

Telephone number: Fax number: E-mail:

**NOTIFICATION/APPLICATION FORM FOR VARIATIONS TO AUTHORISED HUMAN MEDICINAL  
PRODUCTS İRD-FR-29 / 31.12.2019 / Rev.02-13.01.2022**

Version 2 13.01.2022

**NOTIFICATION/APPLICATION FORM FOR VARIATIONS TO AUTHORISED HUMAN MEDICINAL  
PRODUCTS**

Revision History Version No Date of Entry into Force Description 1 20.12.2021 First publication 2 13.01.2022 Fields designated as "application" were corrected to "notification/application". The reference to the relevant regulation article for unforeseen variations was specified only as Article 5. A section explaining the transition to implementation was added. Editorial arrangements were made.

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**NOTIFICATION/APPLICATION FORM FOR VARIATIONS TO AUTHORISED HUMAN MEDICINAL  
PRODUCTS**

**İRD-FR-29 / 31.12.2019 / Rev.02-13.01.2022**

**1. NOTIFICATION/APPLICATION FOR A VARIATION TO AUTHORISED HUMAN MEDICINAL  
PRODUCTS**

**Notification/Application type (tick all applicable options)**

**Single variation**

**Grouped variations**

**Type IA immediate**

**Type IA**

**Type IB unforeseen**

**\***

**Type IB**

**Type II**

**The change(s) concerns**

**Medical Device Presented Together with a Human Medicinal Product**

\* If the proposed variation has not been classified as a Type IB minor variation according to the classification guideline or pursuant to Article 5 of the relevant regulation, it is defined as "unforeseen". If the change does not meet one or more of the conditions required for the change to be a Type IA variation under the guideline and cannot be classified as a Type II major variation, a Type IB variation may be submitted for the change.

Matters to which the changes relate (only for Type IB and Type II variations, all applicable changes may be ticked) Indication Safety Quality Annual change for human influenza vaccines Other

Name and address of the marketing authorisation holder:

Name and address of the person authorised for communication on behalf of the notification/application holder: Title: First and last name: Company name and address: Telephone

number: Fax number: E-mail:

## **2. PRODUCT(S) RELATED TO THIS NOTIFICATION/APPLICATION**

Product name Active substance(s) Pharmaceutical form Strength Marketing authorisation number

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### **3. TYPE OF CHANGE / TYPES OF CHANGES (Tick the applicable change as appropriate)**

A copy of the relevant page(s) from the Guideline has been annexed for this change, and the relevant boxes for the conditions and documentation have been ticked.

THE VARIATIONS IN THIS NOTIFICATION/APPLICATION; Number and title of the variation (as given in the classification guideline)

Procedure type a) The variation submitted as given in the classification guideline Type (In this section, add by selecting from the list of variations provided at the very end of this variation notification/application form template. The example above and the list of variations at the end of the form must be deleted after the form is completed, and the notification/application must be made with the form arranged in this manner)

SCOPE AND BACKGROUND OF THE CHANGE(S) (Please provide a brief background description of the proposed changes and briefly state their scope)

JUSTIFICATION FOR GROUPED CHANGES (if applicable)

CLASSIFICATION FOR UNFORESEEN CHANGES (if applicable)

OTHER NOTIFICATIONS/APPLICATIONS (Please provide brief information on ongoing variation(s) submitted in parallel or variations of the product in different dosage forms)

## **CURRENT 3,4**

## **PROPOSED 3,4**

3 Please state precisely the current and proposed text or specification.

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4 For changes to the SmPC, packaging, label and patient information leaflet / annex, underline the changed words either in the table above or in a separate ANNEX. Changes made in these documents must be related only to the submitted variation(s). Changes outside the scope of the variation are not valid even if they have been submitted in the annex to the notification/application and the notification/application has been approved.

ANNEX DOCUMENTS (where applicable)

The following revised product information text drafts (annexes) are submitted, where applicable: Summary of Product Characteristics Patient information leaflet/annex Specimen of packaging Product sample

## **DECLARATION OF THE NOTIFICATION/APPLICATION HOLDER**

Hereby, a notification/application is being made to change the relevant marketing authorisation(s) in conformity with the draft given above. I declare that (please tick the appropriate declarations):

There are no changes other than those specified in this notification/application (except those addressed in other changes submitted in parallel; such parallel changes must be indicated under "Other Notifications/Applications").

Changes have been made only in places related to the specified variation in documents such as the summary of product characteristics, patient information leaflet or specimen of packaging submitted in connection with the notification/application, and these changes are clearly shown in the colourised draft.

The change(s) will not adversely affect the quality, efficacy or safety of the product.

All variation conditions laid down for the relevant notification(s)/application(s) have been fulfilled (where applicable).

The documents required, as specified in the guideline for Type IA notifications, have been submitted.

The fees relating to the notification(s)/application(s) have been paid. The change(s) 5 ; will start to be implemented from the next manufacturing batch / next print as of the date ...../...../..... Explanation (where necessary, briefly state the details regarding the date of transition to implementation):

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5 To be completed only for Type IB and Type II variations.

### **SIGNATURE**

Amount of the fee(s) paid (if applicable):

First and last name of the person authorised for communication on behalf of the notification/application holder:

Title:

Signature:

Date:

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LIST OF VARIATION(S) (to be deleted after completion of the form)

Please select the relevant variation(s) from the list given below and add them in accordance with the instructions provided in the "Type of Change / Types of Changes – The Variations in this Notification/Application" section.

