APP-1

LIST AND CONDITIONS OF TYPE IA AND TYPE IB MINOR VARIATIONS TO BE CONDUCTED E IN ACCORDANCE WITH ARTICLES 5 AND 6

1. Variation in the name and/or address of the applicant	**Conditions to be fulfilled**	**Procedure type**
	1	**IA**
Conditions		
○ 1.The applicant should remain as the same real or legal person.		

2. Variation in the name of the medicinal product for human use	**Conditions to be fulfilled**	**Procedure type**
	1	**IB**
Conditions		
○ 1. It should not lead to a confusion with the names of medicinal products for human use already in the market, or with international non-registered names (INN).		

3. Variation in the name of the active substance	**Conditions to be fulfilled**	**Procedure type**
	1	**IA**
Conditions		

○ 1. The active substance should stay unchanged.

4. In case where there's no Certification of Suitability to the European Pharmacopeia, variation in the name and/or address of the manufacturer of active substance	**Conditions to be fulfilled**	**Procedure type**
	1	**IA**
Conditions		
○ 1. Production site should stay unchanged.		

5. Name and/or address variation for the manufacturer of the finished product	**Conditions to be fulfilled**	**Procedure type**
	1	**IA**
Conditions		
○ 1. Production place should stay unchanged.		

6. Variation in the ATC code	**Conditions to be fulfilled**	**Procedure type**
	1	**IA**
Conditions		

○ 1. A variation made by WHO (World Health Organization) concerning acceptance or amendment of the ATC code.

7. Variation or addition of a production site for part or all of the production process of the finished product.	**Conditions to be fulfilled**	**Procedure type**
a) Secondary packing site for all types of pharmaceutical forms	**1**	**IA**
b) Primary packing site		
1. Solid pharmaceutical forms; ie, tablets and capsules	**1,2,4**	**IA**
2. Semi-solid or liquid pharmaceutical forms,	**1,2,4**	**IB**
3. Liquid pharmaceutical forms (suspensions, emulsions)	**1,2,3,4**	**IB**
c) All other production operations except batch release	**1,3,4**	**IB**
Conditions		
○ 1. Having a GMP certificate showing suitability of the production site (for producing the referred pharmaceutical form or product), and an inspection report filed within the last three years.		
○ 2. The product not being a sterile product		
○ 3. Having a validation plan or having the validation of at least three industrially produced batches completed in accordance with the existing protocol at the new production site.		
○ 4. The product should not be a biological medicinal product for human use.		

8. Variation in batch release arrangements and quality control tests of the finished product	**Conditions to be fulfilled**	**Procedure type**

a) Variation of the site where batch controls/analyses are done; or addition of a new site	**2,3,4,**	**IA**
b) Changing a manufacturer responsible for releasing the batch, or adding a new responsible manufacturer		
1. Not including batch control /analysis	**1,2**	**IA**
2. Including batch control /analysis	**1,2,3,4**	**IA**
Conditions		
○ 1. Statement that the manufacturer responsible with releasing the batch is resident in the country		
○ 2. This production site should have been approved accordingly.		
○ 3. The product should not be a biological medicinal product for human use.		
○ 4. Declaration that method transfer from the old production site to the new production site or new test lab has been completed.		

9. Exclusion of any production site (including production site of an active substance, intermediate product or finished product, packing plant, manufacturer responsible for releasing the batch, the plant where batch controls are done)	**Conditions to be fulfilled**	**Procedure type**
	NA	**IA**

I0. A minor variation in the production method of active substance	**Conditions to be fulfilled**	**Procedure type**
	1,2,3	**IB**

Conditions
○ 1. There should be no qualitative or quantitative variation in the impurity profile or the physiochemical characteristics of the active substance.
○ 2. The active substance should not be a biological substance.
○ 3. The relevant synthesis method should stay unchanged; ie, intermediate products should stay unchanged. In herbal medicinal products for human use the geographical source, production of the herbal substance, and production style should stay unchanged.

11. Variation in the batch size of the active substance or intermediate product	**Conditions to be fulfilled**	**Procedure type**
a) In comparison with the original batch size approved during registration, up to ten times	**1,2,3,4**	**IA**
b) Reduction of the batch size	**1,2,3,4,5**	**IA**
c) In comparison with the original batch size approved during registration, more than ten times	**1,2,3,4**	**IB**

Conditions
○ 1. All changes in the production method should be only about increasing the size; for example, use of equipment of different size.
○ 2. For the prescribed batch size, there should be test results for at least two batches in accordance with specifications.
○ 3. The active substance should not be a biological substance.
○ 4. The variation should not affect the repeatability of the production process.
○ 5. The variation should be a result of unexpected situations arising during the production process, or because of stability.

