Case No.18. Standard Operating Procedures for approval of post-registration variations..

Registration Board in its 240th meeting held on 07th November, 2013 approved various SOPs for processing of post registration variations. These SOPs were again considered by the Board in various meetings (278th, 279th, 281st and 282nd) for further rationalizing the requirements and deferred for comments of stakeholders. Accordingly, the Board reviewed and approved following SOPs for further implementation

A. Locally manufactured products:

1. Change in excipients (inactive) including colour.

a) In case of any addition, deletion or substitution of excipient, it shall be sufficient to inform along with stability data and technical information {b)-g)} in writing for which acknowledgment shall be obtained for record, as required vide SRO 662(I)/2005 dated 25-06-2005.
b) Copy of registration letter and last renewal status.
c) Specification of existing and proposed excipients / Colour.
d) Document confirming that proposed excipient / inactive is of pharmaceutical grade.
e) Results of stability testing (as per conditions of zone IV-A) with a minimum of 3 months of accelerated and 3 months of long-term testing on 03 lab scale batches or developmental scale batches as set by Registration Board in 276th meeting. Description and composition of the FPP including Batch formula, description of manufacturing process and process controls, if different from previous one.
f) An undertaking that:
    i. The provided information is true & correct.
    ii. There is no change in specifications of FPP.
    iii. All excipients are of Pharmacopeial grade.
    iv. All excipients do not include the use of materials of human or animal origin for which TSE/BSE risk assessment/safety data is required.
    v. For any change in the quantity of excipient(s) except for those excipient(s) in which a duty drawback is claimed, no prior permission shall be required.
    vi. That the new excipient does not interfere with the analytical procedures for the FPP.
    vii. In case of any quality complaint/ OOS result observed by the marketing authorization holder as a result of this change, the same shall be reported to Registration Board and all the stock shall be recalled from the market immediately.

2. Change of Source of Half Finished Products (Pellets / Granules / Ready to Fill Bulk etc)

a) Application with required fee as per relevant SRO.
b) Copy of registration letter and last renewal status.
c) Both real time & accelerated stability studies of Half finished products (pellets / granules / ready to fill bulk) conducted by manufacturer of half finished product as per conditions of zone IV-A or zone IV-B on 3 commercial scale batches.
d) Certificate of analysis of manufacturer.
e) Documents confirming that the proposed source has valid permission for manufacturing of pellets / granules / ready to fill bulk by the regulatory authority of country of origin.
f) Valid & legalized GMP certificate issued by regulatory authority of exporting country if not already submitted in DRAP during last 1 year.
g) An Undertaking that:

a. Shelf life of finished product would be assigned after conducting product development studies, real time and accelerated stability studies on 3 batches of commercial scale, validation of manufacturing process and method of analysis before sale of drug.
b. In case of any quality complaint/ OOS result observed by the marketing authorization holder as a result of this change, the same shall be reported to registration board and all the stock shall be recalled from the market immediately.
c. That the provided information is true & correct.

3. Registration of Product from One Manufacturer to another Manufacturer with Change in Manufacturing Site.

a) Application with Form-5 and required fee as per relevant SRO.
b) Copy of registration letter and last renewal status.
c) Copy of approved section by Central Licensing Board or panel inspection report conducted for renewal of DML as evidence of approved sections (in cases of DML before 2005).
d) Copy of last inspection report conducted by DRAP within last 12 months.
e) NOC (issued within last 6 Months) from existing manufacturer / registration holder permitting for registration of product to another manufacturer.
f) Statement / undertaking that applicant do not have registration of same products. If so, it has to apply for cancellation of product.
g) Undertaking that firm will conduct product development, accelerated and real time stability studies, validation of manufacturing process and method of analysis before sale of drug.
h) An Undertaking that:
   i. Validated method of analysis, master formula and product development data shall be provided.
   ii. In case of any quality complaint/ OOS result observed by the marketing authorization holder as a result of this change, the same shall be reported to registration board and all the stock shall be recalled from the market immediately.
   iii. Undertaking that the provided information is true & correct.

