Definition of level</td><td>Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance.
Examples:
a. Deletion or partial deletion of an ingredient intended to affect the colour or flavour of the drug product; or change in the ingredient of the printing ink to another approved ingredient.
b. Changes in nonrelease controlling excipients, expressed as percentage (w/w) of total formulation, less than or equal to the following percent ranges:
<table>
<tr><th>EXCIPIENT</th><th>PERCENT EXCIPIENT (w/w) OUT OF TOTAL TARGET DOSAGE FORM WEIGHT</th></tr>
<tr><td>Filler</td><td>±5</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td>
<table>
<tr><td>Disintegrant
Starch
Others</td><td>
±3
±1</td></tr>
<tr><td>Binder</td><td>±0.5</td></tr>
<tr><td>Lubricant
Calcium (Ca) or
Magnesium (Mg) Stearate
Other</td><td>
±0.25

±1</td></tr>
<tr><td>Glidant
Talc
Other</td><td>
±1
±0.1</td></tr>
<tr><td>Film Coat</td><td>±1</td></tr>
</table>
The total additive effect of all nonrelease controlling excipient changes should not be more than 5%. {Example: In a product consisting of active ingredient A, lactose, microcrystalline cellulose, and magnesium stearate, the lactose and microcrystalline cellulose should not vary by more than an absolute total of 5% (e.g., lactose increases by 2.5% and microcrystalline cellulose decreases by 2.5%) relative to the target dosage form weight if it is to stay within the level 1 range.}</td></tr>
<tr><td>Test documentation</td><td></td></tr>
<tr><td>Chemistry documentation</td><td>Application/compendial release requirements.
Stability: First production batch on long-term stability data reported in annual report.</td></tr>
<tr><td>Dissolution documentation</td><td>None beyond application/compendial requirements.</td></tr>
<tr><td>Bioequivalence Documentation</td><td>None</td></tr>
<tr><td>Filing documentation</td><td>Annual report (all information including long-term stability data).</td></tr>
</table>

LEVEL 2 changes

<table>
<tr><td>Definition of level</td><td>Level 2 changes are those that could have a significant impact on
formulation quality and performance
Examples:
a. Change in the technical grade of an excipient. (Example:
Avicel PH102 vs. Avicel PH200.)
b. Changes in excipients, expressed as percent (w/w) of total
formulation, greater than those listed above for a Level 1 change but less than or equal to the following percent ranges (which represent a two fold increase over Level 1 changes):
<table>
<tr><th>EXCIPIENT</th><th>PERCENT EXCIPIENT (w/w) OUT OF TOTAL TARGET DOSAGE FORM WEIGHT</th></tr>
<tr><td>Filler</td><td>±10</td></tr>
<tr><td>Disintegrant
Starch
Others</td><td>
±6
±2</td></tr>
<tr><td>Binder</td><td>±1</td></tr>
<tr><td>Lubricant
Calcium (Ca) or
Magnesium (Mg) Stearate
Other</td><td>
±0.5

±2</td></tr>
<tr><td>Glidant
Talc
Other</td><td>
±2
±0.2</td></tr>
<tr><td>Film Coat</td><td>±2</td></tr>
</table>
The total additive effect of all nonrelease controlling excipient changes should not change by more than 10%.</td></tr>
<tr><td>Test documentation</td><td></td></tr>
</table>

Chemistry documentation	Application/compendial product release requirements and updated executed batch records. Stability: One batch with three months accelerated stability data reported in prior approval supplement and long-term stability data of first production batch reported in annual report.
Dissolution documentation	Extended release: In addition to application/compendial release requirements, multipoint dissolution profiles should be obtained in three other media, for example, in water, 0.1N HCl, and USP buffer media at pH 4.5, and 6.8 for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached. A surfactant may be used with appropriate justification. Delayed release: In addition to application/compendial release requirements, dissolution tests should be performed in 0.1 N HCl for 2 hours (acid stage) followed by testing in USP buffer media, in the range of pH 4.5-7.5 (buffer stage) under standard (application/compendial) test conditions and two additional agitation speeds using the application/ compendial test apparatus (three additional test conditions). If the application/compendial test apparatus is the rotating basket method (Apparatus 1), a rotation speed of 50, 100, and 150 rpm may be used, and if the application/compendial test apparatus is the rotating paddle method (Apparatus 2), a rotation speed of 50, 75, and 100 rpm may be used. Multipoint dissolution profiles should be obtained during the buffer stage of testing. Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached. The above dissolution testing should be performed using the changed drug product and the biobatch or marketed batch (unchanged drug product). All modified release solid oral dosage forms: In the presence of an established in vitro/in vivo correlation[12], only application/compendial dissolution testing need be performed (i.e., only in vitro release data by the correlating method need to be submitted). The dissolution profiles of the changed drug product and the biobatch or marketed batch (unchanged drug product) should be similar. The sponsor should apply appropriate statistical testing with justifications (e.g., the f equation) for comparing 2 dissolution profiles[13]. Similarity testing for the two dissolution profiles (i.e., for the unchanged

	drug product and the changed drug product) obtained in each individual medium is appropriate.
Bioequivalence Documentation	None.
Filing documentation	Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

LEVEL 3 changes

Definition of level	Level 3 changes are those that are likely to have a significant impact on formulation quality and performance. Example: a. Changes in the nonrelease controlling excipient range beyond those listed in Level 2 Example 2. The total weight of the dosage form may be within or outside the approved original application range.
Test documentation	
Chemistry documentation	Application/compendial product release requirements and updated executed batch records. Stability: Significant body of information available: One batch with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report. Significant body of information not available: Three batches with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.
Dissolution documentation	Extended release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained using the application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 1, 2, and 4 hours and every two hours thereafter, until either 80% of the drug from the drug product is released or an asymptote is reached. Delayed release: In addition to application/compendial release requirements, a multipoint dissolution profile should be

	obtained during the buffer stage of testing using the application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached.
Bioequivalence Documentation	A single-dose bioequivalence study[14]. The bioequivalence study may be waived in the presence of an established in vitro/in vivo correlation.[12]
Filing documentation	Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

Release Controlling Excipient

LEVEL 1 changes

Definition of level	Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance. Example: a. Changes in the release controlling excipient(s), expressed as percentage (w/w) of total release controlling excipient(s) in the formulation less than or equal to 5% w/w of total release controlling excipient content in the modified release solid oral dosage form
Test documentation	
Chemistry documentation	Application/compendial product release requirements. Stability: First production batch on long-term stability data reported in annual report.
Dissolution documentation	None beyond application/compendial requirements
Bioequivalence Documentation	None
Filing documentation	Annual report (all information including long-term stability data).

LEVEL 2 changes

Definition of level	Level 2 changes are those that could have a significant impact on formulation quality and performance. Test documentation for a level 2 change would vary depending on whether the product could be considered to have a narrow therapeutic range. Examples: a. Change in the technical grade and/or specifications of the release controlling excipient(s). b. Changes in the release controlling excipient(s), expressed as percentage (w/w) of total release controlling excipient(s) in the formulation, greater than those listed above for a level 1 change, but less than or equal to 10% w/w of total release controlling excipient content in the modified release solid oral dosage form.
Test documentation	
Chemistry documentation	Application/compendial product release requirements and updated executed batch records. Stability: Nonnarrow therapeutic range drugs: One batch with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first production batch reported in annual report. Narrow therapeutic range drugs: Three batches with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.
Dissolution documentation	Nonnarrow therapeutic range drugs Extended release: In addition to application/compendial release requirements, multipoint dissolution profiles should be obtained in three other media, for example, in water, 0.1N HCl, and USP buffer media at pH 4.5, and 6.8 for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached. A surfactant may be used with appropriate justification. Delayed release: In addition to application/compendial release

	requirements, dissolution tests should be performed in 0.1 N HCl for 2 hours (acid stage) followed by testing in USP buffer media in the range of pH 4.5-7.5 (buffer stage) under standard (application/compendial) test conditions and two additional agitation speeds using the application/compendial test apparatus (three additional test conditions). If the application/compendial test apparatus is the rotating basket method (Apparatus 1), a rotation speed of 50, 100, and 150 rpm may be used, and if the application/compendial test apparatus is the rotating paddle method (Apparatus 2), a rotation speed of 50, 75, and 100 rpm may be used. Multipoint dissolution profiles should be obtained during the buffer stage of testing. Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached. The above dissolution testing should be performed using the changed drug product and the biobatch or marketed batch (unchanged drug product). All modified release solid oral dosage forms: In the presence of an established in vitro/in vivo correlation[12], only application/compendial dissolution testing should be performed (i.e., only in vitro release data by the correlating method should be submitted). The dissolution profiles of the changed drug product and the biobatch or marketed batch (unchanged drug product) should be similar. The sponsor should apply appropriate statistical testing with justifications (e.g., the f equation) for comparing dissolution profiles[13]. Similarity testing for the two dissolution profiles (i.e., for the unchanged drug product and the changed drug product) obtained in each individual medium is appropriate. Narrow therapeutic range drugs Extended release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained in application/compendial medium for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached. Delayed release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained during the buffer stage of testing using the application/compendial medium for the changed drug product

	and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example, at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached.
Bioequivalence Documentation	Nonnarrow therapeutic range drugs: None. Narrow therapeutic range drugs: A single-dose bioequivalence study.[14] The bioequivalence study may be waived in the presence of an established in vitro/in vivo correlation.[12] Changes in release controlling excipients in the formulation should be within the range of release controlling excipients of the established correlation.
Filing documentation	Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

LEVEL 3 changes

Definition of level	Level 3 changes are those that are likely to have a significant impact on formulation quality and performance affecting all therapeutic ranges of the drug. Examples: a. Addition or deletion of release controlling excipient(s) (e.g., release controlling polymer/plasticizer). b. Changes in the release controlling excipient(s), expressed as percentage (w/w) of total release controlling excipient(s) in the formulation, greater than those listed above for a level 2 change (i.e., greater than 10% w/w of total release controlling excipient content in the modified release solid oral dosage form). Total weight of the dosage form may be within or outside the original approved application range.
Test documentation	
Chemistry documentation	Application/compendial product release requirements and updated executed batch records. Stability: Three batches with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.