12. Variation in the specifications of an active substance or of an initial substance/ intermediate product or chemical used in the production process of an active substance	**Conditions to be fulfilled**	**Procedure type**
a) Narrowing down the specification limits	**1,2,3,**	**IA**
	2,3	**IB**
b) Addition of a new testing parameter to the specifications		
1. Of the active substance	**2,4,5**	**IB**

2. Of an initial substance/ intermediate product/ chemical used in the production process of the active substance	**2,4**	**IB**
Conditions :		
○ 1. This variation should not be a result of a previous evaluation aimed to revise specification limits (for example, that done for a registration application or a Type II variation procedure).		
○ 2. the referred variation should not be a result of unexpected events arising during the production process.		
○ 3. Any variation should be within existing approved limits.		
○ 4. Any test procedure should not concern a non-standard new technique or a standard technique used in a new way.		
○ 5. The active substance should not be a biological substance.		
13. Variation in the test procedure of the active substance; or of the initial substance, intermediate product, or chemical used in the production of the active substance .	**Conditions to be fulfilled**	**Procedure type**
a) Minor variations in the approved test procedure	**1,2,3,5**	**IA**
b) Other changes in the analysis method, including a variation or addition of a test procedure.	**2,3,4,5**	**IB**
Conditions		
○ 1. The method of analysis should remain unchanged. For example, the length and temperature of the colon may variation, but the colon type or method of analysis should not variation. In other words, no impurity should be detected.		
○ 2. Appropriate revalidation studies conducted in accordance with relevant guides.		
○ 3. Method validation results should show that the test procedure is at least equivalent to the former procedure.		
○ 4. Any test procedure should not concern a non-standard new technique or a standard technique used in a new way.		
○ 5. The active substance should not be an initial material, intermediate product, or a chemical biological substance.		

14. Variation in the active substance that does not have a Certification of Suitability to the European Pharmacopeia; or in the initial material/intermediate product/ chemical/ manufacturer of intermediate product that is used in the production of the active substance	**Conditions to be fulfilled**	**Procedure type**
a) Variation (variation or addition) in the production site of an already approved manufacturer	**1,2,4**	**IB**
b) New manufacturer (variation or addition)	**1,2,3,4**	**IB**
Conditions		
o 1. Specifications (including in-process controls, and methods of analysis for all materials), production method (including the batch size), and detailed synthesis method should be the same as those approved previously.		
o 2. In processes where materials of human or animal origin are used, the manufacturer does not use a new supplier for whom an evaluation for conformity to regulations on viral safety or on minimizing the risk of transmitting animal spongiform encephalopathies (BSE/TSE) through available medical products for human use is required.		
o 3. Present or new manufacturer of active substance should not use an active substance master file.		
o 4. The variation should not concern a medicinal product for human use containing a biological active substance.		
15. Declaration of a new or updated Certification of Suitability to the European Pharmacopeia for the active substance or for an initial material/ intermediate product/ chemical used in the production method of the active substance	**Conditions to be fulfilled**	**Procedure type**
a) From an actual approved manufacturer	**1,2,4**	**IA**
b) From a new manufacturer (variation or addition)		
1. Sterile substance	**1,2,3,4**	**IB**
2. Other substances	**1,2,3,4**	**IA**

Conditions
○ 1. Specifications on finished product's release and shelf life stay unchanged.
○ 2. If applicable, unchanged additional specifications (for the European Pharmacopeia) for impurities, and specific conditions for the product (for example, particle size profiles, polymorphic form).
○ 3. If the repeat test period is not included in the Suitability Certification for the European Pharmacopeia or data supporting the repeat-test period is not offered, the active substance should immediately be tested before use.
○ 4. The main production method of this active substance/ initial material/ chemical/ intermediate product should not include use of materials of human or animal origin that require viral safety evaluation.