4. Registration of Product after Change in Name / Title of Manufacturer (Site of Manufacturing Remains the Same)

a) Application on Form-5 with required fee as per relevant SRO.
b) Copy of registration letter and last renewal status.
c) Approval of new name / title from CLB.
d) Undertaking that:
   i. The formulation, API source & Specifications, manufacturing process, release & shelf life specifications have not changed.
   ii. Provided information is true & correct.

5. Extension in Shelf life

a. Application with required fee as per relevant SRO.
b. Copy of registration letter and last renewal status.
c. Proposed shelf-life, justification & data of long-term stability testing (as per conditions of zone IV-A) including chromatograms for a minimum of 3 commercial scale batches or development scale batches as set by Registration Board in 276th meeting up to the proposed shelf-life.
d. An undertaking that:
   - No change to the primary packaging type that is in direct contact with the FPP and to the recommended conditions of storage.
   - No change in formulation and specification either of finished product, API and excipients etc.

- In case both the above conditions are involved then manufacturer will submit complete requisite information as per procedure.
- In case of any quality complaint/ OOS result observed by the marketing authorization holder as a result of this change, the same shall be reported to registration board and all the stock shall be recalled from the market immediately.

6. **Reduction in Shelf Life.**

a. Application with required fee as per relevant SRO.
b. Copy of registration letter and last renewal status.
c. If proposed shelf-life is for more than two years, justification & data of long-term stability testing (as per conditions of zone IV-A) including chromatograms for a minimum of 3 commercial scale batches or development scale batches up to the proposed shelf-life.
d. If the reduction is necessitated because of stability concerns, declaration of reason for reduction in shelf life.
e. Undertaking that:
    a. Provided information is true & correct.
    b. The change is not necessitated by failure to meet specifications or resulting from unexpected events arising during manufacture.
    c. In case of any quality complaint/ OOS result observed by the marketing authorization holder, the same shall be reported to registration board and all the stock shall be recalled from the market immediately.

7. Change in Labelled Storage Conditions

a) Application with required fee as per relevant SRO.
b) Copy of registration letter and last renewal status.
c) Proposed change is supported by documentary evidence from reference regulatory authorities and/ or innovator product.
d) Undertaking that:
    i. The change is in accordance with innovator's product/ Reference Regulatory Authorities
    ii. Provided information is true & correct.
    iii. The change is not necessitated by failure to meet specifications or resulting from unexpected events arising during manufacture.
    iv. If the change is necessitated because of stability concerns, declaration of relevant reason for change in storage condition.
    v. In case of any quality complaint/ OOS result observed by the marketing authorization holder, the same shall be reported to registration board and all the stock shall be recalled from the market immediately.

8. Change in Prescribing Information (PI)

a) Application with required fee as per relevant SRO.
b) Copy of registration letter and last renewal status.
c) Difference between existing and proposed information in tabulated form.
d) Justification of proposed changes.
e) Reference of prescribing information approved by Reference Regulatory Authorities and innovator product.
f) Copy of approval from regulatory agency / authority from country of origin for innovator's product
g) Copy of label outer pack in case of changes in indication/ dose/ administration etc.
h) Undertaking that the provided information is true & correct.

9. Change in Primary Packaging Material/ Container Closure System.

a) Application with required fee as per relevant SRO.
b) Copy of registration letter and last renewal status.
c) Justification of proposed change including data on the suitability of the container-closure system (e.g. extractable/ leachable testing (where applicable), permeation testing, light transmission) demonstrating equivalent or superior protection compared to the current packaging system. For changes to functional packaging related to container closure (e.g MDIs etc), data to demonstrate the functioning of the new packaging.
d) If the container closure system of applied formulation is different from that of the reference product, manufacturer will place first three lab scale batches or developmental scale batches as set by Registration Board in 276th meeting, at 3 months of accelerated and 3months of real time studies for compatibility of applied formulation with container closure system as directed by Pharmacopeia of Reference Regulatory Authorities. Registration Board shall be informed immediately and along with market withdrawal in case of any significant change about result of stability studies.
e) Shelf life of the drug product supported with justification.
f) Existing and proposed container closure system with differences (e.g. description, materials of construction of primary packaging components, specifications, if appropriate) highlighted in tabular form.
g) If the proposed change requires change in manufacturing section/ facility, then a new registration application with prescribed fee shall be submitted.
h) Undertaking:
    i. To perform stress studies.
    ii. In case of any quality complaint/ OOS result observed by the marketing authorization holder as a result of this change, the same shall be reported to registration board and all the stock shall be recalled from the market immediately.
    iii. Provided information is true & correct.