Dissolution documentation	Extended release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained using application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 1, 2, and 4 hours and every two hours thereafter until either 80% of the drug from the drug product is released or an asymptote is reached. Delayed release: In addition to application/compendial release requirements, a multipoint dissolution profile should be obtained during the buffer stage of testing using the application/compendial test conditions for the changed drug product and the biobatch or marketed batch (unchanged drug product). Adequate sampling should be performed, for example at 15, 30, 45, 60, and 120 minutes (following the time from which the dosage form is placed in the buffer) until either 80% of the drug from the drug product is released or an asymptote is reached.
Bioequivalence Documentation	A single-dose bioequivalence study.[14] The bioequivalence study may be waived in the presence of an established in vitro/in vivo correlation.[12] Changes in release controlling excipients in the formulation should be within the range of release controlling excipients of the established correlation.
Filing documentation	Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

2.3.4.3 Non sterile semisolid Dosage Form

LEVEL 1 changes

Definition of level	Level 1 changes are those that are unlikely to have any detectable impact on formulation quality and performance. Examples: Deletion or partial deletion of an ingredient intended to affect the colour, fragrance, or flavour of the drug product. Any change in an excipient up to 5% of approved amount of that excipient.

	The total additive effect of all excipient changes should not be more than 5%. Changes in the composition should be based on the approved target composition and not on previous level 1 changes in the composition. A change in diluent (q.s. excipient) due to component and composition changes in excipient may be made and is excluded from the 5% change limit. Change in a supplier of a structure forming excipient that is primarily a single chemical entity (purity≥95%) or change in a supplier or technical grade of any other excipient.
Test documentation	
Chemistry documentation	Application/compendial product release requirements and stability testing. Stability testing: First production batch on long-term stability reported in annual report.
In vitro release documentation	None.
In Vivo Bioequivalence Documentation	None.
Filing documentation	Annual report (all information including long-term stability data).

LEVEL 2 changes

Definition of level	Level 2 changes are those that could have a significant impact on formulation quality and performance. Examples: Changes of >5% and ≥10% of approved amount of an individual excipient. The total additive effect of all excipient changes should not be more than 10%. Changes in the composition should be based on the approved target composition and not on previous level 1 or level 2 changes in the composition. Changes in diluent (q.s. excipient) due to component and composition changes in excipients are acceptable and are excluded from the 10% change limit. Change in supplier of a structure forming excipient not covered under level 1.

	Change in the technical grade of structure forming excipient. Change in particle size distribution of the drug substance, if the drug is in suspension.
Test documentation	
Chemistry documentation	Application/compendial product release requirements and executed batch records. Stability testing: One batch with three months accelerated stability data reported in changes being effected supplement and long-term stability data of first production batch reported in annual report.
In vitro release documentation	The in vitro release rate of a lot of the new/modified formulation should be compared with that of a recent lot of comparable age of the pre-change formulation of the product. The median in vitro release of the two formulations should be demonstrated to be within acceptable limits using the testing
In vivo Bioequivalence Documentation	None
Filing documentation	Changes being effected supplement (all information including accelerated stability data); annual report (long-term stability data).

LEVEL 3 changes

Definition of level	Level 3 changes are those that are likely to have a significant impact on formulation quality and performance affecting all therapeutic ranges of the drug. Examples: a. Addition or deletion of release controlling excipient(s) (e.g., release controlling polymer/plasticizer). b. Changes in the release controlling excipient(s), expressed as percentage (w/w) of total release controlling excipient(s) in the formulation, greater than those listed above for a level 2 change (i.e., greater than 10% w/w of total release controlling excipient content in the modified release solid oral dosage form). Total weight of the dosage form may be within or outside the original approved application range.
Test documentation	

Chemistry documentation	Application/compendial product release requirements and updated executed batch records. Stability: Three batches with three months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report.
In vitro release documentation	The in vitro release rate of the new/modified formulation should be established as a point of reference. Under this level 3 change, in vitro release documentation is not required, but sponsors are encouraged to develop this information for use in subsequent changes under this guidance.
In vivo Bioequivalence Documentation	Full bioequivalence study on the highest strength, with in vitro release/other approach on the lower strength(s).
Filing documentation	Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

Preservatives

LEVEL 1 Changes	
Definition of Level	Quantitatively 10% or less change in the approved amount of preservative.
Test Documentation	Application/compendial product release requirements. Preservative Effectiveness Test carried out at lowest specified preservative level.
Filing Documentation	Annual report
LEVEL 2 Changes	
Definition of Level	Quantitatively greater than 10% and up to 20% change in the approved amount of preservative.
Test Documentation	Application/compendial product release requirements. Preservative Effectiveness Test at lowest specified preservative level.
Filing Documentation	Changes being effected supplement
LEVEL 3 Changes	

Definition of Level	Quantitatively greater than 20% change in the approved amount of preservative (including deletion) or use of a different preservative.
Test Documentation	Application/compendial product release requirements. Preservative Effectiveness Test at lowest specified preservative level. Analytical method for identification and assay for new preservative. Validation studies to show that the new preservative does not interfere with application/compendial test. Executed batch records. Stability testing: One batch with three months accelerated stability data reported in prior approval supplement and long-term stability data of first production batch reported in annual report.
Filing Documentation	Prior approval supplement (all information including accelerated stability data); annual report (long-term stability data).

2.3.5 Site changes

Site changes consist of changes in the manufacturing location of both the company-owned and contracted manufacturing facilities, including scale-up changes, manufacturing changes (including processes and / or equipment), or components and configurations. No changes are included. New location should have cGMP inspection.

LEVEL 1 changes

Definition of level	Level 1 changes consist of site changes within a single facility where the same equipment, standard operating procedures (SOP's), environmental conditions (e.g., temperature and humidity) and controls, and personnel common to both manufacturing sites are used, and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility. Common is defined as employees already working on the campus who have suitable experience with the manufacturing process.
Test documentation	

Chemistry documentation	None beyond application/compendial release requirements.
Dissolution documentation	None beyond application/compendial release requirements.
In Vivo Bioequivalence Documentation	None.
Filing documentation	Annual report.

LEVEL 2 changes

Definition of level	Level 2 changes consist of site changes within a contiguous campus, or between facilities in adjacent city blocks, where the same equipment, SOP's, environmental conditions (e.g., temperature and humidity) and controls, and personnel common to both manufacturing sites are used, and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility.
Test documentation	
Chemistry documentation	Location of new site and updated batch records. None beyond application/compendial release requirements. One batch on long-term stability data reported in annual report.
Dissolution documentation	None beyond application/compendial release requirements.
In Vivo Bioequivalence Documentation	None.
Filing documentation	Changes being effected supplement; annual report (long-term stability test data).

LEVEL 3 changes

Definition of level	Level 3 changes consist of a change in manufacturing site to a different campus. A different campus is defined as one that is not on the same original contiguous site or where the facilities are not in adjacent city blocks. To qualify as a Level 3 change, the same equipment, SOP's, environmental conditions, and controls should be used in the manufacturing process at the new site, and no changes may be made to the manufacturing batch records except for administrative information, location and language translation where needed.
Test documentation	
Chemistry documentation	Location of new site and updated batch records. Application/compendial release requirements. Stability: Significant body of data available: One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report. Significant body of data not available: Up to three batches with three months accelerated stability data reported in supplement; up to three batches on long-term stability data reported in annual report.
Dissolution documentation	Case B: Multi-point dissolution profile should be performed in the application/compendial medium at 15, 30, 45, 60 and 120 minutes or until an asymptote is reached. The dissolution profile of the drug product at the current and proposed site should be similar.
In Vivo Bioequivalence Documentation	None.
Filing documentation	Changes being effected supplement; annual report (long-term stability test data).

2.3.6 Change in batch size (scale-up/scale-down)

LEVEL 1 changes

Definition of level	Change in batch size, up to and including a factor of 10 times the size of the pilot/bio batch, where: 1) the equipment used to produce the test batch(es) is of the same design and operating principles; 2) the batch(es) is (are) manufactured in full compliance with cGMP's; and 3) the same standard operating procedures (SOP's) and controls, as well as the same formulation and manufacturing procedures, are used on the test batch(es) and on the full-scale production batch(es).
Test documentation	
Chemistry documentation	Application/compendial release requirements. Notification of change and submission of updated batch records in annual report. One batch on long-term stability reported in annual report.
Dissolution documentation	None beyond application/compendial release requirements.
In Vivo Bioequivalence Documentation	None.
Filing documentation	Annual report (long-term stability data).