16. For an actual approved manufacturer or an actual approved production method, declaration of a new or updated TSE Certification of Suitability to the European Pharmacopeia for active substance, or initial material/ intermediate product/ chemical used in the production process of the active substance	**Conditions to be fulfilled**	**Procedure type**
Conditions	**NA**	**IA**
17. Variation	**Conditions to be fulfilled**	**Procedure type**
a) In the re-testing period of the active substance	**1,2,3**	**IB**
b) In storing conditions of the active substance	**1,2**	**IB**
Conditions :		
○ 1. Stability studies should have been done in accordance with the stability guide. The results of this study should be in conformance with relevant approved specifications.		

○ 2. The variation should not be a result of unexpected situations in the production process or because of stability.
○ 3. Active substance should not be a biological substance.

18. Exchanging an excipient with another, comparable excipient	**Conditions to be fulfilled**	**Procedure type**
	1,2,3,4,5	**IB**
Conditions :		
○ 1. Functional characteristics of the excipient should be identical.		
○ 2. The dissolution profile of the new product determined over a minimum of two pilot batches should be comparable to the dissolution profile of the former product. Absence of suggested discrepancies in comparing the profiles is determined according to regulations on bioavailability/bioequivalence. For herbal medicinal products where the dissolution test is not applicable, distribution time of the new product can be compared to that of the old product.		
○ 3. An excipient should not include use of materials of human or animal origin that require viral safety data evaluation.		
○ 4. Is not valid for a medicinal product for human use with biological active substance.		
○ 5. Stability studies in accordance with the stability guide should start with at least two pilot batches or industrial-size batches, and satisfactory stability data for at least three months should be available. Completion of these studies should be guaranteed. At the end of approved shelf life, if any data other than specifications are collected or if there's a potential for collecting data other than specifications, immediate submission of these data to the Ministry should be guaranteed.		
19. Variation in the specifications of an excipient	**Conditions to be fulfilled**	**Procedure type**
a) Narrowing down the specification limits	**1,2,3**	**IA**
	2,3	**IB**
b) Addition of a new test parameter to the specifications	**2,4,5,**	**IB**
Conditions :		

○ 1. This variation should not be resulting from an evaluation to revise specification limits (for ex., that done for registration application during procedure, or for a Type II variation procedure).
○ 2. The variation should not be a result of unexpected events in production.
○ 3. Any variation should be within approved actual limits.
○ 4. A test procedure does not consider a non-standard new technique or a standard technique used in a new way.
○ 5. The variation should not include vaccines or a substance to replace a biological excipient.

20. Variation in the test procedure of an excipient	**Conditions to be fulfilled**	**Procedure type**
a) Minor variations in the approved test procedure	**1,2,3,5**	**IA**
b) Minor variations in the approved test procedure for a biological excipient	**1,2,3**	**IB**
c) Other changes in the test procedure; including replacing an approved test procedure with a new test procedure	**2,3,4,5**	**IB**
Conditions :		
○ 1. The method of analysis should stay unchanged (for ex., colon length or tempreature may variation, but colon type and method of analysis should not variation).		
○ 2. Appropriate revalidation studies should be carried out in accordance with relevant guides.		
○ 3. Method validation results should show the new procedure to be at least equivalent to the previous one.		
○ 4. A test procedure does not consider a non-standard new technique or a standard technique used in a new way.		
○ 5. The substance should not be a biological excipient.		
21. Declaration of a new or updated Certification of Suitability with the European Pharmacopeia for an excipient	**Conditions to be fulfilled**	**Procedure type**
a) From an actual approved manufacturer	**1,2,3**	**IA**

b) From a new manufacturer (variation or addition)		
1. Sterile substance	**1,2,3**	**IB**
2. Other substances	**1,2,3**	**IA**
Conditions :		
○ 1. Specifications on the release or shelf-life of a finished product should stay unchanged.		
○ 2. If applicable, unchanged additional specifications (for the European Pharmacopeia) for product-specific conditions (ie, particle size profiles, polymorphic form),		
○ 3. Production method of the excipient concerned should not include materials of human or animal origin that require viral safety data evaluation.		

22. Declaration of a new or updated TSE Certification of Suitability with the European Pharmacopeia for an excipient	**Conditions to be fulfilled**	**Procedure type**
From an actual approved manufacturer or a new manufacturer (variation or addition)	**None**	**IA**

23. Variation in the chemical or excipient source of an herbal or synthetic material with a TSE risk.	**Conditions to be fulfilled**	**Procedure type**
a) Excipient or chemical used in the production of biological active substance or of finished product including a biological active substance	**1**	**IB**
b) Other situations	**1**	**IA**
Conditions :		
○ 1. Specifications concerning release or shelf-life of excipient or finished product stay unchanged.		