10. Change in the Shape or Dimensions of the Container Closure System

a) Application with required fee as per relevant SRO.
b) Copy of registration letter and last renewal status.
c) Information on the proposed container-closure system (e.g. description, materials of construction, and specifications).
d) Undertaking that:
    i. Other specifications of the product would remain the same.
    ii. There is no change in the qualitative & quantitative composition of the product and manufacturer will conduct product development, accelerated and real time stability studies, validation of manufacturing process and method of analysis before sale of drug.
    iii. In the case of changes to the thickness of a packaging component or for sterile FPPs: stability data (as per conditions of zone IV-A), where applicable, results of photo-stability studies shall be conducted on 03 lab scale batches or developmental scale batches as set by Registration Board in 276th meeting.
    iv. In the case of a change in the headspace or a change in the surface/volume ratio for non-sterile FPPs, a commitment for the above studies to ensure appropriate delivery.
    v. Revalidation studies shall be conducted in the case of terminally sterilized products. The batch numbers of the batches used in the revalidation studies should be indicated, where applicable.
    vi. No change in the qualitative or quantitative composition of the container and/or Closure.
    vii. The change does not concern a fundamental part of the packaging material, which could affect the delivery, use, safety or stability of the FPP.

viii. In case of any quality complaint/ OOS result observed by the marketing authorization holder as a result of this change, the same shall be reported to registration board and all the stock shall be recalled from the market immediately.

ix. Undertaking that the provided information/ documents are true/ correct.

11. Change of Secondary Packaging Materials.

a) Application with required fee as per relevant SRO.
b) Copy of registration letter and last renewal status.
c) Justification of proposed change.
d) Existing and proposed packaging materials.
e) Difference between existing and proposed information in tabulated form.
f) Confirmation and undertaking that proposed label complies all provisions of Drugs (Labeling & Packing) Rules,1986.
g) An undertaking that:
    a. The proposed colour scheme / label has no resemble with already registered Products. In case of resemblance, new label will be changed immediately. Moreover, no case is pending at any forum / court of law regarding this matter.
    b. Dosage, administration, indication & direction for use etc. on the label be in line with marketing authorization.

12. Registration of Drugs (for Export Purpose).

a) Application on Form 5/Form 5D/ form5F (CTD) with required fee as per relevant SRO.
b) Copy of approved section from CLB or Panel Inspection Report for Renewal of DML as evidence of approved sections for DML before 2005.
c) Copy of last inspection report conducted by DRAP within last 12 months.
d) An undertaking that applied registration is exclusively for export purpose and will not be sold in Pakistan.
e) Evidence of generic / approval status by Reference Regulatory Authorities for applied formulation. In cases where the formulations are neither generic nor approved by Reference Regulatory Authorities, applicant will provide evidence of approval status of applied formulation by regulatory authority of importing country.
f) Copy of DML along with its renewal status.
g) An undertaking that the proposed names/ label/ color do not resemble with already registered brands in importing country. In case of resemblance/similarity with already registered drug product in importing country, the applicant will be liable to change immediately.