Only the main heading of the change should be added in relation to the variation(s) subject to the notification/application. Where an application is intended to be made for a variation not foreseen in the guideline, marketing authorisation holders must submit their applications, including their proposed classification, as an "other variation" ("z") under the lowest possible level of variation relevant to the guideline (specifically under a variation or under the applicable guideline section). Please indicate if the application falls within the scope of Article 5 of the Regulation. Examples for "z" variations have already been included for convenience.

For Type IA variations, marketing authorisation holders must add to the last column the date of transition to implementation for the variation.

The precise scope of the variation, provided in detail, must be specified in the "scope of the variation" section of the form.

How the variation(s) should be indicated in the "Type of variation/Types of variations" section is given in the examples below.

E.g. In applications for changes falling outside the approved specifications for the active substance:

B.I.b.1 Change in the specification parameters or limits of an active substance or of a starting material/intermediate/reagents used in the manufacturing process of the active substance  
Procedure type f) Changes falling outside the approved specification limits for the active substance  
II

E.g. In a notification made for an "unforeseeable" variation regarding the specification limits of the active substance: B.I.b.1 Change in the specification parameters or limits of an active substance or of a starting material/intermediate/reagents used in the manufacturing process of the active substance  
Procedure type z) Other variation IB II Article 5

E.g. In a notification made for an "unforeseeable" variation regarding the controls of the active substance:

B.I.b Control of the Active Substance Procedure type z) Other variation IB II Article 5

The complete list of variations is provided in the remainder of this document, to be deleted when the notification/application is made.

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A. Administrative changes Procedure type z) Other variation IA IB

A IB

Article 5 Date of implementation:

z.1) Change in the name/address of the inner packaging supplier IA Date of implementation:

z.2) Change in the name/address of the outer packaging supplier IA Date of implementation:

z.3) Change in the name/address of the licensee company IADB Date of implementation:

z.4) Design change to be made in the inner or outer packaging IADB Date of implementation:

Procedure type A.1 Change in the name or address of the marketing authorisation holder IADB

Date of implementation:

Procedure type A.2 Change in the name of the medicinal product for human use IB

Procedure type A.3 Change in the name of the active substance or excipient IADB

Date of implementation:

Procedure type A.4 Change in the name or address of the following: - The manufacturer (including the relevant quality control test centres); - or the holder of the ASMF; - or, in cases where a Certificate of Suitability to the European Pharmacopoeia (CEP) is not included in the approved dossier, the supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (if specified in the technical dossier); - or the manufacturer of a new excipient (if specified in the technical dossier) IA

Date of implementation:

A.5 Change in the name or address of the manufacturing site of the finished product (including sites performing batch release or quality control testing) Procedure type a) Manufacturing site including batch release activity IADB

Date of implementation:

b) Manufacturing site not including batch release activity IA

Date of implementation:

Procedure type A.6 Change in the ATC Code IA

Date of implementation:

Procedure type A.7 Deletion of any manufacturing site\* (Active substance, intermediate or finished product, packaging site, site where batch control is performed, manufacturing site responsible for batch release or, if specified in the dossier, suppliers of starting materials, reagents or excipients) IA

Date of implementation:

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B.I.a Change in the manufacture of the active substance Procedure type z) Other variation IB II Article 5

B.I.a.1 In cases where a Certificate of Suitability to the European Pharmacopoeia (CEP) is not included in the approved dossier, change in the manufacturing site of the starting material/reagent/intermediate used in the manufacturing process of the active substance, or in the manufacturing site of the active substance (including the manufacturing site where the relevant quality control testing is performed) Procedure type a) The proposed manufacturer is part of the same pharmaceutical group (company) as the currently approved manufacturer IADB

Date of implementation:

b) Introduction of a new active substance manufacturing site supported by an ASMF (Active Substance Master File) II c) Where a significantly different synthesis route or manufacturing

conditions, which may have the potential to alter important quality characteristics of the active substance, such as the qualitative or quantitative impurity profile requiring qualification or the physicochemical properties affecting bioavailability, are used by the proposed manufacturer II d) New manufacturer of material for which viral safety or TSE (transmissible spongiform encephalopathy) risk needs to be evaluated II e) Change in the manufacturer of a starting material/reagent/intermediate used in the manufacture of a biological active substance or a biological/immunological medicinal product II f) Change in the quality control testing arrangements of the active substance — Replacement or addition of a site where batch controls/assays are performed IA

Date of implementation:

g) Introduction of a new active substance manufacturer not supported by an ASMF (Active Substance Master File) and requiring a significant update in the relevant active substance section of the dossier II

h) Addition of an alternative sterilisation site using a European Pharmacopoeia method for the active substance IB

i) Introduction of a new micronisation site IA

Date of implementation:

j) Change in the quality control testing arrangements of a biological active substance — Replacement or addition of a site where batch controls/tests are performed for a biological active substance, including a biological/immunological/immunochemical method among them II

k) New storage site for the Master Cell Bank or working cell banks IB

z) Other variation IB II Article 5

B.I.a.2 Changes in the manufacturing process of the active substance Procedure type a) Minor change in the manufacturing process of the active substance IA

Date of implementation:

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b) Major change in the manufacturing process of the active substance, which may have a significant impact on the quality, safety or efficacy of the medicinal product for human use II c) Change consisting of the use of a biological/immunological substance, or of a substance obtained by a different chemical route in the manufacture of such a substance, which may have a significant impact on the quality, safety or efficacy of the medicinal product for human use and which is not associated with a protocol, where justified. II d) Change in the geographical source/manufacturing route/manufacture of a herbal medicinal product II e) Minor change in the closed part of the Active Substance Master File IB z) Other variation IB II Article 5

