ANNEX I

APPLICATION FORM FOR SUBSTANTIAL CHANGE OF THE DRUG CLINICAL DEVELOPMENT DOSSIER (DDCM)

	Document Identification
Brazilian National Health Surveillance Agency Clinical Research Petition Form for Substantial Change of the Drug Clinical Development Dossier (DDCM)	(For use of the receiver agency)

1	DDCM Case Number	2	Hours (Day / Month / Year) / /

Company Details

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

DDCM data

7	**Change Type**: a) Inclusion of clinical trial(s) protocol(s) not foreseen or other than that of the previously established clinical trial(s) in the initial development plan? b) Exclusion of clinical trial(s) protocol(s)? c) Changes that potentially impact the quality or safety of the investigational product? a. If yes, see item 8. d) Change resulting from recommendations or alerts issued by health authorities?	a) ( ) Yes ( ) No b) ( ) Yes ( ) No c) ( ) Yes ( ) No d) ( ) Yes ( ) No

8	**Reasons for Substantial Change**: **a) Modifications related to the Active Pharmaceutical Ingredient - API/Active Substance (biological products)?** i. Replacement/Inclusion of a new manufacturing site or manufacturing steps? ii. Change of the synthesis route (synthetic/semi-synthetic)? iii. Change in the manufacturing process of the active substance in biological products? iii.1 Change in cell banks, involving: iii.1.1 Generation of a new Master Cell Bank (MCB) from the same expression construct with the same cell line or highly similar cell line? iii. 1.2 Generation of new MCB from a different expression construct with the same coding sequence and the same cell line? iii. 1.3 Adaptation of a new MCB to a new culture medium? iii.1.4 Generation of new MCB for a recombinant product or viral vaccine? iii.2 Change in seed banks, involving: iii. 2.1 Establishment of a new Master Seed Bank (MSB)? iii. 2.2 Extension of the number of passes from the Working Seed Bank (WSB) beyond the approved level? iii.3 Change in the manufacturing location of the cell bank or seed bank? iii.4 Change of the fermentation or viral or cellular propagation process, fractionation or extraction: iii.4.1 Critical change (change with a high potential impact on the quality of the active substance or finished product, for example, incorporation of disposable bioreactor technology)? iii.4.2 Change with a moderate potential impact on the quality of the active substance or the finished product (for example, in vitro extension of cell age beyond validated parameters). iii.5 Change of the purification process: iii.5.1 Critical change (change with a high potential impact on the quality of the active substance and the finished product, for example, a change that can potentially impact the ability to remove/inactivate the virus 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 (for example, change in the method of chemical separation, as a substitution of ion exchange HPLC for reverse phase HPLC)? iii.6 Change in the scale of the manufacturing process: iii.6.1 In the stage of fermentation or viral or cellular propagation? iii.6.2 In the purification stage? iv. Change, inclusion or exclusion of API production equipment/active substance with different design and working principle? v. Changes in the physical-chemical properties of the API/Active substance with influence on the quality of the experimental drug (for example, 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 regarding critical quality parameters such as content and impurity quantification, provided that the method is not equivalent or superior to the original method?	**a) ( ) Yes ( ) No** i. ( ) Yes ( ) No ii. ( ) Yes ( ) No iii. ( ) Yes ( ) No iii.1.1 ( ) Yes ( ) No iii.1.2 ( ) Yes ( ) No iii.1.3 ( ) Yes ( ) No iii.1.4 ( ) Yes ( ) No iii.2.1 ( ) Yes ( ) No iii.2.2 ( ) Yes ( ) No iii.3 ( ) Yes( ) No iii.4.1 ( ) Yes ( ) No iii.4.2 ( ) Yes ( ) No iii.5.1 ( ) Yes ( ) No iii.5.2 ( ) Yes ( ) No iii.6.1 ( ) Yes ( ) No iii.6.2 ( ) Yes ( ) No iv. ( ) Yes ( ) No v. ( ) Yes ( ) No vi. ( ) Yes ( ) No