13. Change of Brand Name.

a) Application with required fee as per relevant SRO (in case of similarity / resemblance with already registered drug, fee will not be required).
b) Copy of registration letter and last renewal status.
c) Justification for proposed change.
d) Information regarding previous change of brand name since registration of drug.
e) Details (batch number, date of manufacture, quantity and stock position) regarding last batch manufactured.
f) An undertaking that the proposed names do not resemble with already registered brands. In case of resemblance /similarity with already registered drug, the applicant will be liable to change immediately. Moreover, no case is pending at any forum / court of law regarding this matter.
g) Undertaking that provided information/ documents are correct.
h) For reports regarding brand name resemblance, following documents/ information will be required:

i. Copy of registration letter & last renewal status of their registered product.
ii. Unit carton/ any other information as evidence of resemblance which is being reported.
iii. Undertaking that the provided information/ documents are true/ correct.

14. Change in Shape of Tablet / Color and Size of Capsule.

a) Application with required fee as per relevant SRO.
b) Copy of registration letter and last renewal status.
c) Justification for proposed change.
d) Undertaking that:
    i. Other specification of the product would remain the same.
    ii. There is no change in the qualitative & quantitative composition of the product and manufacturer will conduct product development, accelerated and real time stability studies, validation of manufacturing process and method of analysis before sale of drug.
    iii. In case of any quality complaint/ OOS result observed by the marketing authorization holder as a result of this change, the same shall be reported to registration board and all the stock shall be recalled from the market immediately.
    iv. Undertaking that the provided information/ documents are true/ correct.

15. Cancellation of Registration of Drug on Firm's Request.

a) Application.
b) Copy of registration letter and last renewal status.
c) Justification
d) List of alternatives brands/ FPPs available in the country.
e) An undertaking that:
    i. No case is pending at any forum / court of law regarding this product.
    ii. Provided information/ documents are true/ correct.

16. Corrigendum for Correction in Registration Letter.

a) Application with required fee as per relevant SRO, if error is on part of firm.
b) Copy of registration letter and last renewal status.
c) Document in support of proposed correction.
d) Undertaking that the provided information/ documents are true/ correct.

17. Standardization of Formulation In Accordance With the Innovator's Product/ Reference Regulatory Authorities and Pharmacopeias.

a) Application with required fee as per relevant SRO.
b) Copy of registration letter and last renewal status.
c) Document in support of proposed correction/evidence of approval status by Reference Regulatory Authorities/ innovator product and/ or Pharmacopeias as adopted by Registration Board.
d) Undertaking that the provided information/ documents are true/ correct.

18. Change of Finished Product Specifications

a) Application with required fee as per relevant SRO.
b) Copy of registration letter and last renewal status.
c) Document in support of proposed change.
d) Analytical reports as per monograph of FPP.
e) Undertaking that :
    i. The change is made exclusively to comply with the pharmacopeia of Reference Regulatory Authorities or as per Innovator's product specifications.
    ii. No case is pending at any forum / court of law regarding this product.

iii. In case of any quality complaint/ OOS result observed by the marketing authorization holder as a result of this change, the same shall be reported to registration board and all the stock shall be recalled from the market immediately.
iv. The provided information/ documents are true/ correct**.**

19. Grant of Additional Pack Size for Locally Manufactured Veterinary Products (Excluding Injectables)

a) Application with required fee as per relevant SRO.
b) Copy of registration letter and last renewal status.
c) Detail of previously granted pack sizes.
d) Generic status/ evidence of availability of applied additional pack sizes.
e) Undertaking that the provided information/ documents are true/ correct.
f) GMP inspection conducted by DRAP during last 12 months.

B. Imported products:

1. Change of Name of Manufacturer/ Marketing Authorization Holder of Imported Drugs.

a) Application with required fee as per relevant SRO.
b) Copy of registration letter and last renewal status.
c) Original and legalized Certificate of Pharmaceutical Product as per WHO format for new manufacturer's name Or Original and legalized GMP certificate of new manufacturing site with free sale certificate from regulatory body of country of origin Or any legalized document of concerned regulatory authority confirming change of name of Manufacturer/ Marketing Authorization Holder without change in manufacturing site
d) Revised Sole Agency Agreement when there is change in MAH.
e) Proof/ evidence of the contract between Product License Holder & manufacturer (with changed/ new name), where the manufacturer and product license holder are different entities.
f) Undertaking that the provided information/ documents are true/ correct.