B.I.a.3 Change in the batch size (including batch size ranges) of the active substance or of the intermediate used in the manufacturing process of the active substance Procedure type a) Increase of up to 10-fold compared to the original batch size approved during authorisation IA

Date of implementation:

b) Reduction of up to 10-fold IA

Date of implementation:

c) Change requiring evaluation of the comparability of a biological/immunological active substance II d) Increase of more than 10-fold compared to the original batch size approved during authorisation IB e) Scale up/scale down without process change for a biological/immunological active substance (e.g., doubling of the line) IB z) Other variation IB II Article 5

B.I.a.4 Change in the in-process tests applied during the manufacture of the active substance or in their limits Procedure type a) Tightening of in-process limits IA

Date of implementation:

b) Addition of a new in-process test and its limits IA

Date of implementation:

c) Deletion of a non-significant in-process test IA

Date of implementation:

d) Widening of approved in-process test limits which may have a significant impact on the overall quality of the active substance II e) Deletion of an in-process test which may have a significant impact on the overall quality of the active substance II f) Addition of or change to an in-process test as a result of a safety or quality issue IB z) Other variation IB II Article 5

B.I.a.5 Changes in the active substance of a seasonal, pre-pandemic or pandemic influenza vaccine Procedure type a) Replacement of the strain/strains in a seasonal, pre-pandemic or pandemic influenza vaccine II

B.I.b Change in the control of the active substance Procedure type z) Other variation IB II Article 5

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B.I.b.1 Change in the specification parameters or limits of an active substance or of a starting material/intermediate/reagents used in the manufacturing process of the active substance Procedure type a) Tightening of specification limits for vaccines, blood products and medicinal products derived from plasma IADB

Date of implementation:

b) Tightening of specification limits IA

Date of implementation:

c) Addition of a new specification parameter to the specification together with the relevant test method IA

Date of implementation:

d) Deletion of a non-significant specification parameter (e.g., deletion of a parameter that is no longer used) IA

Date of implementation:

e)

Deletion of a specification parameter that may have a significant effect on the overall quality of the active substance or finished product II f) Changes outside the range of approved specification limits for the active substance II g) Widening of the approved specification limits of starting materials/intermediate products that may have a significant effect on the overall quality of the active substance or finished product II h) As a result of a safety or quality issue, the addition of a specification parameter, together with the relevant test method, or its replacement with a new one (except for biological or immunological substances) IB i) In cases where the active substance monograph is not found in a pharmacopoeia, a change from an in-house specification to a pharmacopoeia specification other than the Turkish Pharmacopoeia, European Pharmacopoeia, United States Pharmacopoeia, British Pharmacopoeia or Japanese Pharmacopoeia IB z) Other variation IB II Article 5

B.I.b.2 Changes in the test procedure of an active substance or of a starting material/reactive/intermediate products used in the active substance manufacturing process Procedure type a) Minor changes to an approved test procedure IA

Implementation date:

b) Where an approved alternative test procedure exists, deletion of the test procedure of the active substance or of a starting material/reactive/intermediate product IA

Implementation date:

c) Other changes in the test procedure of a reactive that has no significant effect on the overall quality of the active substance (including replacement with a new one or addition) IA

Implementation date:

d) Switching to a biological/immunological/immunochemical test method, or to a method using a biological reactive for a biological active substance, or replacing the method with a new one II e) Other changes in a test procedure of the active substance or of a starting material/intermediate product (including replacement with a new one or addition) IB z) Other

variation IB II Article 5

B.I.c Changes in the container-closure system Procedure type z) Other variation IB II Article 5

B.I.c.1 Changes in the immediate packaging of the active substance Procedure type a) Qualitative or quantitative composition IA Implementation date:

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b) Qualitative or quantitative composition for sterile and non-frozen biological/immunological active substances II c) Qualitative or quantitative composition for liquid active substances (non-sterile) IB z) Other variation IB II Article 5

B.I.c.2 Changes in the specification parameters or limits of the immediate packaging of the active substance Procedure type a) Tightening of the specification limits IA

Implementation date:

b) Addition of a new specification parameter to the specification together with the relevant test method IA

Implementation date:

c) Deletion of a non-significant specification parameter (for example, deletion of a parameter that is no longer used) IA

Implementation date:

d) Addition of a specification parameter or its replacement with a new one as a result of a safety or quality issue IB z) Other variation IB II Article 5

B.I.c.3 Changes in the test procedure of the immediate packaging of the active substance Procedure type a) Minor changes to an approved test procedure IA

Implementation date:

b) Other changes in the test procedure (including replacement with a new one or addition)

IA

Implementation date:

c) Deletion of a test procedure in cases where an approved alternative test procedure exists

IA

Implementation date:

z) Other variation IB II Article 5

B.I.d.1 In cases where a Certificate of Suitability to the European Pharmacopoeia (CEP) covering the re-test period is not included in the approved dossier, changes in the re-test period or storage period or storage conditions of the active substance Procedure type a) Re-test period/storage period

### **1. Reduction IA**

Implementation date:

2. Extension of the re-test period based on extrapolation of stability data that is not in accordance with ICH guidelines II

3. Extension of the storage period of a biological/immunological active substance not in accordance with the approved stability protocol II

4. Submission or extension of a re-test period/storage period supported by real-time data IB b) Storage conditions 1. Change of the storage conditions of the active substance to more restrictive conditions IA