	b) Changes related to the Experimental Drug? i. Replacement/Inclusion of a new manufacturing site or manufacturing steps, except for synthetic and semi-synthetic drugs with immediate/conventional release? ii. Modifications with an impact on the release of the API or active substance of the experimental drug or critical quality parameters, including stability and impurities, and: ii.1 Qualitative changes in composition? ii.2 Change of the manufacturing process and inclusion or exclusion of equipment with different design and operating principle? ii.3 Increase in batch size over 10 (ten) times the size of the batch initially approved? ii.4 Change of 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 regarding critical quality parameters such as content and impurity quantification, provided that the method is not equivalent or superior to the original method? iv. Expansion of the expiration date 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 expiration date 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 new concentration? vii. Inclusion of a new dosage form? viii. Inclusion of a new route of administration with changes in dosage form? **c) Modifications related to Placebo or Modified Active Comparator?** i. Inclusion of placebo and/or modified active comparator not previously provided for in the DDCM?	**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 v. ( ) Yes ( ) No vi. ( ) Yes ( ) No vii. ( ) Yes ( ) No viii. ( ) Yes ( ) No **c) ( ) Yes ( ) No** i. ( ) Yes ( ) No
	d) d) Others, at the sponsor's discretion (including rationales)	**d) ( ) Yes ( ) No**

ATTACHMENT II
APPLICATION FORM FOR SUBSTANTIAL CHANGE TO THE CLINICAL TRIAL PROTOCOL

Brazilian National Health Surveillance Agency
Clinical Research
Application Form for Substantial Amendment to Clinical Trial Protocol

Document Identification
(For use of the receiver agency)

1	Case Number of the Specific Clinical Trial Dossier	2	Hours (Day / Month / Year) / /

Company Details

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

Clinical Trial Protocol Data

7	Petition Subject (codes and description)	8	Generator Factor (datavisa)	
9	Title and Code of the Clinical Trial Protocol	10	Protocol number (version and date)	
		11	Trial Phase I ( ) II ( ) III ( ) IV ( )	

12	**Reasons for Substantial Amendment**:	
	a) Change of the primary objective of the clinical protocol?	a) ( ) Yes ( ) No
	b) Change of the primary endpoints?	b) ( ) Yes ( ) No
	c) Use of new parameter to measure the primary endpoint?	c) ( ) Yes ( ) No
	d) Removal of the Independent Data Monitoring Committee originally planned for the study?	d) ( ) Yes ( ) No
	e) Change of the sample size calculation provided for the study?	e) ( ) Yes ( ) No
	f) Reduction of the sample size due to the interim analysis foreseen in the study?	f) ( ) Yes ( ) No
	g) Change of the statistical analysis for primary endpoints?	g) ( ) Yes ( ) No
	h) Changes related to the dosage, which are not foreseen in the protocol?	h) ( ) Yes ( ) No
	i) Extension or continuity of clinical research with removal of the control arm or active arm, crossover between arms (cross-over) change in the blinding of the study or inclusion of new participants?	i) ( ) Yes ( ) No
	j) Major changes related to adaptive studies, such as change/exclusion/addition of treatment arms, change of endpoints, change of dose and/or duration of treatment or adaptation of randomization schemes?	j) ( ) Yes ( ) No
	k) Inclusion of a new route of administration?	k) ( ) Yes ( ) No
	l) Expansion of use?	l) ( ) Yes ( ) No
	m) d) Others, at the sponsor's discretion (including rationales).	m) ( ) Yes ( ) No

ATTACHMENT III

MODEL FOR SENDING UPDATED STABILITY INFORMATION

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

Product:
Active ingredient:
API Manufacturer Name and Address:
Name and Address of the Finished Product Manufacturer:
Primary packaging:
Dosage form:
Manufacturing date:
Number of samples analyzed per period:

Study Start Date:
Study End Date:
Batch:
API Batch:
Batches size (API and Finished Product):
Dosage:
Destination of the batch:
Packing Position:

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

* Also inform if it is pharmacopeial or not

** Rationales must be provided for any methods that will not or have not been performed at all times of analysis.