2. Change of Address of Manufacturing Site/Source/Marketing Authorization Holder (MAH).

a) Application on Form 5A with required fee as per relevant SRO.
b) Copy of registration letter and last renewal status.
c) Original and legalized Certificate of Pharmaceutical Product as per WHO format for new manufacturer's name OR Original and legalized GMP certificate of new manufacturing site with free sale certificate from regulatory body of country of origin.
d) Site master file of new manufacturing site in case of change of manufacturing site/ source.
e) Revised Sole Agency Agreement when there is change in MAH.
f) Proof/ evidence of the contract between Product License Holder & manufacturer (with changed/ new name), where the manufacturer and product license holder are different entities.
g) Undertaking that the provided information/ documents are true/ correct.

3. Change in Shelf Life.

a) Application on Form 5A with required fee as per relevant SRO.
b) Copy of registration letter and last renewal status.
c) Proposed shelf-life, justification & data of long-term stability testing (as per conditions of zone IV-A) including chromatograms for a minimum of 3 commercial scale batches or development scale batches upto the proposed shelf-life.
d) Approval of regulatory body of country of origin or Original and legalized Certificate of Pharmaceutical Product as per WHO format.
e) Undertaking that:
    i. Provided information is true & correct.
    ii. *For reduction in shelf life:*

- The change is not necessitated by failure to meet specifications or resulting from unexpected events arising during manufacture.
- If the reduction is necessitated because of stability concerns, declaration of reason for reduction in shelf life.

iii. *For extension in shelf life:*

- No change to the primary packaging type in direct contact with the FPP and to the recommended conditions of storage.
- No change in formulation and specification either of finished product, API and excipients etc.
- In case both the above conditions are involved then manufacturer will submit complete requisite information as per procedure.

4. Change in Labelled Storage Conditions

a) Application with required fee as per relevant SRO.
b) Copy of registration letter and last renewal status.
c) Undertaking that:
   i. The change is in accordance with innovator's product/ Reference Regulatory Authorities
   ii. Provided information is true & correct.
   iii. The change is not necessitated by failure to meet specifications or resulting from unexpected events arising during manufacture.
   iv. If the change is necessitated because of stability concerns, declaration of reason for change in storage condition.

5. Registration of Product from One importer to another Importer.

a) Application on Form 5A with required fee as per relevant SRO.
b) Copy of registration letter and last renewal status.
c) Termination letter (original) from manufacturer for previous importer.
d) Authority letter/sole agent letter (original) from manufacturer.
e) Document confirming NOC (issued within last 6 Months) from existing registration holder permitting for registration of product to another importer.
f) Original and legalized Certificate of Pharmaceutical Product as per WHO format for new manufacturer's name OR Original and legalized GMP certificate of new manufacturing site with free sale certificate from regulatory body of country of origin.
g) Undertaking that the provided information/ documents are true/ correct.

6. Change in Primary Packaging Material/ Container Closure System

a) Application with required fee as per relevant SRO.
b) Copy of registration letter and renewal status.
c) Justification of proposed change including data on the suitability of the container-closure system (e.g. extractable/ leachable testing (where applicable), permeation testing, light transmission) demonstrating equivalent or superior protection compared to the current packaging system. For changes to functional packaging related to container closure (e.g MDIs etc), data to demonstrate the functioning of the new packaging.
d) If the container closure system of applied formulation is different from that of the reference product, manufacturer will place first three commercial scale batches at 3 months of accelerated and 3months of real time studies for compatibility of applied formulation with container closure system as directed by Pharmacopeia of Reference Regulatory Authorities. Registration Board shall be informed immediately and along with market withdrawal in case of any significant change about result of stability studies.
e) Shelf life of the drug product supported with justification.

f) Existing and proposed container closure system with differences (e.g. description, materials of construction of primary packaging components, specifications, if appropriate) highlighted in tabular form.
g) Undertaking
   - To perform stress studies.
   - That the provided information is true & correct.

