FREQUENTLY ASKED QUESTIONS ABOUT FORM 5F

(COMMON TECHNICAL DOCUMENT)

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Scope:

This document primarily covers most frequently asked questions related to registration / marketing authorization of pharmaceutical drug products for Form-5F (CTD) for further guidance of applicants.

For detailed guidance, please refer to *Guidance document for submission of application on form 5-F (CTD) for registration of pharmaceutical drug products for human use (PE&R/GL/AF/004)* available on DRAP's website. (https://www.dra.gov.pk/Home/Download?ImageName=Guidance%20Document%20on%20CTD-Doc%20No.%20PE%26R-GL-AF-004.pdf)

I. Frequently Asked Questions

1. **What is the applicable Form for application for registration / marketing authorization of new and generic drug product (locally manufactured and imported)?**

   Application for registration / marketing authorization of new and generic drug product (locally manufactured and imported) shall be submitted on Form-5F (CTD) available at DRAP's website (https://www.dra.gov.pk/Home/Download?ImageName=sro_713%28I%29_2018.pdf)

2. **What is the applicable Form for application for registration / marketing authorization of new and generic drug product for export purpose only?**

   Application for registration / marketing authorization of new and generic drug product for export purpose only can be submitted on both Form-5 / 5D (https://www.dra.gov.pk/Home/Download?ImageName=Application%20Form%20for%20Registration%20of%20a%20Drug%20for%20Local%20Manufacture.pdf) or Form-5F (CTD).

3. **What is the applicable Form for application for registration / marketing authorization of veterinary pharmaceutical drug product?**

   Applications for registration / marketing authorization of veterinary drug product are required to be submitted on Form 5 / Form 5D / Form 5A not on Form 5F (CTD).

4. **What are the regulatory requirements for submission of registration / marketing authorization application of finished drug product (locally manufactured and imported)?**

   - For locally manufactured drug product, Drug Manufacturing License is prerequisite for submission of application for registration along with requisite manufacturing facility/section approved by Licensing Division, DRAP.
   - For finished imported drug product, Drug Sale License issued by relevant licensing authority is prerequisite for submission of application for registration along with requisite storage facility.

5. **What is the fee for registration of drug product for human use?**

   Currently fee for different categories of registration applications is as below:

Category of application	Fee (Rs.)
Locally manufactured generic drug	20,000/-
Locally manufactured new drug	50,000/-
Imported generic drug	100,000/-

Imported new drug	50,000/-
Contract manufacturing drug	50,000/-

6. **What are main steps for submission of application on Form 5F (CTD)?**
   i. Application (after submission of required fee) as per *Guidance document for submission of application on form 5-F (CTD) for registration of pharmaceutical drug products for human use (PE&R/GL/AF/004)* will be screened by in the Pharmaceutical Evaluation Cell, PE&R, DRAP as per checklist available on DRAP's website (https://www.dra.gov.pk/Home/Download?ImageName=form_5-f.pdf).
   ii. If application qualifies screening step, it will be submitted in R & I Section, DRAP Islamabad office otherwise it will be returned to applicant for completion.
7. **Where can guidance document be found for submission of application on CTD?**
   Detailed guidance document "*Guidance document for submission of application on form 5-F (CTD) for registration of pharmaceutical drug products for human use (PE&R/GL/AF/004)*" is available on DRAP's website. (https://www.dra.gov.pk/Home/Download?ImageName=Guidance%20Document%20on%20CTD-Doc%20No.%20PE%26R-GL-AF-004.pdf).
8. **What will be procedure for submission of registration / marketing authorization application in case of contract manufacturing?**
   The applicant (contract giver) shall submit fee and registration application. However, the technical data, relevant details including manufacturing facility in the application shall be of manufacturer (contract acceptor/manufacturer).
9. **What is the format of Quality Overall Summary (QOS) in module 2?**
   i. The applicant of innovator drug products may submit QOS either as per WHO QOS-PD template or as per ICH template.
   ii. For drug products other than innovator's product, Quality Overall Summary (QOS) shall only be provided in WHO QOS-PD Template or template provided in the "*Guidance document for submission of application on form 5-F (CTD) for registration of pharmaceutical drug products for human use (PE&R/GL/AF/004)*".
10. **Do we need to submit Drug Master File (DMF) separately with CTD application?**
    Submission of DMF is optional. However, the required details of drug substance in relevant sections as defined by the "*Guidance document for submission of application on form 5-F (CTD) for registration of pharmaceutical drug products for human use (PE&R/GL/AF/004)*".