LEVEL 2 changes

Definition of level	Changes in batch size beyond a factor of ten times the size of the pilot/bio batch, where: 1) the equipment used to produce the test batch(es) is of the same design and operating principles; 2) the batch(es) is (are) manufactured in full compliance with cGMP'S; and 3) the same SOP's and controls as well as the same formulation and manufacturing procedures are used on the test batch(es) and on the full-scale production batch(es).
Test documentation	
Chemistry documentation	Application/compendial release requirements. Notification of change and submission of updated batch records. Stability testing: One batch with three months accelerated stability data and one batch on long-term stability.

Dissolution documentation	Case B dissolution profile.
In Vivo Bioequivalence Documentation	None
Filing documentation	Changes being effected supplement; annual report (long-term stability data).

2.3.7 Manufacturing

It affects both the equipment and the process used during manufacturing.

2.3.7.1 Equipment

LEVEL 1 changes

Definition of level	This category consists of: 1) change from non-automated or non-mechanical equipment to automated or mechanical equipment to move ingredients; and 2) change to alternative equipment of the same design and operating principles of the same or of a different capacity.
Test documentation	
Chemistry documentation	Application/compendial release requirements. Notification of change and submission of updated batch records. Stability: One batch on long-term stability.
Dissolution documentation	None beyond application/compendial release requirements.
In Vivo Bioequivalence Documentation	None.
Filing documentation	Annual report (long-term stability data).

LEVEL 2 changes

Definition of level	Change in equipment to a different design and different operating principles.
Test documentation	

Chemistry documentation	Application/compendial release requirements. Notification of change and submission of updated batch records. Stability testing: Significant body of data available: One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report. Significant body of data not available: Up to three batches with three months accelerated stability data reported in supplement; up to three batches on long-term stability data reported in annual report.
Dissolution documentation	Case C dissolution profile.
In Vivo Bioequivalence Documentation	None.
Filing documentation	Prior approval supplement with justification for change; annual report (long-term stability data).

2.3.7.2 Process

LEVEL 1 changes

Definition of level	This category includes process changes including changes such as mixing times and operating speeds within application/validation ranges.
Test documentation	
Chemistry documentation	None beyond application/compendial release requirements.
Dissolution documentation	None beyond application/compendial release requirements.
In Vivo Bioequivalence Documentation	None.
Filing documentation	Annual report (long-term stability data).

LEVEL 2 changes

Definition of level	This category includes process changes including changes such as mixing times and operating speeds outside of application/validation ranges.
Test documentation	
Chemistry documentation	Application/compendial release requirements. Notification of change and submission of updated batch records. Stability testing: One batch on long-term stability.
Dissolution documentation	Case B dissolution profile.
In Vivo Bioequivalence Documentation	None.
Filing documentation	Changes being effected supplement; annual report (long-term stability data).

LEVEL 3 changes

Definition of level	This category includes change in the type of process used in the manufacture of the product, such as a change from wet granulation to direct compression of dry powder.
Test documentation	
Chemistry documentation	Application/compendial release requirements. Notification of change and submission of updated batch records. Stability testing: Significant body of data available: One batch with three months accelerated stability data reported in supplement; one batch on long-term stability data reported in annual report. Significant body of data not available: Up to three batches with three months accelerated stability data reported in supplement; up to three batches on long-term stability data reported in annual report.

Dissolution documentation	Case B dissolution profile.
In Vivo Bioequivalence Documentation	In vivo bioequivalence study. The bioequivalence study may be waived if a suitable in vivo/in vitro correlation has been verified.
Filing documentation	Prior approval supplement with justification; annual report (long-term stability data).

CHAPTER 5

COMPARISON

3 COMPARISON

3.1 Comparison between Europe and USA

Country	**EU**	**USA**
Regulatory Agency	EMA	USFDA
Designation	Variation	SUPAC, changes to approved NDA and ANDA
Classification	Type IA Type IAIN Type IB Type II	As per changes to approved NDA and ANDA • Major • Minor • Moderate As per SUPAC • Level I - Minor • Level II - Moderate • Level III - Major
Reporting Category	Type I: Annual Report Type IAIN: Immediate Notification Type IB: 30 days before distributing the product Type II: Prior Approval Supplement	Minor: Annual report Moderate: CBE-30, CBE-0 Major: Prior Approval Supplement
Notification Type	Annual report and Immediate notification	Annual report
Timelines	Type IAIN: 30 Type IB: 30 Type II: 30,60,90	CBE 30: 30 days CBE-0: Immediate after receipt of filing

	Type II Extension: 210	PAS: 6 to 8 months
Dosage Form Covered	OSDs, Biologics & Medical Devices	OSDs, biotechnology and specified synthetic biological products, sterile

3.2 Comparative Post Approval Regulatory Requirement of Manufacturing sites[7,10,18-24]

Sr. no	**Changes**	**USA**	**EU**
1.	If a manufacturing operation for a drug product is moved to a new site that has not been inspected for that type of operation, or if the operation has been discontinued at the new site for more than two years, and then restarted, it would require regulatory approval before implementation.	PAS	Type II
2.	Moving the manufacturing operations to a different site (except for those involved in drug substance intermediate manufacturing) requires a satisfactory cGMP inspection of the new site for the type of operation being moved.	PAS	Type II
3.	Moving the manufacturing site for (1) drug products where the primary packaging components control the dose delivered to the patient or the formulation modifies the rate or extent of availability of the drug, or (2) in-process materials with modified-release characteristics, to a different location.	PAS	Type II
4.	The transfer of the production of a sterile drug substance or product that has been processed aseptically to either a new aseptic processing facility/area or an existing one that does not manufacture similar approved drug products.	PAS	Type IB
5.	Moving the production of a terminal sterilized finished drug product to a new facility located at a different manufacturing site.	CBE-30	Type IB
6.	This regulatory requirement refers to a change in the physical location of the manufacturing or processing of any drug substance, in-process material, or drug product to a different manufacturing site.	CBE-30	Type IB

7.	A change involving the relocation of aseptically processed sterile drug substance or product to another aseptic processing facility or area within the same or a different manufacturing site.	CBE-30	Type IB
8.	A relocation to a different manufacturing site for the primary packaging of drug products that are not considered a major change, as well as modified-release solid oral dosage form drug products.	CBE-30	Type IAIN
9.	A change of testing site for drug products, drug substances, or in-process materials.	CBE-30	Type IA
10.	A change in the manufacturing site for the production or processing of the last intermediate material.	CBE-0	Type IB
11.	A move to a different manufacturing site for the secondary packaging refers to the transfer of the packaging process, such as labeling, cartoning, or blistering, from one manufacturing site to another. This change can impact the packaging materials, the labeling process, or the final appearance of the product.	Ann. report	Type IAIN
12.	A change in manufacturing site for the purpose of labelling of drug products.	Ann. report	Type IB
13.	A change in the manufacturing site for the production or processing of drug substance intermediates that are not the final intermediate.	Ann. report	Type IB
14.	This refers to a change in the location where packaging components are sterilized under a contract with a third-party service provider, provided that the sterilization process used by the new site is not significantly different from the process described in the original approved application.	Ann. report	Type IB
15.	This refers to moving the production of a finished product that has been sterilized through terminal processes to a new building that has been recently constructed or to an existing building at the same manufacturing site.	Ann. report	Type IB
16.	A relocation to a different manufacturing facility for the imprinting of ink on solid oral dosage form drug products.	Ann. report	Type IB

3.3 Comparative Post Approval Regulatory Requirement of Manufacturing process[7,10,18-24]

Sr. no	Changes	USA	EU
1.	The changes that could impact the release, delivery or characteristics of the dose received by the patient, such as changes in controlled or modified-release, metering, or particle size. This also includes any addition or removal of a code imprint by embossing, debossing or engraving on a modified-release solid oral dosage form.	PAS	Type II
2.	Changes that may impact the safety of the drug product by affecting the removal or inactivation of viruses or adventitious agents or by altering the source material or cell line used for the drug substance or drug product. Specifically, changes to the methods used to remove or inactivate viruses or adventitious agents, changes to the source material (such as microorganisms or plants) or cell line, or the establishment of a new master cell bank or seed may require additional evaluation and testing to ensure the safety of the drug product.	PAS	Type II
3.	Changes that may affect drug product sterility assurance include changes in the container closure system, filling equipment, and aseptic processing procedures. Any changes that could potentially impact the sterility of the drug product must be thoroughly evaluated and validated to ensure that the product remains sterile and safe for patient use. Such changes would typically require submission of a supplement to the FDA for approval prior to implementing the change.	PAS	Type II
4.	Changes in the synthesis or manufacture of the drug substance can affect its impurity profile and physical, chemical, or biological properties, which can impact the safety and efficacy of the drug product. Therefore, such changes require evaluation and approval by the regulatory authorities before implementation.	PAS	Type II
5.	Any change in the process, process parameters, and/or equipment used in the manufacturing of drug products is considered a change that may impact the identity, strength, quality, purity, or potency of the product. Such changes may require regulatory approval before the modified product can be distributed in the market.	CBE-30	Type IA
6.	Any change in the process, process parameters, and/or equipment for natural protein drug substances and natural protein drug products may impact the physical, chemical, or biological properties of the product. Therefore, such changes need to be evaluated and approved by regulatory authorities before	CBE-30	Type IA