24. Variation in the synthesis or recycling of an excipient not included in the Pharmacopeia	**Conditions to be fulfilled**	**Procedure type**
	1,2	**IB**
Conditions :		
○ 1. Specifications should not be affected negatively. There should be no qualitative or quantitative changes in the impurity profile or in physiochemical characteristics.		
○ 2. The excipient should not be a biological substance.		

25. Variation for suitability to the European Phramacopeia or the National Pharmacopeia	**Conditions to be fulfilled**	**Procedure type**
a) Variation for suitability to the European Phramacopeia or the National Pharmacopeia in the specifications of a substance not included in the previous European Pharmacopeia		
1. Active substance	**1,2**	**IB**
2. Excipient	**1,2**	**IB**
b) Variation for suitability to updated relevant monograph in the European or National Pharmacopeia		
1. Active substance	**1,2**	**IA**
2. Excipient	**1,2**	**IA**
Conditions :		
○ 1. Variation should be made only for suitability to the Pharmacopeia.		

26. Variation in primary ready-packing specifications of the finished product	**Conditions to be fulfilled**	**Procedure type**
a) Narrowing down the specification limits	**1,2,3**	**IA**
	2,3	**IB**
b) Adding a new test parameter	**2,4**	**IB**
Conditions :		
○ 1. The variation should not result from a pledge in previous evaluations done for revising specification limits (for ex., registration application or Type II amendment application)		
○ 2. Variation should not result from unexpected situations during production.		
○ 3. Any variation should be within actual approved limits.		
○ 4. A new test procedure should not be related to a non-standard new technique or a standard technique used in a new way.		
○ 2. Where applicable, unchanged specifications for product-specific characteristics (i.e., particle size profiles, polymorphic form).		

27. Variation in the primary packing test procedure of the finished product	**Conditions to be fulfilled**	**Procedure type**
a) Minor variation in the approved test procedure	**1,2,3**	**IA**
b) Other changes including changing or adding a test procedure	**2,3,4**	**IB**
Conditions :		
○ 1. The analysis method concerned should stay unchanged (for ex., length or temperature of colon may variation, but colon type or method of analysis should stay unchanged. A different type of colon and not as the main method.)		
○ 2. Revalidation studies should be conducted in accordance with relevant guides.		

○ 3. Method validation data should show that the new test procedure is at least equivalent to the previous procedure.		
○ 4. Any test procedure should not be related to a non-standard new technique or a standard technique used in a new way.		
28. Variation in any part of the primary packing not in contact with the finished product formulation (for ex., such as colors of easy-to-open closures, color codes on ampoules, variation in syringe container-such as use of a different plastic).	**Conditions to be fulfilled**	**Procedure type**
	1	**IA**
Conditions :		
○ 1. The variation should not be concerning the basic components that may affect purchase, usage, reliability or stability of the packing material or finished product.		
Documents		
○ 1. Information and documents on the variation made in relevant parts of the IIC Chapter or their equivalent in CTD format.		

29. Qualitative and/or quantitative variation in the composition of the primary packing material	**Conditions to be fulfilled**	**Procedure type**
a) Semi-solid or liquid pharmaceutical forms	**1,2,3,4**	**IB**
b) All other pharmaceutical forms	**1,2,3,4**	**IA**
	1,3,4	**IB**
Conditions :		
○ 1. The product should not be a biological and sterile product.		
○ 2. This variation concerns only the same packing types and materials (ie, from blister to blister)		
○ 3. On relevant characteristics, suggested packing material should be equivalent to at least approved packing material		

○ 4. Stability studies in accordance with the stability guide should start with at least two pilot batches or industrial-size batches, satisfactory stability data for at least three months should be available, and completion of these studies should be guaranteed. At the end of the approved shelf life, if any data other than specifications are collected or if there's a potential for collecting data other than specifications, submission of these data along with the given activity plan to the Ministry at the shortest time should be guaranteed.