Implementation date: 2. In cases where stability studies have not been carried out in accordance with a currently approved stability protocol, changes in the storage conditions of biological/immunological active substances II 3. Changes in the storage conditions of the active substance IB c) Change in an approved stability protocol IA

Implementation date:

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z) Other variation IB II Article 5

B.I.e.1 With regard to the following; widening of the approved design space of the active substance or submission of a new design space Procedure type a) A single unit operation in the manufacturing process of the active substance and the related in-process controls or test procedures II b) Starting material/reactive/intermediate product or active substance test procedures II

Procedure type

B.I.e.2 Submission of a post-approval change management protocol regarding the active substance II

Procedure type

B.I.e.3 Deletion of an approved change management protocol relating to the active substance IA DB Implementation date:

B.I.e.4 Changes in an approved change management protocol Procedure type a) Major changes in an approved change management protocol II b) Minor changes in an approved change management protocol that do not cause a change in the strategy defined in the protocol IB

B.I.e.5 Implementation of changes foreseen in an approved change management protocol Procedure type a) Implementation of the change not requiring additional supporting data IA DB

Implementation date:

b) Implementation of the change requiring additional supporting data IB c) The implemented change being for a biological/immunological medicinal product IB

B.II.a Changes in the description and composition of the finished product Procedure type z) Other variation IB II Article 5

B.II.a.1 Changes in, or addition of, printing, embossing or other markings, including replacement or addition of the inks used for product marking Procedure type a) Changes in printing, embossing or other markings IA DB

Implementation date:

b) Changes in the score/break line used for dividing into equal doses IB z) Other variation IB II Article 5

B.II.a.2 Change in the shape or dimensions of the pharmaceutical form Procedure type a) Immediate-release tablets, capsules, suppositories and ovules IA DB

Implementation date:

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b) Gastro-resistant, modified or extended-release pharmaceutical forms and tablets with a score line intended for dividing into equal doses IB c) Addition of a new kit for a radiopharmaceutical preparation with a different filling volume II z) Other variation IB II Article 5

B.II.a.3 Changes in the composition of the finished product (excipients) Procedure type a) Changes in the components of sweetening/flavouring agents or colouring agents

1. Addition, deletion or replacement with a new one IA DB

Implementation date:

## **2. Increase or decrease IA**

Implementation date:

b) Other excipients 1. Any changes of a minor adjustment nature made with regard to excipients in the quantitative composition of the finished product IA

Implementation date:

2. In one or more excipients of a human medicinal product

ed qualitative or quantitative changes that may have a significant impact on the safety, quality or efficacy of the product II 3. A variation related to a biological/immunological product II 4. Any new excipient involving the use of materials of human or animal origin requiring an assessment relating to viral safety data or TSE (transmissible spongiform encephalopathy) risk II 5.

A variation supported by a bioequivalence study II 6. Replacement of a single excipient with a comparable excipient having the same functional characteristics and at a similar level IB z) Other variation IB II Article 5

B.II.a.4 Changes in the coating weights of oral dosage forms or in the capsule shell weight Procedure type a) Solid oral pharmaceutical forms IA

Implementation date:

b) Pharmaceutical forms providing enteric coating, modified or extended release where the coating is a critical factor in terms of the release mechanism II z) Other variation IB II Article 5

Procedure type

B.II.a.5 A change in the concentration of a single-dose parenteral product of which the entire product is used at once, where the amount of active substance per unit dose (e.g. loss) remains the same II

Procedure type B.II.a.6 Removal of the solvent/diluent from the package IB

B.II.b Changes in the manufacture of the finished product Procedure type z) Other variation IB II Article 5

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B.II.b.1 A change in the manufacturing site or the addition of a new manufacturing site for part or all of the finished product manufacturing process Procedure type a) Outer packaging site IA DB

Implementation date:

b) Inner packaging site IA DB

Implementation date:

c) A site where any manufacturing operation other than batch release, batch control and outer packaging is carried out, for biological/immunological medicinal products or pharmaceutical forms manufactured with complex manufacturing processes II d) A site requiring a product-specific inspection II e) A site where any manufacturing operation other than batch release, batch control, inner and outer packaging is carried out, for non-sterile human medicinal products IB f) A site where any manufacturing operation other than batch release, batch control and outer packaging is carried out, for sterile human medicinal products other than biological/immunological medicinal products (including those manufactured aseptically) IB z) Other variation IB II Article 5

B.II.b.2 A change in the batch release and quality control site of the finished product Procedure type a) Replacement of the site where batch control/testing is carried out with a new one or addition of a new site IA

Implementation date:

b) Replacement of the site where batch control/testing is carried out with a new one or addition of a new site for a biological/immunological medicinal product, and any test method carried out at that site being a biological/immunological method II c) Replacement of a manufacturer responsible for batch release with a new one or addition of a new responsible manufacturer

### **1. Not including batch control/testing IA DB**

Implementation date:

### **2. Including batch control/testing IA DB**

Implementation date:

3. Including batch control/testing for a biological/immunological medicinal product and any test method carried out at that site being a biological/immunological method II

B.II.b.3 A change in the manufacturing process of the finished product (including an intermediate product used in the manufacture of the finished product) Procedure type a) A minor change in the manufacturing process IA