	implementing them. An increase or decrease in production scale during finishing steps that involves different equipment, and replacement of equipment with equipment of different design that does not affect the process methodology or process operating parameters are also considered as changes that require regulatory approval.		
7.	Changes to the dry heat depyrogenation processes used for glass container systems, changes to filtration parameters used in aseptic processing, changes to the filtration process that involve switching from a single sterilizing filter to dual filters in series or repeated filtration of a bulk are considered changes for sterile drug products, drug substances, and components. Changes from one validated sterilization chamber to another for in-process or terminal sterilization that result in changes to the operating parameters (such as time, temperature, and F0) are also considered changes. Additionally, changes in manufacturing scale for terminally sterilized drug products that result in an increase in bulk solution storage time of more than 50% beyond the validated limits are considered changes.	CBE-30	Type II
8.	A modification in the methods or controls that leads to an increase in the level of assurance can also be considered a change that requires approval. For instance, if a new analytical method or testing procedure is implemented, which provides improved accuracy or sensitivity in detecting impurities or contaminants, it may require approval as a change that impacts the quality of the drug product. Similarly, if new quality control measures or in-process controls are introduced, which can better monitor the manufacturing process and ensure consistent quality of the drug product, it may also require approval as a change that impacts the control strategy.	CBE-0	Type IA
9.	Elimination of in-process filtration for sterile drug products would be considered a significant change that requires evaluation and regulatory approval. In-process filtration is a critical step in ensuring the sterility of the product, and removing this step could potentially compromise the quality and safety of the product. Therefore, the elimination of in-process filtration would require a thorough evaluation of the potential impact on product quality and sterility assurance, and the implementation of alternative methods or controls to provide equivalent or improved assurance.	CBE-0	Type IA
10.	Changes to equipment of the same design and operating principle, as well as changes in scale, are considered changes that require evaluation and potential submission of a post-approval supplement (PAS). These changes may include changes in the size or capacity of equipment, changes in the type of equipment used for a process, or changes in the operating conditions of the equipment. Even if the new equipment is of the same design and principle as the	Ann. report	Type IA

	original equipment, it is still important to evaluate the potential impact of the change on the product quality, safety, and efficacy.		
11.	A minor change in an existing code imprint for a dosage form could be a change in the font size, font style, or location of the imprint that does not affect the release or performance of the drug.	Ann. report	Type IA
12.	Adding or removing a code imprint by embossing, debossing, or engraving on a solid dosage form drug product, except for modified-release dosage forms, would be considered a change that requires evaluation and potential approval by regulatory agencies.	Ann. report	Type IA
13.	For natural protein drug products and natural protein drug substances, an increase or decrease in production scale during finishing steps that does not involve an equipment change or replacement of equipment with equipment of the same design, operating principle, and capacity with no change in production scale are considered minor changes that may not require prior approval from regulatory authorities.	Ann. report	Type IA

3.4 Comparative Post Approval Regulatory Requirement of Specification[7,10,18-24]

Sr. no	Changes	USA	EU
1.	Relaxing an acceptance criterion	PAS	Type II
2.	Deleting any part of a specification	PAS	Type II
3.	Change outside the approved specification limits range	PAS	Type II
4.	Tightening of acceptance criteria	Ann. report	Type IA
5.	Addition of new test and limits	CBE-0	Type IA
6.	Addition or replacement of a specification parameter as a result of a safety or quality issue	CBE-0	Type IB
7.	Deletion of a non-significant specification parameter	CBE-0	Type IA
8.	A change in an analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency.	CBE-30	Type IB

3.5 Comparative Post Approval Regulatory Requirement of Container closure system[7,10,18-24]

Sr. no	Changes	USA	EU
1.	This refers to a change in the polymeric materials used for primary packaging components (such as bottles or containers) for liquid or semisolid dosage forms.	PAS	Type IB
2.	Change in the ink or adhesive used on permeable or semipermeable packaging components of liquid and semisolid dosage forms. Specifically, the change would be from an ink or adhesive that has been previously used and approved for the same dosage form and route of administration to a new ink or adhesive that has not been used in any approved drug product of the same type. This applies only when the packaging component is permeable or semipermeable.	PAS	Type IB
3.	Any modification to the primary packaging components of a drug product that affects the dose delivered to the patient.	PAS	Type II
4.	Any change that may affect the sterility assurance of a sterile drug product, including but not limited to the following changes: - Changing from a glass ampule to a glass vial with an elastomeric closure - Changing to a flexible container system (bag) from another container system - Changing to a prefilled syringe dosage form from another container system - Changing from a single unit dose container to a multiple dose container system - Adding or deleting silicone treatments to container closure systems - Changing the size and/or shape of a container for a sterile drug product.	PAS	Type II
5.	Removal of a packaging component that is not part of the primary packaging but provides extra protection to the drug product. It can also refer to any change made to the composition of an existing	PAS	Type II

	secondary packaging component or the addition of a new one that could potentially alter the impurity profile of the drug product.		
6.	If a different container closure system is used, it must provide the same or better protective properties than the approved container closure system.	PAS	Type II
7.	A change in the container closure system that does not impact the quality of the drug product.	CBE-30	Type IB
8.	Changes in the size or shape of a container for a sterile drug substance would be considered a change that requires regulatory approval. This is because any modification to the container can potentially impact the quality, safety, or efficacy of the drug substance. Therefore, regulatory authorities require that any changes to the container closure system be evaluated and approved before implementation.	CBE-30	Type IB
9.	A change in the quantity of units (such as tablets or capsules) or the labeled amount (such as grams or milliliters) of a non-sterile drug product in a single-use container.	CBE-30	Type IAIN (within the range) Type IB (outside the range)
10.	Change in the size and/or shape of a container for a nonsterile drug product without a change from one container closure system to another is considered a minor change. However, it is still subject to review and approval by the regulatory authorities. The change should be justified and the impact on the product quality and stability should be evaluated.	CBE-0	Type IA
11.	A change in the labelled amount of drug product for a nonsterile drug product in a multiple-unit container, except for solid dosage forms, would be considered a minor change.	CBE-0	Type IB
12.	A change, addition or deletion of a desiccant refers to any modification made to the packaging material that is designed to absorb moisture from the environment in order to maintain the quality of the drug product. This can include changes in the type, amount or placement of the desiccant within the packaging.	CBE-0	Type IA
13.	A change in the container closure system for a nonsterile drug product would typically be	Ann.	Type IA

	considered a major change, as it could affect the stability, efficacy, and safety of the drug product. The type of change and its impact on the drug product would need to be evaluated on a case-by-case basis.	report	
14.	A change in the size and/or shape of a container for a nonsterile solid dosage form is considered a change that may impact the drug product, and therefore would require regulatory approval before implementation.	Ann. report	Type IA
15.	A change in the number of units (e.g., tablets, capsules) or labelled amount (e.g., grams) of nonsterile solid dosage form in a multiple-unit container is considered a change in the drug product and requires evaluation and approval by regulatory authorities. The change may affect the quality, safety, and efficacy of the drug product, and thus it is important to assess and document the impact of the change.	Ann. report	Type IAIN (within range) Type IB(outside range)
16.	Here is a paraphrased version: Changes in the packaging of drug products are allowed as long as the new package provides the same or better protection for the product. Examples of changes that are allowed include adding or changing a child-resistant closure, changing from one plastic container to another of the same type of plastic, and changes in packaging materials used to control odor. Other changes such as increasing the wall thickness of the container, adding or changing a cap liner, adding or changing a seal, and changing certain components used in the production of the container and/or closure are also permitted. Additionally, a change to a new container closure system is allowed if the system has already been approved in the NDA or ANDA for other strengths of the drug product.	Ann. report	Type IA
17.	A modification in the colour of a flip seal cap is allowed as long as the new colour aligns with the existing colour coding system for the same type of drug products.	Ann. report	Type IAIN (If affect product info.) Type IA (if not affect product info.)

3.6 Comparative Post Approval Regulatory Requirement of Batch Size[7,11]

Sr. no	Changes	USA	EU
1.	Upto 10 fold increase compared to originally approved batch size	Ann. Report	IA
2.	More than 10 fold increase compared to originally approved batch size with same equipment/ operating principal	CBE-30	IB
3.	More than 10 fold increase compared to originally approved batch size with different equipment/ operating principal change	PAS	II

3.7 Comparative Post Approval Regulatory Requirement of Labelling[7,10,18-24]

Sr. no	Changes	USA	EU
1.	Changes based on post marketing study results, labelling changes associated with new indications and usage.	PAS	Type II
2.	Change in, or addition of, pharmacoeconomic claims based on clinical studies.	PAS	Type IB
3.	Changes to the clinical pharmacology or the clinical study section reflecting new or modified data.	PAS	Type IB
4.	Changes based on data from preclinical studies	PAS	Type II
5.	Revision (expansion or contraction) of population based on data	PAS	Type II
6.	Claims of superiority to another drug product.	PAS	Type II
7.	Change in the labelled storage conditions	PAS	Type IB

8.	Addition of an adverse event due to information reported to the applicant or Agency	CBE-0	Type II
9.	Addition of a precaution arising out of a post marketing study	CBE-0	Type IB
10.	Clarification of the administration statement to ensure proper administration of the drug product	CBE-0	Type IA
11.	Changes in the layout of the package or container label without a change in the content of the labelling.	Ann. report	Type IA
12.	Editorial changes, such as adding a distributor's name	Ann. report	Type IA

3.8 Comparative Post Approval Regulatory Requirement of Miscellaneous changes[7,10,18-24]

Sr. no	Changes	USA	EU
1.	Addition of a stability protocol or comparability protocol.	PAS	Type II
2.	Changes to an approved stability protocol or comparability protocol	PAS	Type IA
3.	An extension of an expiration dating period based on (1) data obtained under a new or revised stability testing protocol that has not been approved in the application or (2) full shelf life data on pilot scale batches using an approved protocol	PAS	Type IB
4.	Reduction of an expiration dating period to provide increased assurance of the identity, strength, quality, purity, or potency of the drug product. Extension of an expiration date that has previously been reduced under this provision should be submitted in a changes-being-effected-in-30-days supplement.	CBE-30	Type IAIN
5.	An extension of an expiration dating period based on full shelf life data on production batches obtained under a protocol approved in the application	Ann. report	Type IB

6.	Addition of time points to the stability protocol or deletion of time points beyond the approved expiration dating period	Ann. report	Type IB
7.	A change from previously approved stability storage conditions to storage conditions recommended in International Conference on Harmonization (ICH) guidance	Ann. report	Type IB
8.	Replacement of an in-house reference standard or reference panel according to procedures in an approved application	Ann. report	Type IA
9.	Tightening of acceptance criteria for existing reference standards to provide greater assurance of drug product purity and potency	Ann. report	Type IA

CHAPTER 6

CASE STUDY

4 CASE STUDY

4.1 Case study of Europe

4.1.1 Deutetrabenazine

There are variation in API and container closure system of Deutetrabenazine are listed below.