11. **What is Quality by Design (QbD)?**

    The quality of drug substances and drug products should be defined by the design, process used, controls applied, validation performed and specifications controlled throughout the development and manufacture.

12. **If one strength of any dosage form is already registered with DRAP, Do we need to submit stability study data, pharmaceutical equivalence data and comparative dissolution profile (CDP) for new strength?**

    Complete Form 5F is required for each strength of any dosage form as per guidance document for registration of different strengths of applied formulation including comparative dissolution profile, pharmaceutical equivalence, stability studies data, etc.

13. **Is pharmaceutical equivalence required for each application?**

    Pharmaceutical equivalence is required for each application regardless of dosage form, strength, volume (in case of injectables).

14. **Is there any need to mention hydrates in label claim of product?**

    The label claim of the applied product shall be same as that of the innovator/reference product.

15. **Can a generic drug product manufacturer claim different indication than that of innovator?**

    A generic drug product manufacturer shall follow information in label/patient information leaflet and medical literature regarding clinical use, route of administration, dosage, storage conditions of finished products in line with the innovator brand or reference regulatory authorities or as approved by Registration Board.

16. **In case of immediate release formulations if drug release is >85% within 15 minutes, is there any need to perform Comparative Dissolution Profile (CDP) and calculate f2 value?**

    The firm has to perform CDP in all cases even if drug belongs to BCS class I i.e., highly soluble and highly permeable category to justify similarity in release profile with innovator drug product. However, in such cases where drug release is more than 85% in 15 minutes, calculation of f_2 value is not required

17. **In case of injectable formulations, where the container closure system of innovator drug product is Type-I glass, what additional data need to be submitted if the applicant wants to get approval with plastic container?**

In such case, in addition to stability studies, the applicant has to demonstrate suitability of container closure system by performing required studies recommended by USP chapter <661>.

18. **Is it compulsory for a generic drug product to have same ingredients for film coating as that of innovator drug product to become qualitatively similar with the innovator?**
    Film coating ingredients may be different in qualitatively similar products.
19. **Is it necessary to perform drug-excipient compatibility studies for a generic product?**
    If the formulation of a generic drug product is qualitatively similar to that of innovator drug product, then performance of compatibility studies is not mandatory.
20. **In case of dry powder injections or suspension, studies after reconstitution with all diluents / vehicles mentioned in the label need to be submitted?**
    Yes, compatibility studies for the dry powder for injections and dry powder for suspension with diluent shall be performed as per the instructions provided in individual label of the drug product.
21. **Are overages allowed in master formulation?**
    Overages for the sole purpose of extending the shelf-life of the FPP are generally not acceptable.
    Justification of an overage to compensate for loss during manufacture should be provided, including the step(s) where the loss occurs, the reasons for the loss and batch analysis release data (assay results).
22. **At what stage one should perform Comparative Dissolution profile?**
    CDP should be performed during product development stage before the initiation of stability studies.
23. **If innovator product is not available for Pharmaceutical equivalence and CDP, can reference or comparator product be used?**
    Pharmaceutical equivalence and comparative dissolution profile (where applicable) of the applied drug shall be established preferably with the innovator / reference product, however comparator product may be used, if fully justified.
24. **Is it necessary to perform analytical method validation studies by drug product manufacturer for both drug substance & drug product?**
    For Drug substance:
    Analytical Method Verification studies including specificity, accuracy and repeatability (method precision) shall be performed by the Drug Product manufacturer for both compendial as well as non-compendial drug substance(s).

For Drug products:

For pharmacopoeial drug product, only Analytical Method Verification of the analytical procedure including specificity, accuracy and repeatability (method precision) shall be performed by the Drug Product manufacturer while in case of non-pharmacopoeial drug product, complete Analytical Method Validation studies of analytical procedures shall be performed.