30. Variation in the supplier of packing components or equipment (variation, addition, removal) (when mentioned in the file); (except measurement devices for measured dosage inhalers)	**Conditions to be fulfilled**	**Procedure type**
a) Removing a supplier	**1**	**IA**
b) Changing or adding a supplier	**1,2,3,4**	**IB**
Conditions :		
○ 1. The packing component or equipment should not be removed.		
○ 2. Qualitative and quantitative composition of the packing component/equipment should stay unchanged.		
○ 3. Specifications and quality control method should at least be equivalent.		
○ 4. If any, sterilization method and conditions should stay unchanged.		

31. Variation in the in-process tests and limits applied during production of the product	**Conditions to be fulfilled**	**Procedure type**
a) Narrowing down the in-process limits	**1,2,3**	**IA**
	2,3	**IB**
b) Adding new tests or limits	**2,4**	**IB**
Conditions :		
○ 1. The variation should not result from pledges in previous evaluations (for ex, procedure relating to registration application or application for a Type II variation).		

○ 2. This variation should not result from an unexpected situation during production or because of stability.
○ 3. Any variation should be within actual approved limits.
○ 4. A new test procedure should not be related to a non-standard new technique or a standard technique used in a new way.

32. Variation in the batch size of the finished product	**Conditions to be fulfilled**	**Procedure type**
a) Variation of upto ten times the original batch size approved during registration	**1,2,3,4,5**	**IA**
b) Reducing the production scale down 10 times	**1,2,3,4,5,6**	**IA**
c) Other situations	**1,2,3,4,5,6,7**	**IB**
Conditions :		
○ 1. The variation should not affect reproduceability and/or consistency of the product.		
○ 2. This variation should only be concerning standard immediate-release oral pharmaceutical forms and non-sterile liquid forms.		
○ 3. All changes in the production method and/or in-process controls should result only from a variation in the batch size (for ex. Use of equipment of different size).		
○ 4. There should be a validation chart, or it should be realized according to actual protocol with at least three batches of the new batch size prescribed in accordance with guides on production validation		
○ 5. It should not concern a medicinal product for human use that includes a biological active substance.		
○ 6. This variation should not result from an unexpected situation during production or because of stability.		

○ 7. Stability studies in accordance with the stability guide should start with at least two pilot batches or industrial-size batches; stability data for at least three months should be available; and completion of these studies should be guaranteed. At the end of the approved shelf life, if any data other than specifications are collected or if there's a potential for collecting data other than specifications, submission of these data along with the activity plan to the Ministry at the shortest time should be guaranteed.

33. Minor variations in the production of finished product	**Conditions to be fulfilled**	**Procedure type**
	1,2,3,4,5	**IB**
Conditions :		
○ 1. The general production principle should stay unchanged.		
○ 2. With the new method, the product should be same as to quality, reliability, and effectiveness.		
○ 3. Medicinal product for human use should not contain a biological active substance.		
○ 4. In case of any variation in the sterilization procedure, it should only be within the scope of the standart pharmacopeia.		
○ 5. Stability studies in accordance with the stability guide should start with at least two pilot batches or industrial-size batches; stability data for at least three months should be available; and completion of these studies should be guaranteed. At the end of the approved shelf life, if any data other than specifications are collected or if there's a potential for collecting data other than specifications, submission of these data along with the activity plan to the Ministry at the shortest time should be guaranteed.		

34. Variation in the coloring agent or flavoring agent presently used in the finished product	Conditions to be fulfilled	Procedure type
a) Reducing or removing one or more components		
1. Coloring agent	**1,2,3,4**	**IA**
2. Flavoring agent	**1,2,3,4**	**IA**
b) Increasing, adding, or changing one or more components		
1. Coloring agent	**1,2,3,4,5,6**	**IB**
2. Flavoring agent	**1,2,3,4,5,6**	**IB**

Conditions :

- 1. There should be no variation in the functional characteristics of the pharmaceutical form; ie, distribution time, dissolution profile, etc.
- 2. Any small adjustments on the formulation to keep the total weight unchanged should be on an excipient which forms much of the finished product formulation.
- 3. Appearance/ smell/ flavor, and if necessary, a recognition test should be devised for finished product specifications, or should be updated within the scope of an addition.
- 4. Stability studies (long-term and expedited) in accordance with the stability guide should start with at least two pilot batches or industrial-size batches; stability data for at least three months should be available; and completion of these studies should be guaranteed. At the end of the approved shelf life, if any data other than specifications are collected or if there's a potential for collecting data other than specifications, submission of these data along with the activity plan to the Ministry at the shortest time should be guaranteed. In addition, photo-stability test should be done where applicable.