I. Quality changes of active substance

Test	**Existing system**	**Proposed change**	**Reason /Justification**	**Regulatory Reference / Reporting**	**Impact analysis**
. Content - of DEUTETRABENAZINE stage - III (By GC)	**Specification :** Not more than **0.10%** Method Code: **M36666** **Method of analysis by GC.**	**Specification :** Not more than **15 ppm** Method Code: **M67911** **Method of analysis by GC.**	DEUTETRABENAZINE stage-III is having structural alert for Genotoxicity. Hence it is decided to control this impurity with a limit of not more than 15 ppm. Existing method is not capable to	Type II	Method transfer to be done for the proposed method.

		Method of Analysis Changed.	detect the DEUTETRABENAZINE stage-III content with limit not more than 15 ppm, since the LOQ of this method is 0.01% (100 ppm). Hence new method is developed & validated with target limit not more than 15 ppm (Ref SPIL (Ahmednagar) STP No.: BD0409O0DF , Rev. No.: 1.0) (Attachment II : Justification report)		
. Residual Solvents (By GC)	**Specification :** Methanol : Not more than 2000 ppm	**Specification :** Methanol : Not more than 2000 ppm	LOD & LOQ established in method validation are not supporting to the current	Type II	Method transfer to be done.

	Isopropyl alcohol : Not more than 1000 ppm Ethyl acetate : Not more than 1000 ppm n-Hexane : Not more than 290 ppm Toluene : Not more than 500 ppm	Isopropyl alcohol : Not more than 1000 ppm Ethyl acetate : Not more than 1000 ppm n-Hexane : Not more than 290 ppm Toluene : Not more than 500 ppm Method of analysis changed.	specification limit, hence more sensitive method is developed using internal standard and validated. (Ref SPIL (Ahmednagar) STP No.: BD0409O0DF , Rev. No.: 1.0) (Attachment II : Justification report)		

II. Container closure

Test/Component	**Present**	**Proposed**	**Reporting**	**Reason /Justification**
Liner [Material of construction]	UNIPAC Folding Box Board PVDC 40 GSM X 0.90 MM	SELIG Folding Box Board PVDC 40 UP coating Single Side 0.90 MM	Type IA	Change in Vendor , but Product Contact layer remains same i.e. PVDC
Cap Dimensions				

Outer Diameter [in mm]	39.75 ± 0.25	39.9 ± 0.25		Tolerance tightened as per supplier's specification
Total Height(Overall) mm	17.62 ± 0.25	17.65±0.25		Minor increase in Height as per supplier's specification
Inner Diameter (without Thread) mm	30.00 ± 0.25	30.00 ± 0.20		Tolerance tightened as per supplier's specification
Inner Diameter (with Thread) mm	32.40 ± 0.25	32.40 ± 0.20		Tolerance tightened as per supplier's specification
Description - of Cap Pictorial View	In Old drawing both ARROWS and ENGLISH TEXT DESIGN is mentioned & supplied	In new drawing VISUAL representation showing HANDS & ARROWS is mentioned		Now Supplier will supply only with VISUAL representation showing HANDS & ARROWS

4.1.2 Pantoprazole

TYPE II

- Change in the specification parameters and/or limits of the finished product

Existing Specification		**Proposed Specification**	
Test	**Shelf-life specification**	**Test**	**Shelf-life specification**
Related substances	a)Known impurities: Impurity A: NMT 0.2% Impurity B: NMT 0.2% Impurity C: NMT 0.2%	Related substances	a)Known impurities: Impurity A: NMT 0.2% Impurity B: NMT 0.2% Impurity C: NMT 0.2%

	Impurity D and F : NMT 0.5% Impurity E : NMT 0.2% b) Any unknown impurity : NMT 0.2% **c) Total impurities** **(Known + unknown) : NMT 1.0%**		**Impurity D and F : NMT 1.0%** Impurity E : NMT 0.2% b) Any unknown impurity : NMT 0.2% **c) Total impurities** **(Known + unknown) : NMT 1.5%**
Assay	**Between 95.0% and 105.0% of label claim.**	Assay	Content of pantoprazole sodium(sesquihydrate) eq to pantoprazole **Between 94.0% and 105.0% of label claim.**

- Change in batch size

Existing Changes	**Proposed Changes**
batch size of 45 L Pantoprazole 40 mg, powder for Solution for injection corresponding to approximately 24000 vials	batch size of 45 L Pantoprazole 40 mg, powder for Solution for injection corresponding to approximately 24000 vials
batch size of 105 L Pantoprazole 40 mg, powder for Solution for injection corresponding to approximately 52500 vials	batch size of 105 L Pantoprazole 40 mg, powder for Solution for injection corresponding to approximately 52500 vials
batch size of 112 L Pantoprazole 40 mg, powder for Solution for injection corresponding to approximately 56000 vials	batch size of 112 L Pantoprazole 40 mg, powder for Solution for injection corresponding to approximately 56000 vials
	batch size of 190 L Pantoprazole 40 mg, powder for Solution for injection corresponding to approximately 95000 vials

TYPE IB

- Change in Shelf life

  Extension of Shelf life from **18 months to 24 months**

- IPC product parameters: Deletion of a non-significant in-process test

Existing		**Proposed**	
Control parameter	**Specification**	**Control parameter**	**Specification**
Description	A clear colourless solution		
pH	Between 9.0 and 11.5		
Absorbance at 420 nm	NMT 0.05 AU		
% Transmittance at 650 nm	NLT 97.0%		
Weight per ml	Between 0.99 to 1.02 g/ml		
Microbiological quality Total aerobic microbial count:	Total aerobic count : Alert limit: Not more than 25 CFU/20 ml. Action limit : Not more than 50 CFU/20 ml.	Microbiological quality Total aerobic microbial count:	Total aerobic count : Alert limit: Not more than 25 CFU/20 ml. Action limit : Not more than 50 CFU/20 ml.
Assay	95.0-105.0% of label claim		

TYPE IA

- Change in supplier of packaging components
- Change in test procedure for API

IR Identification test procedure	
Existing	**Proposed**
Triturate 1-2 mg of substance with 300-400 mg of finely powdered and dried potassium bromide. Transfer the triturated mixture to the sample holder and record the IR spectrum of sample in the region of 4000-650 cm-1.Similarly prepare triturated mixture of working standard and record the IR	Triturate 1-2 mg of substance with 300-400 mg of finely powdered and dried potassium bromide. Carefully grind the mixture, spread it uniformly in a suitable die and make a disc using pellet maker and record the IR spectrum of sample in the region of 4000-650 cm-1. In the similar manner, prepare

spectrum under same operational conditions. The transmission minima (absorption maxima) in the spectrum obtained with the substance correspond in position and relative size to those in spectrum obtained with the working standard.	the standard and record the IR spectrum under same operational conditions. The transmission minima (absorption maxima) in the spectrum obtained with the substance correspond in position and relative size to those in spectrum obtained with the working standard.

4.1.3 Letrozole

TYPE IA

- Addition of a new specification parameter to the specification with its corresponding test method

Existing		**Proposed**			
Test	**Specification**	**Test**	**Specification**	**Test**	**Specification**
Description	112 mm 25 Mic Push through Al Foil with 6-8 GSM Heat Seal Lacquer. The dull side of the foil is coated with Nitrocellulose Base Lacquer & the bright side is coated with vinyl base HSL.	Description	212 mm 25 Mic Push through Al Foil with 6-8 GSM Heat Seal Lacquer. The dull side of the foil is coated with Nitrocellulose Base Lacquer & the bright side is coated with vinyl base HSL.	Description	226 mm 25 Mic Push through Al Foil with 6-8 GSM Heat Seal Lacquer. The dull side of the foil is coated with Nitrocellulose Base Lacquer & the bright side is coated with vinyl base HSL.
Material of construction	Al alloy: Chemical composition Dull side Al: Lacquer: Nitrocellulose Base	Material of construction	Al alloy: Chemical composition Dull side Al: Lacquer: Nitrocellulose Base	Material of construction	Al alloy: Chemical composition Dull side Al: Lacquer: Nitrocellulose Base