25. What are the parameters of analytical method validation?

i. Specificity
ii. Linearity
iii. Range
iv. Accuracy
v. Precision
vi. Detection Limit
vii. Quantification limit
viii. Robustness

26. On what parameters an analytical method is verified?

Analytical method is verified on following three parameters:

i. Specificity
ii. Accuracy
iii. Precision

27. Is it necessary to submit process validation report in Form 5F (CTD) dossier for locally manufactured?

For applications of locally manufactured products, it is not mandatory to submit process validation report, however, protocols of process validation shall be submitted. Process validation shall be performed upon first three Commercial batches.

28. What is the recommendation regarding use of primary and secondary reference standards?

Feature	**Primary reference standard**	**Secondary reference standard**
Definition	A designated primary chemical reference substance is one that is widely acknowledged to have the appropriate qualities within a specified context, and whose	A secondary chemical reference substance is a substance whose characteristics are assigned and/or calibrated by comparison with a primary chemical reference substance.

	assigned content when used as an assay standard is accepted without requiring comparison with another chemical substance	
Use	• May be used for the routine analysis of the drug substance. • May be used for the standardization of the secondary reference standard.	• May be used for the routine analysis of the drug substance. • Could not be used for further standardization of any reference standard.

29. If a drug substance is non-pharmacopoeial than what will be the primary reference standard?

In such cases, reference standard developed by drug substance manufacturer by purifying it up to the level of absolute purity is considered as primary reference standard.

30. Can a generic drug product have different manufacturing method from that of innovator's method?

A generic manufacturer may have different manufacturing method provided it is scientifically justified that it does not impact the products quality, safety & efficacy.

31. How can we access the details of quality attributes of innovator / reference drug product?

Public assessment reports / review documents issued by reference regulatory authorities can be used to study the quality attributes of innovator drug product.

32. What is meant by holding time studies?

In manufacturing of a pharmaceutical drug product all processes are interconnected. For example; if during manufacturing of tablet dosage form, a powder mix & now you have to compress it but compression machine got out of order suddenly & it will take four days to repair. At this stage you should perform holding time studies for four days after testing the mix powder after four days to make sure that in case of any unwanted situation for how long your formulation (mix powder in this case) is stable if it is not processed further.

33. What are four zones of WHO based upon climatic conditions?

Zone I: Temperate climate, includes Canada, Russia, and Europe

Zone II: Subtropical and Mediterranean climates, includes America, Australia, Israel, Iran, some regions of China

Zone III: Hot, dry climate includes Iraq, Jordan

Zone IVA; Hot, humid climate includes Pakistan.

Zone IVB; Hot and very humid climate includes India.

34. If the drug substance manufacturer is not performing stability studies at zone IVA for a particular drug substance, then what will be scenario?

Its preferable to qualify vendor having stability studies of the drug substance as per Zone-IV-a condition. However, if it is not available or risk-benefit ratio permits use of such material then in such situations, Registration Board has decided as follows:

- The firm shall submit the record of data logger for the storage conditions throughout the transportation.
- Firm shall submit long term stability studies data of the drug product for 1 year along with degradation studies in the finished pharmaceutical product.

35. For how long can a sample from stability batches be kept un-tested after pulling it out from stability chamber?

For each time point, samples should generally be withdrawn within 7 days and tested within the next 30 days. For example, if the six-month time point corresponds to the date 1st July 2020, the product should be tested no later than 1st August 2020. The actual test dates should be recorded.

36. Are clinical and non-clinical overview / summary requirements exempted for New Drug Product?

The data requirements against the sections of Clinical & non-clinical overview/summary is optional for both New drug product and Generic drug product.

