Common deficiencies found in applications submitted for registration

Screening and Evaluation for:

1. Human Allopathic Medicine
2. Veterinary Medicinal Products
3. Complementary Medicines

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Overview

Applications possessing a large number of unnecessary and obvious deficiencies will necessitate more interaction between the Authority and the manufacturer during the assessment process, thus increasing the turnaround times for registration of medicines.

To note that from 2024, the Authority will only be conducting only 2 review cycles after which your product will **be registered if successful** or **refused to be registered if unsuccessful.**

Unless you voluntarily withdraw your product before a final regulatory decision is given (before the final decision is given).

Overview

- Most common queries and issues sent out applicants and/or manufacturers between the period of April and October 2024.
- The aim of presentation is to assist applicants and manufacturers who wish to submit future products and those to respond to future query letters to anticipate and avoid these common pitfalls.
- Consequentially, this will help in reducing unnecessary and avoidable delays in the registration of products. **WIN-WIN**
- We have noted that we have been encountering the same deficiencies as those presented in the stakeholders meeting.
- Please note the Authority will be stricter henceforth as so to ensure that we are able to keep to timelines and manage our resources (staff and time) efficiently.

Common deficiencies (Screening)

MODULE 1	
Cover letter	• Absence of full details including full name and email address of responsible person for correspondence with the Authority • Not signed and dated
MC8 form	• Incomplete or not correctly filled • An example, incomplete address of the principal and name of manufacturer or inclusion of strength and form of product under approved name/ trade name. • Not signed and dated
LABELLING AND PRODUCT INFORMATION	
Summary of product characteristics (SmPC)	• Absence of SmPC in MS Word version
Labelling (primary and secondary packaging)	• Incorrect labels that not consistent with the requirements of Medicines And Allied Substance Control Regulations
Package insert and patient information leaflet	• Incorrect package inserts and patient information leaflet that not consistent with the requirements of Medicines And Allied Substance Control Regulations
Samples	• Absence of samples of the finished product packaged in the proposed container closure system. • Submit only 2 samples

Common deficiencies (Screening)

MODULE 3 (API)	
Description of manufacturing process and process controls of API	• Flow diagram of the synthetic process(es) is not describing all the manufacturing steps and critical process parameters. • Unacceptable starting materials (not as per ICH Q11) • For example Ceftriaxone potassium --> Ceftriaxone sodium (as a single step)
API Process validation and/or evaluation	• Process Validation of API aseptic processing and sterilization is not submitted. • Critical for sterile APIs
API Impurities	• Absence of genotoxic impurities Risk assessment reports.
API Specifications	• Absence of API and/or FPP manufacturer's API specifications (used in routine testing of API). • Not signed, dated and version-controlled specifications • Absence of test and limits for benzene where applicable
API Stability Summary and Conclusions	• Failure to propose shelf-life/retest period and storage conditions
API Post – approval Stability Protocol and Stability Commitment	• Absence of authorized post-approval stability protocol • Absence of signed and dated post-approval stability commitment letters.
API Stability data	• Absence of Up-to-date stability results and updated the summary of stability. • Absence of the ongoing stability study for the recent batches. Please note: The minimum stability data for API required at the time of submitting the dossier are **6 months** for both accelerated and long-term stability data.

Common deficiencies (Screening)

MODULE 3 (FPP)	
FPP Pharmaceutical Development	• Absence of comparative dissolution data • Absence of studies demonstrating discriminatory nature of a dissolution method.

FPP Manufacturing Process Development	• Absence of justification for selection of sterilization process.
	• For sterile products
	  ○ Filter-drug product compatibility studies
	  ○ Filter microbial retention studies
	  ○ Filter integrity studies

FPP Manufacturer(s)	• Absence of discussion for the responsibility of each manufacturer involved in the manufacturing process of the FPP. • Addresses of manufacturing sites do not include blocks or units.