	Bright side Al: Heat Seal Lacquer: vinyl base		Bright side Al: Heat Seal Lacquer: vinyl base		Bright side Al: Heat Seal Lacquer: vinyl base
Visual Inspection	Push through lidding foil rolls should be free from following visual defects: Damaged rolls Oil, grease and dirt on rolls Telescoping	Visual Inspection	Push through lidding foil rolls should be free from following visual defects: Damaged rolls Oil, grease and dirt on rolls Telescoping	Visual Inspection	Push through lidding foil rolls should be free from following visual defects: Damaged rolls Oil, grease and dirt on rolls Telescoping
		Identification by IR	IR of heat seal lacquer shall be concordant with the standard IR of the specimen attached with the specification	Identification by IR	IR of heat seal lacquer shall be concordant with the standard IR of the specimen attached with the specification
Width	111 – 113 mm	Dimension-total width	211 – 213 mm	Dimension-total width	225 – 227 mm
Total GSM of foil	69 – 80 gsm	Grammage of Total GSM foil	70 – 81 gsm	Grammage of Total GSM foil	70.30 – 81.30 gsm
GSM of Al foil	63.7 – 71.9 gsm	Grammage of Al foil	63.50 - 71.60 gsm	Grammage of Al foil	63.50 - 71.60 gsm
GSM of heat seal lacquer	6 – 8 gsm	Grammage of heat seal lacquer	6 – 8 gsm	Grammage of heat seal lacquer	6 – 8 gsm
Thickness of Al foil	23 – 27 micron	Thickness of Al foil	24 – 27 micron	Thickness of Al foil	24 – 27 micron

			Thickness of foil	30.10 – 35.90 micron
	Pin hole test	Impression should not found on the back paper	Pin hole test	Impression should not found on the back paper

- Change in batch size

Existing	**Proposed**
Batch size of 15 kg letrozole 2.5 mg, corresponding to approximately 1,50,000 tablets	Batch size of 15 kg letrozole 2.5 mg, corresponding to approximately 1,50,000 tablets
Batch size of 60 kg letrozole 2.5 mg, corresponding to approximately 6,00,000 tablets	Batch size of 60 kg letrozole 2.5 mg, corresponding to approximately 6,00,000 tablets
	Batch size of 120 kg letrozole 2.5 mg, corresponding to approximately 12,00,000 tablets

TYPE IAIN

Addition of secondary packaging site

Below addressed site is manufacturing, testing [including stability], packing and storage site for the Letrozole 2.5 mg Film-coated Tablets: **SUN Pharmaceutical Industries Ltd.** Halol-Baroda highway, Halol-389350 Gujarat India.	Below addressed site is manufacturing, testing [including stability], packing and storage site for the Letrozole 2.5 mg Film-coated Tablets: **SUN Pharmaceutical Industries Ltd.** Halol-Baroda highway, Halol-389350 Gujarat India.
	Packaging (secondary) of the finished product: 1. Company Name: **Biokanol Pharma** Address: Kehler str. 7 76437 Rastatt

	Country: Germany 2. Company name: **Central Pharma (Contract Packaging) Limited** Address: Caxton Road Bedford Bedfordshire MK041 0XZ Country: United Kingdom

4.1.4 Venlafaxine

TYPE IB

- Change in batch size

Existing	**Proposed**
Venlafaxine 37.5 mg prolonged release tablet	
Batch size of 56.620 kg, Venlafaxine 37.5 mg corresponding to approximately 3,80,000 tablets	Batch size of 56.620 kg, Venlafaxine 37.5 mg corresponding to approximately 3,80,000 tablets
Batch size of 230.950 kg, Venlafaxine 37.5 mg corresponding to approximately 15,50,000 tablets	Batch size of 230.950 kg, Venlafaxine 37.5 mg corresponding to approximately 15,50,000 tablets
	Batch size of 32.780 kg, Venlafaxine 37.5 mg corresponding to approximately 2,20,000 tablets
Venlafaxine 75 mg prolonged release tablet	
Batch size of 149.000 kg, Venlafaxine 75 mg corresponding to approximately 5,00,000 tablets	Batch size of 149.000 kg, Venlafaxine 75 mg corresponding to approximately 5,00,000 tablets
Batch size of 56.620 kg, Venlafaxine 75 mg corresponding to approximately 1,90,000 tablets	Batch size of 56.620 kg, Venlafaxine 75 mg corresponding to approximately 1,90,000 tablets
Batch size of 715.200 kg, Venlafaxine 75 mg corresponding to approximately 24,00,000 tablets	Batch size of 715.200 kg, Venlafaxine 75 mg corresponding to approximately 24,00,000 tablets

	Batch size of 238.400 kg, Venlafaxine 75 mg corresponding to approximately 8,00,000 tablets
Venlafaxine 150 mg prolonged release tablet	
Batch size of 113.240 kg, Venlafaxine 150 mg corresponding to approximately 1,90,000 tablets	Batch size of 113.240 kg, Venlafaxine 150 mg corresponding to approximately 1,90,000 tablets
Batch size of 685.400 kg, Venlafaxine 150 mg corresponding to approximately 11,50,000 tablets	Batch size of 685.400 kg, Venlafaxine 150 mg corresponding to approximately 11,50,000 tablets

- Change in composition of finished product

Existing		**Proposed**	
Name of ingredient	Quantity	Name of ingredient	Quantity
SUSTAINED RELEASE LAYER		**SUSTAINED RELEASE LAYER**	
Granulation		Granulation	
Venlafaxine Hydrochloride	84.855	Venlafaxine Hydrochloride	84.855
Hypromellose (Methocel K4M CR premium,2208)	**16.500**	**Hypromellose (Methocel K4M CR premium,2208)**	**18.000**
Povidone (K-30)	20.000	Povidone (K-30)	20.000
Lactose Monohydrate (Pharmatose 200 M)	**87.645**	**Lactose Monohydrate (Pharmatose 200 M)**	**86.145**
Granulating fluid		Granulating fluid	
Purified water	---	Purified water	---
Lubrication		Lubrication	
Methacrylic Acid-Ethyl Acrylate Co polymer (1:1) – (Eudragit L 100-55)	20.000	Methacrylic Acid-Ethyl Acrylate Co polymer (1:1) – (Eudragit L 100-55)	20.000
Purified Talc	1.500	Purified Talc	1.500
Magnesium Stearate	1.500	Magnesium Stearate	1.500

Weight of Sustained Release layer	232.000	Weight of Sustained Release layer	232.000
OPENABLE LAYER		**OPENABLE LAYER**	
Blend for slugging		Blend for slugging	
Silicified Microcrystalline cellulose [Prosolv SMCC 90]	52.865	Silicified Microcrystalline cellulose [Prosolv SMCC 90]	52.865
Crospovidone (Polyplasdone XL)	9.900	Crospovidone (Polyplasdone XL)	9.900
Colloidal Anhydrous silica	1.650	Colloidal Anhydrous silica	1.650
Sodium Lauryl Sulphate	0.660	Sodium Lauryl Sulphate	0.660
FD and C Red No.40 Aluminium Lake (38-42%) / Allura red (E 129)	0.066	FD and C Red No.40 Aluminium Lake (38-42%) / Allura red (E 129)	0.066
Lubrication before slugging		Lubrication before slugging	
Magnesium stearate	0.530	Magnesium stearate	0.530
Sub total	65.670	Sub total	65.670
Lubrication after slugging		Lubrication after slugging	
Magnesium stearate	0.165	Magnesium stearate	0.165
Purified talc	0.165	Purified talc	0.165
Weight of openable layer	66.000	Weight of openable layer	66.000
BILAYER TABLET		**BILAYER TABLET**	
Weight of bilayered tablet	298.000	Weight of bilayered tablet	298.000
Functional coating		Functional coating	
Ethyl cellulose Aqueous Dispersion (Aquacoat ECD-30)	15.586	Ethyl cellulose Aqueous Dispersion (Aquacoat ECD-30)	15.586
Mannitol (Mannitol 25)	2.806	Mannitol (Mannitol 25)	2.806

Povidone (K-30)	0.701	Povidone (K-30)	0.701
Dibutyl Sebacate	3.897	Dibutyl Sebacate	3.897
Triethyl Citrate	0.779	Triethyl Citrate	0.779
Polysorabate 20	0.070	Polysorabate 20	0.070
Purified Water	---	Purified Water	---
Total	321.840	Total	321.840
Top coating		Top coating	
Opadry II 85F19250 clear	14.483	Opadry II 85F19250 clear	14.483
Purified water	---	Purified water	---
Coated tablet weight	336.323	Coated tablet weight	336.323
Tablet printing		Tablet printing	
Opacode- S-1-17823 Black	---	Opacode- S-1-17823 Black	---
Isopropyl Alcohol	---	Isopropyl Alcohol	---

TYPE IA

- Tightening of specification limits

Existing			**Proposed**		
Parameter	Finished product specification		Parameter	Finished product specification	
	Release limit	Shelf life limit		Release limit	Shelf life limit
Description	Oval, pink and white colored biconvex bilayer coated tablet imprinted with “758” with black ink on one side and plain on the other side.	Oval, pink and white colored biconvex bilayer coated tablet imprinted with “758” with black ink on one side and plain on the other side.	Description	Oval, pink and white colored biconvex bilayer coated tablet imprinted with “758” with black ink on one side and plain on the other side.	Oval, pink and white colored biconvex bilayer coated tablet imprinted with “758” with black ink on one side and plain on the other side.