○ 5. All new prescribed components should be in accordance with relevant notifications (for ex., Notification on Coloring Agents Used in Medical Products for Human and Veterinary Use, published in the Official Gazette dated 18.01.2005 no. 25704; Notification on Flavorings Used in Food Products, published in the Official Gazette dated 25.08.2002, no. 24857)
○ 6. No new component should contain materials of human or animal origin that require conformity to regulation on viral safety evaluation, or on minimizing the risk of transmitting animal spongiform encephalopathies in medicinal products for human use (BSE/TSE) through medical products.

35. Variation in coating weights or capsule case weights of tablets	**Conditions to be fulfilled**	**Procedure type**
a) Immediate release pharmaceutical forms	**1,3,4**	**IA**
b) Dosage forms that are enteric coated, changed, or that enable long-term release	**1,2,3,4**	**IB**
Conditions :		
○ 1. For the new product concerned, the dissolution profile that is determined over two pilot size batches should be comparable to the dissolution profile of the previous product. For herbal medicinal products for human use where dissolution test may not be meaningful, distribution time of the new product may be compared to that of the previous product.		
○ 2. Coating should not be a critical factor for the release mechanism.		
○ 3. If any, specifications of the finished product as to weight and size should be updated.		
○ 4. Stability studies in accordance with the stability guide should start with at least two pilot batches or industrial-size batches; stability data for at least three months should be available; and completion of these studies should be guaranteed. At the end of the approved shelf life, if any data other than specifications are collected or if there's a potential for collecting data other than specifications, submission of these data along with the activity plan to the Ministry at the shortest time should be guaranteed.		

36. Variation in the shape or size of the container or closure.	**Conditions to be fulfilled**	**Procedure type**
a) Sterile pharmaceutical forms or biological medical products for human use	**1,2,3**	**IB**

b) Other pharmaceutical forms	**1,2,3**	**IA**
Conditions :		
○ 1. There should be no variation in the qualitative or quantitative composition of the container.		
○ 2. This variation should not concern the main component of the packing material that may affect distribution, usage, reliability, or stability of the finished product.		
○ 3. In case of a variation in unused volume or surface/volume ratio of the container, in accordance with the stability guide, stability studies should start with at least two pilot batches (three for biological products) or industrial-size batches; stability data for at least three months (six months for biological medicinal products for human use) should be available; and completion of these studies should be guaranteed. At the end of the approved shelf life, if any data other than specifications are collected or if there's a potential for collecting data other than specifications, submission of these data along with the activity plan to the Ministry at the shortest time should be guaranteed.		

37. Variation in the specifications of the finished product	**Conditions to be fulfilled**	**Procedure type**
a) Narrowing down the specification limits	**1,2,3**	**IA**
	2,3	**IB**
b) Adding a new test parameter	**2,4,5**	**IB**
Conditions :		
○ 1. The variation should result from pledges at previous evaluations to revise specification limits (for ex. That done during registration application or application for a Type II amendment).		
○ 2. The variation should not result from unexpected events in production.		
○ 3. Any variation should be within actual approved limits.		
○ 4. A new test procedure should not concern a non-standard new technique or a standard technique used in a new way.		
○ 5. The test procedure should not be applied to a biological active substance, or a biological excipient in the medicinal product for human use.		

38. Variation in the test procedure of the finished product	**Conditions to be fulfilled**	**Procedure type**
a) Minor variation in the approved test procedure	**1,2,3,4,5**	**IA**

b) Minor variation in the test procedure on biological active substance or biological excipient	**1,2,3,4**	**IB**
c) Other changes in a test procedure, including changing or adding a test procedure	**2,3,4,5**	**IB**
Conditions :		
○ 1. The method of analysis should stay unchanged (e.g., length and temperature of colon may variation, but colon type or analysis method should not be changed).		
○ 2. Appropriate validation studies should be carried out in accordance with relevant guides.		
○ 3. Method validation results should show that the new test procedure is at least equivalent to the previous one.		
○ 4. Any new test procedure should not concern a non-standard new technique or a standard technique used in a new way.		
○ 5. The test procedure should not be applied to a biological active substance or to a biological excipient in the medicinal product for human use.		
39. Changes in imprints, embosses or other signs (except indentures) on tablets or printing on capsules (including a variation or addition in inks used for marking)	**Conditions to be fulfilled**	**Procedure type**
	1,2	**IA**
Conditions :		
○ 1. Specifications regarding release of finished product or shelf life should not variation (except appearance).		
○ 2. Any new ink should be in in accordance with the Notification on Coloring Agents Used in Medical Products for Human and Veterinary Use, published in the Official Gazette dated 18.01.2005, no 25704.		