FPP Process Validation and/or Evaluation	• Absence of Process Validation on 3 primary batches. (If applicable)
	• Process validation of all batch sizes is missing.
	• For sterile products:
	  ○ Manufacturing process validation
	  ○ Media fill studies
	  ○ Validation of sterilisation of vials, rubber bungs, etc

FPP Specification(s)	• Absence of FPP manufacturer's release and shelf-life specifications (used in routine testing of FPP). • Not signed, dated and version-controlled specifications
FPP Container Closure System	• Absence of Identification spectrum (IR) of test packaging materials. • Absence of chemical test for aluminium in specifications
Post-approval Stability Protocol and Stability Commitment	• Absence of signed and dated post-approval stability commitment letters. • Absence of authorized post-approval stability protocol

Common deficiencies (Screening)

FPP Stability Data	• Absence of Up-to-date stability results • Absence of the ongoing stability study for the recent batches. • Absence of in-use stability study. For multi-use/multi-dose products. • Absence of long-term stability data for vials in inverted position (sterile products). Please note: The minimum data of FPP required at the time of submitting the dossier are **6 months accelerated stability data** and **12 months for long-term stability data**.
3.2.R REGIONAL INFORMATION	
Executed production documents	• Absence of the production batch record of the manufactured three batches Absence of production documents for bio-batch (clinical) and biowaiver batches.
MODULE 5	
Bioequivalence Studies	The following bioequivalence data are commonly absent from submissions: • Comparator product source and storage conditions • COA for reference and test product • GCP, GLP • Bioanalytical method and bioanalytical method validation **Please note that all documents must be indexable and searchable.**

Common deficiencies (During evaluation)

Documentation	• Indexed and searchable documentation.
MC8 form	• Changing information from what was originally submitted.
Certificates	• Changing information from what was originally submitted.
QOS	• Applicant should provide the QOS on the MCAZ template and in MS Word format
Labels and Package Insert	• Applicants are implored to address labelling queries when raised during evaluation
Specifications	• Applicants are encouraged to provide updated and the current specifications on submission
Dissolution	• Provide comparative dissolution data of biobatch against reference in physiological media of pH 1.2, 4.5, and 6.8 (including release medium) • Should include dissolution data of individual units and their averages (including % RSDs) at each time point.
Bioequivalences	• Resolving queries raised during screening and first review cycle.

Common deficiencies (During evaluation)

Stability	• Applicant should provide updated long-term stability data to support proposed shelf-life
Characterisation	• Should provide a discussion for a risk of benzene contamination • Test for benzene should be included in API specs • Skip test if only there is appropriate justification
PSD	• PSD should be characterized at d (10), d (50) as a range and d (90).
Container closure system	• Aluminium chemical test for primary packaging with aluminium material • Should provide IR as identification test for other primary packaging material

Common deficiencies for Veterinary Medicinal Products

1. GMP compliance of the API and FPP manufacturer
2. API starting material
3. Identification of potential impurities
4. Monitoring for benzene
5. API and FPP manufacturer’s API specifications
6. FPP specifications
7. Analytical method validation for assay, related substances and residual solvents
8. Stability data

Common deficiencies for Complementary Medicines

Cover letter	• Absence of signed and dated cover letter that includes the full details of the local representative, and this should have included the full name and email address of the responsible person.
CM1 form	• Incomplete, not signed, and dated CM1 form with incomplete details for example complete address of the principal and name of manufacturer.
Declaration by the applicant	• Absence of signed and dated declaration by the applicant attesting to the accuracy of the contents of the application.
Proof of compliance with current Good Manufacturing Practices (cGMP)	• Absence of valid cGMP certificates manufacturers issued by a governmental organisation not an accrediting or quality assurance company
Excipients	• Formulations containing restricted excipients (preservatives e.g. bronopol)
Document control	• CoAs, specifications are not signed dated, or version controlled.
Labelling (primary and secondary packaging)	• Incorrect labels that not consistent with the requirements of S.I 97 of 2015 and Complementary medicines guidelines
Package insert and patient information leaflet	• Incorrect package inserts S.I 97 of 2015 and Complementary medicines guidelines • Absence of the package insert
Stability	• Absence adequate stability data to support the proposed shelf life.

Please remember!!!!

The aim of presentation was to assist applicants and manufacturers who wish to submit future products and those to respond to future query letters to anticipate and avoid these common pitfalls.

Consequentially, this will help in reducing unnecessary and avoidable delays in the registration of products.

WIN-WIN

THANK YOU