Implementation date:

b) Significant changes in the manufacturing process that may have a marked impact on the quality, safety and efficacy of the human medicinal product II c) The product being a biological/immunological medicinal product and the change requiring a comparability assessment II d) Introduction of a non-standard terminal sterilisation method II e) Use of an excess dose of the active substance or an increase in the amount II f) A minor change in the manufacturing process of an aqueous oral suspension IB z) Other variation IB II Article 5

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B.II.b.4 A change in the batch size (including batch size ranges) of the finished product Procedure type a) An increase of up to 10-fold compared to the batch size approved at the time of authorisation IA

Implementation date:

b) A reduction of up to 10-fold IA

Implementation date:

c) A change requiring an assessment of the comparability of a biological/immunological medicinal product or requiring a new bioequivalence study for the batch size II d) A change related to all other pharmaceutical forms manufactured with complex manufacturing processes II e) An increase of more than 10-fold compared to the batch size approved at the time of authorisation, for immediate-release (oral) pharmaceutical forms IB f) Scale-up/scale-down (for example, doubling of the line) without a process change for a biological/immunological medicinal product IB z) Other variation IB II Article 5

B.II.b.5 A change in the in-process tests applied during the manufacture of the finished product or in the limits Procedure type a) Tightening of in-process limits IA

Implementation date:

b) Addition of a new test/tests and limits IA

Implementation date:

c) Deletion of a non-significant in-process test IA

Implementation date:

d) Deletion of an in-process test that may have a significant impact on the overall quality of the finished product II e) Extension of approved in-process control limits that may have a significant impact on the overall quality of the finished product II f) Addition of an in-process test or replacement with a new one as a result of a safety or quality issue IB z) Other variation IB II Article 5

B.II.c Changes in the control of excipients Procedure type z) Other variation IB II Article 5

B.II.c.1 A change in the specification parameters or limits of an excipient Procedure type a) Tightening of specification limits IA

Implementation date:

b) Addition of a new specification parameter to the specification together with the relevant test method IA

Implementation date:

c) Deletion of a non-significant specification parameter (for example, deletion of a parameter no longer in use) IA

Implementation date:

d) A change falling outside the range of approved specification limits II e) Deletion of a specification parameter that may have a significant impact on the overall quality of the finished product II f) As a result of a safety or quality issue, addition of a specification parameter together with the relevant test method, or replacement with a new one (except for biological or immunological substances) IB

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g) In cases where the excipient monograph is not included in a pharmacopoeia, a change from an in-house specification to a pharmacopoeial specification other than the Turkish Pharmacopoeia, European Pharmacopoeia, United States Pharmacopoeia, British Pharmacopoeia or Japanese Pharmacopoeia IB z) Other variation IB II Article 5

B.II.c.2 A change in the test procedure for an excipient Procedure type a) Minor changes to an approved test procedure IA

Implementation date:

b) Deletion of a test procedure in cases where an approved alternative test procedure already exists IA

Implementation date:

c) A switch to a biological/immunological/immunochemical test method or to a method using biological reagents, or replacement of the method with another method II d) Other changes in the test procedure (including replacement or addition) IB z) Other variation IB II Article 5

B.II.c.3 Change in an excipient or reagent sourced from material carrying a TSE (Transmissible Spongiform Encephalopathy) risk Procedure type a) Change from material carrying a TSE risk to material of vegetable or synthetic origin

1. For excipients or reagents not used in the manufacture of a biological/immunological active substance or in a biological/immunological medicinal product IA Implementation date:

2. For excipients or reagents used in the manufacture of a biological/immunological active substance or in a biological/immunological medicinal product IB b) Introduction or addition of a TSE-risk material, or replacement of a TSE-risk material with a different TSE-risk material that does not have a TSE Certificate of Suitability II z) Other variation IB II Article 5

B.II.c.4 Change in the synthesis or recovery of an excipient not included in a pharmacopoeia (if described in the dossier) or of a new excipient Procedure type a) Minor change in the synthesis or recovery of an excipient not included in a pharmacopoeia or of a new excipient IA

Implementation date:

b) Affecting the specifications, or a change in the physicochemical properties of the excipient that may affect the quality of the finished product II c) The excipient being a biological/immunological substance II z) Other variation IB II Article 5

B.II.d Change in the control of the finished product Procedure type z) Other variation IB II Article 5

B.II.d.1 Change in specification parameters or limits of the finished product Procedure type a) Tightening of specification limits IA

Implementation date:

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b) Tightening of specification limits for vaccines, blood products and human medicinal products derived from plasma IADB

Implementation date:

c) Addition of a new specification parameter to the specification together with the relevant test method IA

Implementation date:

d) Deletion of a non-significant specification parameter (for example, deletion of a parameter no longer used, such as odour and taste or identification test of a colouring or flavouring substance) IA

Implementation date:

e) Changes falling outside the range of approved specification limits II f) Deletion of a specification parameter that may have a significant impact on the overall quality of the finished product II g) As a result of a safety or quality issue, addition of a specification parameter or its replacement with a new one, together with the corresponding test method (excluding biological or immunological medicinal products) IB h) Updating of the dossier in order for the finished product

to comply with the current monographs of the European Pharmacopoeia IADB

Implementation date:

i) Replacement of the currently approved method, European Pharmacopoeia 2.9.5 (Uniformity of Weight) or European Pharmacopoeia 2.9.6 (Uniformity of Content), with European Pharmacopoeia 2.9.40 Uniformity of Dosage Units IA

Implementation date:

z) Other variation IB II Article 5

B.II.d.2 Change in the test procedure of the finished product Procedure type a) Minor changes made to the approved test procedure IA