Identification			Identification		
By HPLC	The retention time of the major peak in the chromatogram of the sample preparation corresponds to that exhibited in the chromatogram of the Standard preparation as obtained in the Assay.	The retention time of the major peak in the chromatogram of the sample preparation corresponds to that exhibited in the chromatogram of the Standard preparation as obtained in the Assay.	By HPLC	The retention time of the major peak in the chromatogram of the sample preparation corresponds to that exhibited in the chromatogram of the Standard preparation as obtained in the Assay.	The retention time of the major peak in the chromatogram of the sample preparation corresponds to that exhibited in the chromatogram of the Standard preparation as obtained in the Assay.
By IR	The infrared absorption spectrum of potassium bromide dispersion of sample exhibits bands at about 1512, 1242, 1178, 829 cm-1 and at 770 cm -1, similar to the standard preparation.	The infrared absorption spectrum of potassium bromide dispersion of sample exhibits bands at about 1512, 1242, 1178, 829 cm-1 and at 770 cm -1, similar to the standard preparation.	By IR	The infrared absorption spectrum of potassium bromide dispersion of sample exhibits bands at about 1512, 1242, 1178, 829 cm-1 and at 770 cm -1, similar to the standard preparation.	The infrared absorption spectrum of potassium bromide dispersion of sample exhibits bands at about 1512, 1242, 1178, 829 cm-1 and at 770 cm -1, similar to the standard preparation.
Color identification	The absorption spectrum of sample preparation exhibits maxima at same wavelength	The absorption spectrum of sample preparation exhibits maxima at same wavelength	Color identification	The absorption spectrum of sample preparation exhibits maxima at same wavelength	The absorption spectrum of sample preparation exhibits maxima at same wavelength

	as that observed in standard preparation.	as that observed in standard preparation.		as that observed in standard preparation.	as that observed in standard preparation.
Average weight	Between 655.48 mg and 696.03 mg	Between 655.48 mg and 696.03 mg	Average weight	Between 655.48 mg and 696.03 mg	Between 655.48 mg and 696.03 mg
% Variation from standard weight	(Standard weight: 675.76mg) ± 3.0% of standard weight.	(Standard weight: 675.76mg) ± 3.0% of standard weight.	% Variation from standard weight	(Standard weight: 675.76mg) ± 3.0% of standard weight.	(Standard weight: 675.76mg) ± 3.0% of standard weight.
Drug release	For 1 hour At L1, Not more than 20% release of label claim. At L2, (L1+L2), average of 12 units should not be more than 20% release of label claim and no unit is more than 30%. **At L3, (L1 + L2 + L3) the average of 24 units should not be more than 20% release of label claim and not more than two units are more**	For 1 hour At L1, Not more than 20% release of label claim. At L2, (L1+L2), average of 12 units should not be more than 20% release of label claim and no unit is more than 30%. At L3, (L1 + L2 + L3) the average of 24 units should not be more than 20% release of label claim and not more than two units are more than	Drug release	For 1 hour At L1, Not more than 20% release of label claim. At L2, (L1+L2), average of 12 units should not be more than 20% release of label claim and no unit is more than 30%.	For 1 hour At L1, Not more than 20% release of label claim. At L2, (L1+L2), average of 12 units should not be more than 20% release of label claim and no unit is more than 30%. At L3, (L1 + L2 + L3) the average of 24 units should not be more than 20% release of label claim and not more than two units are more than

	than 30% and no unit is more than 40%. For 4 hours At L1, no unit lies outside 20 %- 40% release of label claim. At L2, (L1+L2), average of 12 units lies between 20 %-40% and none is outside the range of 10 %-50% release of label claim. **At L3, (L1 + L2 + L3) the average of 24 units lies between 20% - 40%. Not more than 2 of 24 units lies outside the range of** **10% - 50% and no unit is more than 60% release of label claim.** For 8 hours	30% and no unit is more than 40%. For 4 hours At L1, no unit lies outside 20 %- 40% release of label claim. At L2, (L1+L2), average of 12 units lies between 20 %-40% and none is outside the range of 10 %-50% release of label claim. At L3, (L1 + L2 + L3) the average of 24 units lies between 20% - 40%. Not more than 2 of 24 units lies outside the range of 10% - 50% and no unit is more than 60% release of label claim.		For 4 hours At L1, no unit lies outside 20 %- 40% release of label claim. At L2, (L1+L2), average of 12 units lies between 20 %-40% and none is outside the range of 10 %-50% release of label claim.	30% and no unit is more than 40%. For 4 hours At L1, no unit lies outside 20 %- 40% release of label claim. At L2, (L1+L2), average of 12 units lies between 20 %-40% and none is outside the range of 10 %-50% release of label claim. At L3, (L1 + L2 + L3) the average of 24 units lies between 20% - 40%. Not more than 2 of 24 units lies outside the range of 10% - 50% and no unit is more than 60% release of label claim.

	At L1, no unit lies outside 40% - 65% release of label claim. At L2, (L1+L2), average of 12 units lies between 40% -65% and none is outside the range of 30% - 75% release of label claim. **At L3, (L1 + L2 + L3) the average of 24 units lies between 40% - 65%. Not more** **than 2 of 24 units lies outside** **the range of 30% -75% and no** **unit is outside the range of** **20%-85% release of label claim.** For 20 hours At L1, each unit is not less than 80% release	For 8 hours At L1, no unit lies outside 40% - 65% release of label claim. At L2, (L1+L2), average of 12 units lies between 40% -65% and none is outside the range of 30% - 75% release of label claim. At L3, (L1 + L2 + L3) the average of 24 units lies between 40% - 65%. Not more than 2 of 24 units lies outside the range of 30% -75% and no unit is outside the range of 20%-85% release of label claim. For 20 hours		For 8 hours At L1, no unit lies outside 40% - 65% release of label claim. At L2, (L1+L2), average of 12 units lies between 40% -65% and none is outside the range of 30% - 75% release of label claim.	For 8 hours At L1, no unit lies outside 40% - 65% release of label claim. At L2, (L1+L2), average of 12 units lies between 40% -65% and none is outside the range of 30% - 75% release of label claim. At L3, (L1 + L2 + L3) the average of 24 units lies between 40% - 65%. Not more than 2 of 24 units lies outside the range of 30% -75% and no unit is outside the range of 20%-85% release of label claim. For 20 hours

	of label claim. At L2, (L1+L2), average of 12 units are not less than 80% and no unit is less than 70% release of label claim. **At L3, (L1 + L2 + L3) the** **average of 24 units are not less than 80% .Not more than 2 of 24 units are less than 70% and no unit is less than 60% release of label claim.**	At L1, each unit is not less than 80% release of label claim. At L2, (L1+L2), average of 12 units are not less than 80% and no unit is less than 70% release of label claim. At L3, (L1 + L2 + L3) the average of 24 units are not less than 80% .Not more than 2 of 24 units are less than 70% and no unit is less than 60% release of label claim.		For 20 hours At L1, each unit is not less than 80% release of label claim. At L2, (L1+L2), average of 12 units are not less than 80% and no unit is less than 70% release of label claim.	At L1, each unit is not less than 80% release of label claim. At L2, (L1+L2), average of 12 units are not less than 80% and no unit is less than 70% release of label claim. At L3, (L1 + L2 + L3) the average of 24 units are not less than 80% .Not more than 2 of 24 units are less than 70% and no unit is less than 60% release of label claim.
Uniformity of Dosage Units by	For n = 10 Acceptance value of the 10 dosage units is less	For n = 10 Acceptance value of the 10 dosage units is less	Uniformity of Dosage Units by	For n = 10 Acceptance value of the 10 dosage units is less	For n = 10 Acceptance value of the 10 dosage units is less

Content Uniformity	than or equal to L1% For n = 30, Final acceptance value of the 30 dosage units is less than or equal to L1% and no individual content of the dosage unit is less than [1-(L2) (0.01)] M nor more than [1+(L2) (0.01)] M L1 is 15.0 and L2 is 25.0.	than or equal to L1% For n = 30, Final acceptance value of the 30 dosage units is less than or equal to L1% and no individual content of the dosage unit is less than [1-(L2) (0.01)] M nor more than [1+(L2) (0.01)] M L1 is 15.0 and L2 is 25.0.	Content Uniformity	than or equal to L1% For n = 30, Final acceptance value of the 30 dosage units is less than or equal to L1% and no individual content of the dosage unit is less than [1-(L2) (0.01)] M nor more than [1+(L2) (0.01)] M L1 is 15.0 and L2 is 25.0.	than or equal to L1% For n = 30, Final acceptance value of the 30 dosage units is less than or equal to L1% and no individual content of the dosage unit is less than [1-(L2) (0.01)] M nor more than [1+(L2) (0.01)] M L1 is 15.0 and L2 is 25.0.
Related substances (By HPLC)			Related substances (By HPLC)		
Any single impurity	Not more than 0.15%	Not more than 0.2%	Any single impurity	Not more than 0.15%	Not more than 0.2%
Total impurities	Not more than 0.5%	Not more than 0.75%	Total impurities	Not more than 0.5%	Not more than 0.75%
Loss on drying	Not more than 5.5%	Not more than 6.5%	Loss on drying	Not more than 5.5%	Not more than 6.5%
Assay by HPLC	Not less than 95.0% and not more than 105.0% of label amount of venlafaxine.	Not less than 95.0% and not more than 105.0% of label amount of venlafaxine.	Assay by HPLC	Not less than 95.0% and not more than 105.0% of label amount of venlafaxine.	Not less than 95.0% and not more than 105.0% of label amount of venlafaxine.
Microbial limit test			Microbial limit test		

Total aerobic	Not more than 1000 cfu/g	Not more than 1000 cfu/g	Total aerobic	Not more than 1000 cfu/g	Not more than 1000 cfu/g
Combined yeast & molds	Not more than 100 cfu/g	Not more than 100 cfu/g	Combined yeast & molds	Not more than 100 cfu/g	Not more than 100 cfu/g
Escherichia coli	Should be absent	Should be absent	Escherichia coli	Should be absent	Should be absent
Salmonella species	Should be absent	Should be absent	Salmonella species	Should be absent	Should be absent

4.2 Case study of USA

4.2.1 Pantoprazole Sodium for Injection

Following are the impurities related changes. There is relaxation in specification and deletion of some test.

