ANNEX I

PETITION FORM FOR SUBSTANTIAL MODIFICATION TO THE PRODUCT UNDER INVESTIGATION

National Health Surveillance Agency
Clinical Research
Substantial Product Modification Petition Form under Investigation

Document Identification

(For use by the receiving agency)

1	DDCM Process Number	2	Office Hours

Company Data

3	Applicant	4	Authorization/Registration Number
5	Manufacturer	6	Authorization/Registration Number

DDCM data

7	**Type of Modification:** a) Modification resulting from recommendations or alerts issued by health authorities?	a) ( ) Yes ( ) No
8	**Reasons for Substantial Modification: a)** **Modifications related to the Active Pharmaceutical Ingredient – a) ( ) Yes ( ) No API/Active Substance (biological products)?** i. Replacement/Inclusion of new manufacturing site or manufacturing steps?	i. ( ) Yes ( ) No

	ii. Change in the synthesis route (synthetic/semisynthetic)? iii. Change in the manufacturing process of the active substance of biological products?	ii. ( ) Yes ( ) No iii. ( ) Yes ( ) No
	iii.1 Change in cell banks, involving:	
	iii.1.1 Generation of a new Master Cell Bank (MBC) from the same expression construct with the same or highly similar cell line? iii.1.2 Generation of new MBC from a different expression construct with the same coding sequence and the same cell line? iii.1.3 Adaptation of a new MBC in a new culture medium? iii.1.4 Generation of new MBC for a recombinant product or viral vaccine?	iii.1.1 ( ) Yes ( ) No iii.1.2 ( ) Yes ( ) No iii.1.3 ( ) Yes ( ) No iii.1.4 ( ) Yes ( ) No
	iii.2 Changes in seed banks, involving: iii. 2.1 Establishment of a new Master Seed Bank (MSB) ? iii. 2.2 Extension of the number of passes of the Working Seed Bank (WSB) beyond the approved level ?	iii.2.1 ( ) Yes ( ) No iii.2.2 ( ) Yes ( ) No
	iii.3 Change of the manufacturing site of the cell bank or seed bank? iii.4 Change of fermentation process or viral or cellular propagation, fractionation or extraction:	iii.3 ( ) Yes ( ) No
	iii.4.1 Critical change (change with high potential impact on the quality of the active substance or finished product, e.g. incorporation of disposable bioreactor technology) ? iii.4.2 Change with moderate potential impact on the quality of the active substance or finished product (e.g. extension of in vitro cell age beyond validated parameters) ?	iii.4.1 ( ) Yes ( ) No iii.4.2 ( ) Yes ( ) No
	iii.5 Change in purification process: iii.5.1 Critical change (change with high potential impact on the quality of the active substance and the finished product, e.g. a change that may potentially impact the viral removal/inactivation capacity or impurity profile of the active substance)? iii.5.2 Change with moderate potential impact on the quality of the active substance and the finished product (e.g. change in chemical separation method, such as switching from ion-exchange HPLC to reversed-phase HPLC)?	iii.5.1( ) Yes ( ) No iii.5.2 ( ) Yes ( ) No
	iii.6 Change in the scale of the manufacturing process:	

	iii.6.1 In the fermentation or viral or cellular propagation stage? iii.6.2 In the purification stage? iv. Change, inclusion or exclusion of API/active substance production equipment with different design and operating principle? v. Changes in the physicochemical properties of the API/active substance with influence on the quality of the investigational drug (e.g. particle size distribution, polymorphism, etc.) ? vi. Changes related to quality control, such as expansion of specification limits, exclusion of tests and change of non-compendial analytical method related to critical quality parameters such as quantification of content and impurities, provided that the method is not equivalent or superior to the original method?	iii.6.1 ( ) Yes ( ) No iii.6.2 ( ) Yes ( ) No iv. ( ) Yes ( ) No v. ( ) Yes ( ) No vi. ( ) Yes ( ) No
	b) Modifications related to the Investigational Drug ? i. Replacement/Inclusion of a new manufacturing site or manufacturing steps, except for immediate/conventional release synthetic and semi-synthetic drugs ? ii. Modifications with an impact on the release of the API or active substance of the investigational drug or critical quality parameters, including stability and impurities, and: ii.1 Qualitative modifications in the composition ? ii.2 Change in the manufacturing process and inclusion or exclusion of equipment with a different design and operating principle ? ii.3 Increase in batch size above 10 (ten) times the initially approved batch size ? ii.4 Change in the primary packaging ? iii. Changes related to quality control, such as expansion of specification limits, exclusion of tests and change of non-compendial analytical method for critical quality parameters, provided that the method is not equivalent or superior to the original method? iv. Extension of the validity period and/or change in conservation care, provided that there has been a change in the previously established stability assessment criteria, that the values are not within the permitted ranges or that the validity period is defined based on reduced models of stability study plan (grouping and matrixing)? v. Inclusion of a new presentation that will require new stability studies? vi. Inclusion of a new concentration?	**b) ( ) Yes ( ) No** i. ( ) Yes ( ) No ii.1 ( ) Yes ( ) No ii.2. ( ) Yes ( ) No ii.3. ( ) Yes ( ) No ii42. ( ) Yes ( ) No iii. ( ) Yes ( ) No iv. ( ) Yes ( ) No

	vii. Inclusion of a new pharmaceutical form? viii. Inclusion of a new route of administration with change of pharmaceutical form? **c) Modifications related to Placebo or Active Comparator Modified?** i. Inclusion of placebo and/or modified active comparator not foreseen previously not DDCM?	v. ( ) Yes ( ) I didn't see. ( ) Yes ( ) I didn't see. ( ) Yes ( ) I didn't see. ( ) Yes ( ) I didn't see. **c) ( ) Yes ( ) No** i. ( ) Yes ( ) No
	d) Others, at the sponsor's discretion (including justifications)	**d) ( ) Yes ( ) No**

ANNEX

TEMPLATE FOR SUBMITTING UPDATED STABILITY INFORMATION

LONG TERM STABILITY STUDY (30°C ± 2°C / 75 RH ± 5% RH)

Product:

Active ingredient:

Name and Address of IFA Manufacturer:

Name and Address of Finished Product Manufacturer:

Primary packaging:

Pharmaceutical form:

Date of Manufacture:

Number of samples analyzed per period:

Study Start Date:

Study End Date:

Batch:

IFA lot:

Batch sizes (IFA and Finished Product):

Dosage:

Lot destination:

Packaging Position:

Test	Specification	Method	Home (t0)	3 months	6 months	9 months	12 months	18 months	24 months	36 months
		*	**	**	**	**	**	**	**	

* Also inform whether it is pharmacopoeial or not

** Justifications must be provided for any methods that will not be or were not performed at all analysis times.