Implementation date:

b) Deletion of a test procedure where an approved alternative method already exists IA

Implementation date:

c) Change to a biological/immunological/immunochemical test method or to a method using biological reagents, or replacement of the method with a new one, or replacement of a biological reference preparation method not covered by an approved protocol with a new one II d) Other changes in the test procedure (including change or addition) IB e) Updating of the test procedure to comply with an updated monograph of the pharmacopoeia IA

Implementation date:

f) Reflecting compliance with the pharmacopoeia and deletion of the in-house test method no longer used, and of the test method number, from the reference \* IA

Implementation date:

z) Other variation IB II Article 5

Procedure type

B.II.d.3 Changes related to the introduction of real-time release or parametric release in the manufacture of the finished product II

B.II.e Change in the container-closure system of the finished product Procedure type z) Other variation IB II Article 5

B.II.e.1 Changes in the immediate packaging of the finished product Procedure type a) Qualitative and quantitative composition

### **1. Solid pharmaceutical forms IA**

Implementation date:

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2. Semi-solid and non-sterile liquid pharmaceutical forms IB 3. Sterile human medicinal products and biological/immunological medicinal products II 4. Change relating to a less protective packaging that causes a change in storage conditions or shortening of the shelf life II b) Change in cap type or addition of a new cap 1. Solid, semi-solid and non-sterile liquid pharmaceutical forms IB 2. Sterile human medicinal products and biological/immunological medicinal products II z) Other variation IB II Article 5

B.II.e.2 Change in specification parameters or limits of the immediate packaging of the finished product Procedure type a) Tightening of specification limits IA

Implementation date:

b) Addition of a new specification parameter to the specification together with the relevant test method IA

Implementation date:

c) Deletion of a non-significant specification parameter (for example, deletion of a parameter no longer used) IA

Implementation date:

d) Addition or modification of a specification parameter as a result of a safety or quality issue IB z) Other variation IB II Article 5

B.II.e.3 Change in the test procedure of the immediate packaging of the finished product  
Procedure type a) Minor changes in an approved test procedure IA

Implementation date:

b) Other changes in the test procedure (including replacement or addition) IA

Implementation date:

c) Deletion of a test procedure where an approved alternative test procedure exists IA

Implementation date:

z) Other variation IB II Article 5

B.II.e.4 Change in the shape or dimensions of the container or closure (immediate packaging) Procedure type a) Non-sterile human medicinal products IA

Implementation date:

b) Change in shape or dimensions related to an essential component of the packaging material that may have a significant impact on the distribution, use, safety or stability of the finished product II c) Sterile human medicinal products IB z) Other variation IB II Article 5

B.II.e.5 Change in pack size of the finished product Procedure type a) Change in the number of units (e.g. tablets, ampoules, etc.) in a pack

1. Change within the range of currently approved pack sizes IA DB

Implementation date:

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2. Change outside the range of currently approved pack sizes IB b) Deletion of pack size/sizes IA

Implementation date:

c) Change in fill weight/fill volume of sterile multi-dose (or single-dose for partial use) parenteral human medicinal products, including biological/immunological human medicinal products II d) Change in fill weight/fill volume of non-parenteral multi-dose (or single-dose for partial use) products IB z) Other variation IB II Article 5

B.II.e.6 Change in any part of the immediate packaging material that does not come into contact with the formulation of the finished product (e.g. colour of snap-on caps, colour code rings on ampoules, replacement of the needle shield (use of a different plastic) Procedure type a) Change affecting the product information (summary of product characteristics, package leaflet, mock-up) IADB

Implementation date:

b)

b) Modification not affecting the product information (summary of product characteristics, patient information leaflet, packaging specimen) IA

Implementation date:

B.II.e.7 Change in the supplier(s) of packaging components or devices (if specified in the dossier) Procedure type a) Deletion of a supplier IA

Implementation date:

b) Replacement or addition of a supplier IA

Implementation date:

c) Changes in the suppliers of canisters for metered dose inhalers II

B.II.f.1 Change in the shelf-life or storage conditions of the finished product Procedure type a) Reduction of the shelf-life of the finished product 1. In the packaging to be placed on the market IA DB

Implementation date:

## **2. After first opening IA DB**

Implementation date:

### **3. After dilution or reconstitution IA DB**

Implementation date:

b) Extension of the shelf-life of the finished product 1. In the packaging to be placed on the market (supported by real-time data) IB 2. After first opening (supported by real-time data) IB 3. After dilution or reconstitution (supported by real-time data) IB 4. Extension of the shelf-life based on extrapolation of stability data not in accordance with ICH guidelines II 5. Extension of the shelf-life of a biological/immunological medicinal product for human use in accordance with the approved stability protocol IB c) Changes in the storage conditions of biological medicinal products in cases where stability studies have not been carried out in accordance with an approved stability protocol II

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d) Changes in the storage conditions of the finished product or of the diluted/reconstituted product IB e) Changes in the approved stability protocol IA

Implementation date:

z) Other variation IB II Article 5

B.II.g.1 Introduction of a new design space for the finished product or extension of an approved design space with regard to the following Procedure type a) One or more unit operations in the manufacturing process of the finished product, including the resulting in-process controls or test procedures II b) Excipient/intermediate product or finished product test procedures II

Procedure type

B.II.g.2 Submission of a post-approval change management protocol relating to the finished product II

Procedure type

B.II.g.3 Removal of an approved change management protocol relating to the finished product IA DB Implementation date:

B.II.g.4 Changes in the approved change management protocol Procedure type a) Major changes in the approved change management protocol II b) Minor changes in the approved change management protocol that do not alter the strategy defined in the protocol IB

B.II.g.5 Implementation of the changes proposed in the approved change management protocol Procedure type a) Implementation of the change requiring no additional supporting data IA DB

Implementation date:

b) Implementation of the change requiring additional supporting data IB c) Implementation of a change for a biological/immunological medicinal product IB

B.II.h.1 Update of the information in the "Safety Evaluation of Unexpected Agents" Procedure type a) Studies relating to the manufacturing steps investigated for the first time for one or more unexpected agents II b) Replacement of invalid studies relating to the manufacturing steps and unexpected agents previously reported in the dossier with new ones

### **1. Together with a risk assessment change II**

### **2. Without a risk assessment change IB**

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B.III.1 Introduction of a new or updated Certificate of Suitability to the European Pharmacopoeia, or removal of a Certificate of Suitability to the European Pharmacopoeia - For an active substance; - For a starting material/reagent/intermediate used in the manufacturing process of the active substance; - For an excipient; Procedure type a) Certificate of Suitability to the European Pharmacopoeia for the relevant European Pharmacopoeia monograph

1. New certificate obtained from an existing approved manufacturer IA DB

Implementation date:

**2. Updated certificate obtained from an existing approved manufacturer IA**

Implementation date:

3. New certificate obtained from a new manufacturer (replacement or addition) IADB

Implementation date:

4. Removal of certificates (where there is more than one certificate for a material) IA

Implementation date:

5. New certificate for a non-sterile active substance to be used in a sterile medicinal product for human use, in cases where water is used in the final steps of the synthesis and it is not stated that the material is free of endotoxins IB

b) Certificate of Suitability to the European Pharmacopoeia (TSE, transmissible spongiform encephalopathy) for an active substance/starting material/reagent/intermediate or excipient

1. New certificate for the active substance obtained from a new or existing approved manufacturer IADB

Implementation date:

2. New certificate for a starting material/reagent/intermediate or excipient obtained from a new or existing approved manufacturer IA

Implementation date:

**3. Updated certificate obtained from an existing approved manufacturer IA**

Implementation date:

4. Removal of certificates (where there is more than one certificate for a material) IA

Implementation date:

5. New/updated certificate from an existing approved/new manufacturer using materials of human or animal origin for which a risk assessment regarding potential contamination with unexpected agents is required II z) Other variation IB II Article 5

B.III.2 Change for compliance with the pharmacopoeia Procedure type a) Changes made to the specifications for compliance with the pharmacopoeia following the inclusion of a substance not previously included in the pharmacopoeia

**1. Active substance IA DB**

Implementation date:

**2. Excipient/starting material of the active substance IA**

Implementation date:

b) Changes made to comply with an update in the relevant monograph of the pharmacopoeia IA

Implementation date:

c) Changes made for the transition from pharmacopoeia specifications other than the Turkish Pharmacopoeia, European Pharmacopoeia, United States Pharmacopoeia, British Pharmacopoeia or Japanese Pharmacopoeia to the specified pharmacopoeias IA

Implementation date:

B.IV.1 Changes in the measuring or administration device Procedure type

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a) Addition or replacement of a device that is not an integral part of the immediate packaging

**1. CE-marked device IA DB**

Implementation date:

2. Air-chambered intermediate piece for metered dose inhalers or other devices that may have a significant impact on the delivery of the active substance in the product (e.g., nebuliser) II b)

Deletion of a device IA DB

Implementation date:

c) Addition or replacement with a new device that is an integral part of the immediate packaging II

B.V.a.1 Inclusion of a new, updated or modified Plasma Master File in the marketing authorisation dossier of a medicinal product for human use Procedure type a) First inclusion of a new Plasma Master File affecting the characteristics of the finished product in the marketing authorisation dossier II b) First inclusion of a new Plasma Master File not affecting the characteristics of the finished product in the marketing authorisation dossier IB c) Inclusion of an updated/modified Plasma Master File in the marketing authorisation dossier in cases where the changes affect the characteristics of the finished product IB d) Inclusion of an updated/modified Plasma Master File in the marketing authorisation dossier in cases where the changes do not affect the characteristics of the finished product IADB

Implementation date:

B.V.a.2 Inclusion of a new, updated or modified Vaccine Antigen Master File (VAMF) in the marketing authorisation dossier Procedure type a) First inclusion of a new Vaccine Antigen Master File in the marketing authorisation dossier II b)

b) Where the changes affect the characteristics of the finished product, inclusion of an updated/amended Vaccine Antigen Master File in the marketing authorisation dossier for the first time IB

c) Where the changes do not affect the characteristics of the finished product, inclusion of an updated/amended Vaccine Antigen Master File in the marketing authorisation dossier for the first time IADB

Implementation date:

C.I.1 Changes to the efficacy and safety information to be implemented in the summary of product characteristics, package leaflet or labelling as a result of assessments made in relation to the safety of medicinal products for human use (e.g., Association-Federation announcements) Procedure type

a) Implementation of wording accepted by the Agency IA DB

Implementation date:

b) The medicinal product for human use does not fall within the defined scope of the procedure, but as a result of the change, the outcome of the procedure is implemented without the submission of new additional data by the marketing authorisation holder IB

c) The medicinal product for human use does not fall within the defined scope of the procedure, but as a result of the change, the outcome of the procedure is implemented with new additional data (e.g., efficacy, safety) submitted by the marketing authorisation holder\* II