PAS submission

Existing Specification			**Proposed Specification**		
Test	**Release**	**Stability**	**Test**	**Release**	**Stability**
Related Substance (by HPLC)			Related Substance (by HPLC)		
Known Impurities			Known Impurities		
Related compound A	NMT 0.2%	NMT 0.2%	Related compound A	NMT 0.2%	NMT 0.2%
Related compound B	NMT 0.15%	NMT 0.2%	Related compound B	NMT 0.15%	NMT 0.2%
Related compound C	NMT 0.15%	NMT 0.2%	Related compound C	NMT 0.15%	NMT 0.2%
			Pantoprazole N-oxide impurity	**NMT 0.1%**	**NMT 0.2%**
Related compound D & F	NMT 0.2%	**NMT 0.5%**	Related compound D & F	NMT 0.2%	**NMT 0.9%**
Unknown Impurities			Unknown Impurities		
Any other individual impurities	NMT 0.15%	NMT 0.2%	Any other individual impurities	NMT 0.15%	NMT 0.2%
Total Impurities	NMT 0.75%	**NMT 1.0%**	Total Impurities	NMT 0.75%	**NMT 1.4%**
Content of Pantoprazole N-oxide impurity (by LCMS)					
Pantoprazole N-oxide impurity	**NMT 2 ppm**	**NMT 6.25ppm**			

4.2.2 Pantoprazole Sodium for Delayed-Release Oral Suspension

CBE-30 Supplement

There are deletion of some identification test of pantoprazole sodium which are included below.

Test	Existing	Proposed	Justification
IDENTIFICATION			
By IR	The infrared absorption spectrum of the sample must be concordant with that of a similar preparation of Sodium Lauryl sulphate working standard.	The infrared absorption spectrum of the sample must be concordant with that of a similar preparation of Sodium Lauryl sulphate working standard.	In the current USP monograph of sodium lauryl sulphate, three Identification tests i.e. by IR, by test for Sodium and by test for Sulphate have been mentioned. Accordingly, **Two Identification tests by chemical shall be deleted to maintain the specifications in line with USP monograph.**
By test for Sodium	A white crystalline precipitate is formed.	A white crystalline precipitate is formed.	
By test for Sulphate	Meets the requirement.	Meets the requirement.	
By Chemical	A copious foam is formed.	-	
By Chemical	An intense blue colour develops in the methylene chloride layer.	-	
HEAVY METALS			
HEAVY METALS	NMT 20	-	**Test deleted** inline with USP monograph.

(ppm) (Method II)			

4.2.3 Testosterone Cypionate injection USP

Following are the post approval changes for testosterone cypionate injection. Changes have been included for PAS, CBE and AR for the same.

PAS submission

- Removal of in process testing (content of Testosterone Cypionate, content of benzyl alcohol, content of benzyl benzoate) of bulk solution for commercial batches.
- Dry heat depyrogenation (DHS) tunnel SH125 (make: Groninger) has been specified in approved ANDA. The current supplement proposes new SHI005 DHS tunnel (make: Bausch & Strobel). Design and operating principal for new tunnel SHI005 is same as SH125.

  Comparison of operating parameters and validation parameters of DHS SHI005 with DHS SH125 is provided below.

Vial size 12.5 mL (for 10 mL vial)

Depyrogenation parameters	**DHS tunnel SH125**		**DHS tunnel SHI005**	
	Process	**Performance qualification**	**Process**	**Performance qualification**
Vial size	12.5ml	12.5ml	12.5ml	12.5ml
HZ set point (°C) (HT Inlet temperature)	320 °C ± 2°C*	320 °C ± 2°C*	320 °C	320 °C
Conveyer speed (mm/minute)	105	110	132	132

* Temperature± 2°C is for heater on/off to maintain the set HT (Hot Zone) temperature

Vial size 2 mL (for 1 mL vial)

Depyrogenation parameters	**DHS tunnel SH125**	**DHS tunnel SHI005**

	Process	**Performance qualification**	**Process**	**Performance qualification**
Vial size	2ml	2ml	2ml	2ml
HZ set point (°C) (HT Inlet temperature)	320 °C ± 2°C*	320 °C ± 2°C*	320 °C	320 °C
Conveyer speed (mm/minute)	35	40	76	76

* Temperature± 2°C is for heater on/off to maintain the set HT (Hot Zone) temperature

CBE-30

Current API Submission	**DMF submitted API submission**	**Justification**
Chromatographic conditions: Column: Poroshell EC 18, (150 x 4.6) mm, 2.7 µ Make: Agilent, Part No. : 695975-902. Flow rate : : 1.0 mL/min Wavelength : 254 nm Run time : 120 min Injection volume : 10 µL Column temp : 60 °C Sample temp : 5 °C Needle wash solvent: Methanol Needle wash type: Double Use Ghost- buster column at the pump head after in line filter. (Make : WELCH, Dimension : 4.6 X 50	Chromatographic conditions: Column : YMC-Pro C18, (250 x 4.0) mm, 3µ Flow rate : 0.7 ml/min Wavelength : 254 nm Run time : 95 min Injection volume : 10 µl Column temp : 50°C	Chromatographic conditions are revised for better separation of unknown impurity peaks in Related substances method.

mm , Part No.- 06100-31000)		
Co-distillation : One additional co-distillation is to be incorporated in the manufacturing process with 0.5 v/w Methylene Chloride (w.r.t Cyclopentyl propionic acid) followed by degassing for 6 hours at 40-45°C under vacuum to ensure effective removal of Thionyl chloride from Cyclopentyl propionyl chloride.	Co-distillation : After distillation there is provision for co-distillation as follows; Distill out Methylene Chloride + Thionyl Chloride completely from the reactor under vacuum below 45°C within 180 min.	Additional co-distillation is included to remove traces of Thionyl chloride for better quality control.
Drying: Dry the product for 360 min. between 45~50°C under vacuum. Milling process is included after drying, then further dry the material for 120 min between 45~50°C, under vacuum. After drying check in-process LOD.	Drying : Dry the product for 480 min. between 45~50°C under vacuum. After drying check in-process LOD.	Milling process is included after 360 minutes drying to get homogenized material.

CBE-0

- Storage statement has been revised to:

  "Vials should be stored at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature]." to "Vials should be stored at controlled room temperature 20° to 25°C (68° to 77°F) [see USP]."

- Change in net content statement:

  The net content statement "l mL vial" & "One 1 mL vial" have been revised to "1 mL Single-dose vial" & "One 1 mL Single-dose vial" respectively.

Annual Report

- Change in US Agent contact

4.2.4 Zolpidem Tartrate Extended-Release Tablets

PAS

- Removal of in-process testing (water content, particle size, bulk density and tapped density) of granules for commercial batches.
- Removal of blend uniformity in-process testing for commercial batches.

CBE-30

- Change in specification limit of particle size determination of RTC granules for Immediate Release layer (IR)

Specification	**Existing**	**Proposed**
% retained on #40 mesh	Not more than 20%	Not more than 20%
Cumulative %retained on #100 mesh	20% to 50%	Not more than 70%
% passed through #200 mesh	Not more than 45%	Not more than 60%

- Change in D 90 specification of particle size in Zolpidem Tartrate USP

Specification	**Existing**	**Proposed**
D10	Not more than 6µ	Not more than 6µ
D50	Between 10µ and 40µ	Between 10µ and 40µ
D90	Between 70µ and 120µ	Between 40 µ and 100µ

- Change in analytical method of particle size in Zolpidem Tartrate USP

In approved ANDA, test of particle size was determined by dry powder method. This supplement provides revision in method for particle size distribution from dry powder method to wet dispersion method for following reasons.

1. Inconsistency and variability in results is observed using dry powder method.
2. Zolpidem tartarate is hygroscopic in nature, so dry powder method is not suitable for analysis.

Method	**Existing: Dry powder Method**	**Proposed: Wet dispersion method**

	D10 (µm)	D50 (µm)	D90 (µm)	D10 (µm)	D50 (µm)	D90 (µm)
Sample 1	3.69	17.93	85.77	4.395	33.14	82.71
Sample 2	3.49	16.17	83.22	4.190	31.71	79.05
Sample 3	3.79	18.59	89.53	4.527	34.52	84.56
Sample 4	4.29	24.93	99.17	4.285	33.04	81.11
Sample 5	4.54	30.75	110.18	4.583	35.09	85.79
Sample 6	3.66	17.6	87.67	4.467	34.23	83.02
Average	3.91	21.00	92.59	4.40	33.62	82.71
%RSD	10.5	27.0	11.0	3.4	3.7	2.9
Limit %RSD	30%	10%	10%	30%	10%	10%

CBE-0

- Change in ampere load limit at granulation stage for 12.5 mg

Product name and strength	**Ampere load at granulation stage (Ampere)**	
	Existing	**Proposed**
Zolpidem Tartrate Extended-Release Tablets USP, 12.5 mg	11-16	17-27

CHAPTER 7

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