7. Change in Secondary Packaging Materials.

a) Application with required fee as per relevant SRO.
b) Copy of registration letter and renewal status.
c) Justification of proposed change.
d) Existing and proposed packaging materials.
e) Difference between existing and proposed information in tabulated form.
f) Confirmation and undertaking that proposed label complies all provisions of Drugs (Labeling & Packing) Rules,1986.
g) An undertaking that the proposed colour scheme / label has no resemble with already registered Products. In case of resemblance, new label will be changed immediately.
Moreover, no case is pending at any forum / court of law regarding this matter.
h) Dosage, administration, indication & direction for use etc. on the label be in line with that authorization.
i) Regulatory approval of change from country of export.
j) Undertaking that the provided information/ documents are true/ correct.

8. Change of Brand Name.

a) Application with required fee as per relevant SRO (in case of similarity / resemblance with drug, fee will not be required).
b) Copy of registration letter and last renewal status.
c) Justification for proposed change.
d) Information regarding previous change of brand name since registration of drug.
e) Details (batch number, date of manufacture, quantity and stock position) regarding last batch imported.
f) An undertaking that the proposed names do not resemble with already registered brands.
In case of resemblance/similarity with already registered drug, the applicant will be liable to change immediately. Moreover, no case is pending at any forum / court of law regarding this matter.
g) Original and legalized Certificate of Pharmaceutical Product as per WHO format for new brand name OR Original and legalized GMP certificate of new brand name with free sale certificate from regulatory body of country of origin.
h) Undertaking that the provided information/ documents are true/ correct.

9. Change in Name of Importer of Drug Product with No Change of Proprietor.

a) Application with required fee as per relevant SRO (in case of similarity / resemblance with drug, fee will not be required).
b) Copy of registration letter and last renewal status.
c) Copy of Drug Sale License with new name.
d) Approval of new name by SECP / registrar of firm.
e) Sole Agency agreement with new name of importer by Manufacturer or product License Holder.
f) Undertaking by the firm that no case is pending at any forum / court of law regarding previous name.
g) Undertaking that the provided information/ documents are true/ correct.

10. Grant of Additional pack size for Veterinary Products Excluding Injectables

a) Application with required fee as per relevant SRO (in case of similarity / resemblance with drug, fee will not be required).
b) Copy of registration letter and last renewal status.
c) Detail of previously granted pack sizes.
d) Evidence of availability of demanded pack size in country of origin.
e) Undertaking that the provided information/ documents are true/ correct.

C. Correction/Changes That Necessitate Submission of New Application (Local Manufacture/Import):

a) Change in the dose and/or strength of one or more APIs.
b) Change from an immediate release product to an extended or delayed-release dosage form or vice versa.
c) Change in dosage form.
d) Case of additional flavor.
e) Change of the API to a different API.
f) Inclusion of an additional API in a multicomponent product.
g) Removal of one API from a multicomponent product.

(Note: Standardization of formulation in accordance with the standard formulation as approved by Reference Regulatory Authorities or innovator product will be done along with post registration variation)

Case No. 19: Approved Product of M/s Helix Pharma (Pvt) Ltd. Karachi.

Following Product of M/s Helix Pharma (Pvt) Ltd. Karachi was approved vide 235th meeting of Registration Board as per details below:

S.No.	Name of Drug(s) with composition	Demanded Pack	Demanded Price	Decision
1.	Sitaglip Tablet 100mg Each Tablet contains: Sitagliptin as Phosphate…..100mg (Anti hyperglycaemic)	28's	Rs.4571.41	Approved Subject to submission of signed undertaking

The firm has now submitted duplicate application on **Form-5D** along with undertaking regarding proposed brand name and photocopies for submission of balance fee of Rs.5000/- and initial fee of Rs.15,000/- and requested for issuance of registration letter.

Furthermore, as per form-5D submitted by the firm, formulation is film coated tablet.

Decision: Registration Board approved the grant of registration for Sitaglip Tablet 100mg with USP specifications.