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C.I.2 Following the assessment of a change made to the reference medicinal product, the same changes made to the summary of product characteristics, labelling or package leaflet of equivalent/hybrid/biosimilar medicinal products Procedure type

a) Implementation of changes that do not require the submission of any new additional data by the marketing authorisation holder IB

b) Implementation of changes that require being supported by new additional data to be submitted by the marketing authorisation holder (e.g., comparability) II

C.I.3 Change(s) made to the summary of product characteristics, labelling or package leaflet of the medicinal product for human use in order to implement the outcome of the assessment made by the Agency under a procedure related to the Periodic Benefit-Risk Evaluation Report (PBRER) or the Risk Management Plan (RMP) or a post-authorisation safety study Procedure type

a) Implementation of wording accepted by the Agency IB b) Implementation of changes that need to be verified with new additional data to be submitted by the marketing authorisation holder II

Procedure type

C.I.4 Changes made to the summary of product characteristics, labelling or package leaflet based on new quality, pre-clinical, clinical or pharmacovigilance data (Efficacy, safety updates) II

C.I.5 Changes to therapeutic indication(s) or posology Procedure type

a) Addition of a new therapeutic indication or posology, or amendment of an approved therapeutic indication or posology II b) Deletion of a therapeutic indication or posology II

C.I.6 For products authorised with a risk management plan, submission of the conditions to be fulfilled and specific obligations, including the risk management plan, or changes to these conditions and specific obligations Procedure type

a) Implementation of the conditions and specific obligations determined by the Agency Type IADB Implementation date:

b) Implementation of the relevant changes with new additional supporting data to be submitted by the marketing authorisation holder, in cases where the Agency considers an assessment necessary II

Procedure type

C.I.7 Addition to or removal from the summary of product characteristics and package leaflet of the inverted triangle and explanatory statement for a medicinal product for human use on the additional monitoring list Type IADB Implementation date:

Procedure type

C.I.8 Other changes not specifically stated in this annex concerning the submission of studies to the Agency Type II

D. Changes made within the scope of the PMF (Plasma Master File)/VAMF (Vaccine Antigen Master File) Procedure type

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z) Other variation IB II Article 5

Procedure type

D.1 Change in the name or address of the holder of a VAMF (Vaccine Antigen Master File) certificate. IA DB Implementation date:

Procedure type

D.2 Change in the name or address of the holder of a PMF (Plasma Master File) certificate IADB

Implementation date:

Procedure type

D.3 Replacement of the holder of an existing PMF (Plasma Master File) certificate with a new PMF certificate holder, or transfer to a new PMF certificate holder IA DB Implementation date:

Procedure type

D.4 Change in the name or address of the blood establishment comprising the blood/plasma collection centre IA

Implementation date:

Procedure type

D.5 Addition of a blood/plasma collection centre belonging to the blood establishment included in the PMF (Plasma Master File), or its replacement with a new one

IB

Procedure type

D.6 Removal of the centre(s) used for the testing of blood/plasma collection or donations and plasma pools, or change of their status (operational or not)

IA Implementation date:

Procedure type  
D.7 Addition of a new blood establishment for the collection of blood/plasma not included in the PMF (Plasma Master File) II  
Procedure type  
D.8 Replacement of a blood establishment for the testing of donations or plasma pools within an establishment included in the PMF, or addition of a new one  
IB  
Procedure type  
D.9 Addition of a new blood establishment for the testing of donations or plasma pools included in the PMF (Plasma Master File) II  
Procedure type  
D.10 Replacement of an establishment where plasma is stored with a new one, or addition of a new one IB  
Procedure type D.11 Removal of an establishment where plasma is stored IA  
Implementation date:  
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Procedure type  
D.12 Replacement of a company involved in the transportation of plasma with a new one, or addition of one IB  
Procedure type D.13 Removal of a company involved in the transportation of plasma IA  
Implementation date:  
Procedure type  
D.14 Addition of a CE-marked test kit, either as a new test kit for the testing of individual donations or as the replacement of an existing test kit with a new one IA  
Implementation date:  
D.15 Addition of a new test kit that is not CE-marked to be used for the testing of individual donations, or replacement of an existing test kit with a new one that is not CE-marked Procedure type  
a) If the new test kit for the testing of donations has not previously been approved in the PMF (Plasma Master File) for any blood establishment II b) If the new test kit has been approved for the other blood establishment(s) included in the PMF for the testing of donations IA  
Implementation date:  
Procedure type  
D.16 Change of the kit/method used for the testing of pools (antibody or antigen or nucleic acid (NAT) testing) II  
Procedure type  
D.17 Implementation or extension of the inventory management procedure IA  
Implementation date:  
Procedure type D.18 Removal of the inventory management period or shortening of the period IB  
D.19 Replacement of blood bags or bottles with new ones, or addition of new ones  
Procedure type  
a) For new blood bags or bottles that are CE-marked IA  
Implementation date:  
b) For new blood bags or bottles that are not CE-marked II  
D.20 Changes to storage/transportation Procedure type  
a) Storage and/or transport conditions IA  
Implementation date:  
b) Maximum storage period for plasma IA  
Implementation date:

Procedure type

D.21 Implementation of viral markers where this change has a significant impact on the viral risk assessment II

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Procedure type

D.22 Change in plasma pool preparation (e.g., manufacturing method, size of the pool, storage of plasma pool samples) IB

Procedure type

D.23 Steps to be taken when it is determined that a donation (donations) must be retrospectively excluded from the process ("look-back" procedure). II

II