37. Which regulatory authorities are considered as reference by Registration Board?

Registration Board in its 275th meeting has considered following regulatory authorities / agencies as reference for molecules/ formulations (in same dosage form and strength) alongwith clinical trials for human purpose:

a. Food & Drug Administration (FDA) of USA
b. Health Canada of Canada
c. Therapeutic Good Administration (TGA) of Australia
d. Pharmaceuticals and Medical Devices Agency (PMDA) of Japan
e. Medicines and Healthcare Regulatory Agency (MHRA) of UK
f. National Agency for the Safety of Medicine and Health Products (ANSM) of France.
g. Federal Institute for Drugs and Medical Devices of Germany
h. Medicines Evaluation Board of Netherland
i. Swissmedic of Switzerland

j. Austrian Agency for Health and Food Safety of Austria
k. Danish Medicines Agency of Denmark
l. Medical Products Agency of Sweden
m. Norwegian Medicines Agency of Norway
n. Federal Agency for Medicines and Health Products of Belgium
o. Finnish Medicine Agency of Finland
p. Italian Medicine Agency (AIFA) of Italy
q. Health Products Regulatory Authority (HPRA) of Ireland
r. Icelandic Medicine Agency of Iceland
s. Spanish Agency for Medicines and Health Products of Spain
t. European Medicines Agency (EMA) of Europe and
u. World Health Organization (WHO)

38. How the information in Drug Substance part presented in case of multiple APIs / drug substances in a drug product?

When more than one drug substance is used in a drug product, information of each drug substance should be presented separately.

39. Are there any exemptions in CTD application related to drug substance?

The following sections of drug substance part are exempted;

- Description of Manufacturing Process and Process Controls
- Control of Materials
- Control of critical steps and Intermediates
- Process Validation and/or Evaluation
- Manufacturing Process Development
- Post-approval Stability Protocol and Stability Commitment

40. Are there any exemptions in CTD application related to drug product?

The following sections of drug product part are optional;

- Product Interchangeability (Bioequivalence Study Reports)

41. What are Electronic review documents?

The applicant shall submit electronic review package of complete dossier in CD / USB including Quality Overall Summary.

42. How many batches of the drug product needs to be manufactured for performing stability studies for CTD application?

For selection of number and size of batches applicant may follow, any of the following options:

a) ICH/WHO guidelines.

b) At least 2 batches having the following minimum batch size considering the scientific reliability

- OSDs: 5000 Units
- Oral Liquid / Suspension: 2000
- Injectable: 2000
- Aerosol and any other specialized preparations: 500

c) At least 3 batches having scientifically rational batch size, sufficient enough to perform complete testing till the claimed shelf life.

43. Do we need to submit Batch Manufacturing Record for the stability batches?

Yes, Batch Manufacturing Record (BMR) of all the batches of drug product for which stability studies data is provided in Module 3 should be submitted.

44. What are the documents / data to be provided along with stability study data?

The stability study data of drug product needs to be submitted in section 3.2.P.8.3 along with the following documents:

- Reference of previous approval of applications with stability study data of the firm (if any)
- Approval of API/ DML/GMP certificate of API manufacturer issued by concerned regulatory authority of country of origin.
- Documents for the procurement of API with approval from DRAP (in case of import).
- Data of stability batches will be supported by attested respective documents like chromatograms, Raw data sheets, COA, summary data sheets etc.
- Compliance Record of HPLC software 21CFR & audit trail reports on product testing.
- Record of Digital data logger for temperature and humidity monitoring of stability chambers (real time and accelerated).

45. What are the recommended storage conditions for performing stability studies of the drug product which are intended to be stored in refrigerator (2-8ºC)?

For the drug product which are intended to be stored in refrigerator, the stability studies should be conducted on following conditions:

Study	Storage condition
Accelerated	25°C ± 2°C / 60% RH ± 5% RH
Long term	5°C ± 3°C

46. What are the recommended storage conditions for performing stability studies of the drug product which are intended to be stored in freezer (- 20°C ± 5°C)?

For the drug product which are intended to be stored in freezer, the stability studies should be conducted on following conditions:

Study	Storage condition
Accelerated	5°C ± 3°C or 25°C ± 2°C
Long term	- 20°C ± 5°C

47. What are the recommended storage conditions for performing stability studies of the drug product which are packed in semi-permeable containers?

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

For the aqueous-based drug product which are packed in semi-permeable containers, the stability studies should be preferably be conducted on following conditions:

Study	Storage condition
Accelerated	40°C ± 2°C / NMT 25% RH
Long term	30°C ± 2°C / 35% RH ± 5% RH