40. Variation in size of tablets, capsules, suppositories, or ovules without any variation in qualitative or quantitative composition or average mass	**Conditions to be fulfilled**	**Procedure type**
a) Enteric coated, changed or long-term release pharmaceutical forms and indented tablets	**1,2**	**IB**
b) All other tablets, capsules, suppositories and ovules	**1,2**	**IA**

Conditions :
o 1. The dissolution profile of the reformulated product should be comparable with the former profile. In herbal medicinal products for human use where dissolution test may not be meaningful, the distribution time of the product should be compared with that of the former product.
o 2. Release and shelf-life specifications of this product should not variation (except dimensions).

41. Variation in package size of the finished product	**Conditions to be fulfilled**	**Procedure type**
a) Variation in number of units within the package (i.e.; tablets, ampoules)		
1. Variation within limits of actual approved package sizes	**1,2**	**IA**
2. Variation outside limits of actual approved package sizes	**1,2**	**IB**
b) Variation in filling weight/ filling volume of non-parenteral multiple dosage products	**1,2**	**IB**
Conditions :		
o 1. The new package size should be consistent with the usage form, dosage, and treatment period as approved in Summary of Product Characteristics (SPC).		
o 2. Primary packaging material should stay unchanged.		

42. Variation	**Conditions to be fulfilled**	**Procedure type**
a) Shelf-life of finished product		
1. In package to be marketed	**1,2,3**	**IB**

2. After initial opening	**1,2**	**IB**
3. After being diluted or mixed	**1,2**	**IB**
b) Storage conditions of the finished product or diluted/mixed product	**1,2,4**	**IB**
Conditions :		
○ 1. Stability studies should be conducted in accordance with the stability guide. This should show that the studies are in accordance with relevant approved specifications.		
○ 2. The variation should not result from unexpected events during production, or be because of stability.		
○ 3. Shelf-life should not exceed 5 years.		
○ 4. The product should not be a biological medicinal product for human use.		

43. Addition or changing or removal of a measurement or application device (except measurement devices for measured dosage inhalers) that is not an integral part of the primary package	**Conditions to be fulfilled**	**Procedure type**
a) For medicinal products for human use		
1. Addition or changing	**1,2**	**IA**
2. Removal	**3**	**IB**
Conditions :		

○ 1. The prescribed measurement device should measure out the right and required dosage for the product concerned, in accordance with the approved usage form and dosage.
○ 2. The new device should be compatible with the medicinal product for human use.
○ 3. The medicinal product for human use should still be able to be given correctly.

APP-2

Cases Specified in Article 2, Paragraph 2, Item (a) of this Regulation, Requiring New Registration Application

The variations listed below, as mentioned in Article 2, paragraph 2, item (a) of this Regulation, shall be deemed as "Additional Application";

Any addition or variation in the existing registration shall be approved by the Ministry.

Variations requiring additional application:

a) Variations in the active substance/substances:

1) Exchanging the active substance/substances with a different salt/ester complex/derivative belonging to the same therapeutic group and with effectiveness/reliability characteristics not significantly different,

2) Exchanging with a different isomer mixture (for ex: racemate with a single enantiomer) with effectiveness/reliability characteristics not significantly different,

3) Exchanging a biological substance or biotechnological product with a substance with slightly different molecular structure. Modification of the vector used for producing antigen/source material including the new main cell bank from a different source with active substance/substances and effectiveness/reliability characteristics not much different.

4) A new ligand or binding mechanism for radiopharmaceuticals,

5) Changing the herbal drug ratio or the extraction solvent in a herbal drug preparation where effectiveness and reliability characteristics are not significantly different.

b) Variations of dosage, pharmaceutical forms, and application method:

1) Variation in bioavailability,

2) Variation in pharmacokinetics (for ex: variation in speed of release)

3) Addition to or variation in potency of new dosage

4) Addition or variation of new pharmaceutical form,

5) Addition or variation of new application method.