Common Quality Aspects To Consider for New Applications

Davis Mahlatji

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SAHPRA

South African Health Products Regulatory Authority

Presentation Outline

- Deficiency
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- API of acceptable quality
- API Common Deficiencies
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  - Starting materials: Guidance
  - Impurities
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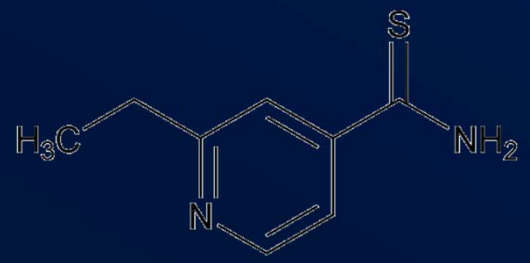
  - Intermediate manufacturing
- Final Pharmaceutical Product (FPP)- Biobatch
- Biobatch as quality reference
- What is solubility
- Specifications
- More Common Deficiencies

Deficiencies?



What is a deficiency?

Definition:

Something that does not meet expectations.

What are our expectations?

An API and FPP of acceptable and consistent quality.

What are the applicant's expectations?

Scientific, consistent, and risk-based decisions

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Scientific, consistent, and risk-based decisions

•Familiarity with scientific guidelines.

•Consistent approach to guidelines.

•Consistent approach to API submission procedures for all applications.

e.g. Open and Closed parts of a DMF always requested

•Consistent quality standards for API information across all procedures.

i.e. API PQ verses, CEP, verses DMF, verses M.3.2.S

•Consistent and comprehensive procedures for API information over the lifecycle of the API.

• i.e. how are API changes handled after approval? Recording of decisions in assessment reports in a clear manner.

•An assessment report system that allows all to locate previous decisions.

•Assessors should be aware of the implications of what you are requesting.

•If you insist on a standard at the time of initial approval how can you ensure this standard will be maintained

API of acceptable quality

Is it the right molecule (API, salt, polymorph)?

Are the API specifications acceptable?

Are the chemicals used in the preparation of acceptable quality?
Is the method of preparation acceptable?

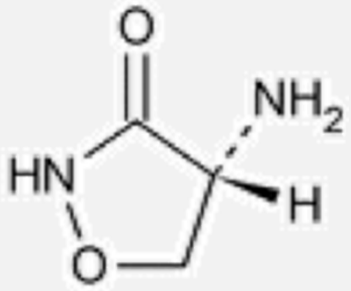
Are the intermediates controlled acceptably?

Are the in-process controls acceptable?

Is the API suitably stable?

Is the manufacturing chain acceptable?

Is manufacture occurring in accordance with GMP?



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API Common Deficiencies

Perhaps the biggest deficiency is the absence of information itself.

Of course we must be pragmatic and recognise the environment in which we work, but we also have to be honest.

Without the open and closed parts of an DMF, or a surrogate like a prequalified API or CEP, we cannot judge the acceptability of the specifications.

And, without GMP we cannot really guarantee anything.

To be more specific then – what are the biggest deficiencies in a complete DMF (Module 3.2.S)?

What are the most common technical deficiencies in a complete DMF (Module 3.2.S)?

- SM selection and justification
- Manufacturing control
- Control of Impurities
- Intermediate manufacturers

The single biggest deficiency in APIMFs we receive is the absence of discussion from the applicant. Too often we are presented just with data.

Close part of the DMF- section 3.2.S.2.2 P&A guideline requires information usually found only in the Close Part of the DMF: How do we deal with this?

Starting materials

The starting material must be selected correctly in order to ensure the quality of the API.

A correctly selected SM will:

- ensure a sufficient amount of the synthesis is provided in the APIMF to judge the acceptability of controls on the API.

  What impurities are introduced, how are they controlled, will they occur in the API

- ensure a sufficient number of manufacturing steps are undertaken under GMP to safeguard the API from future changes up-stream in manufacture.

In addition to quality concerns, an incorrectly selected Starting material will delay an application because:

- Redefinition requires revision to multiple sections of the APIMF.
- Redefinition often requires the introduction of a new manufacturer (external).
- Until the correct SM is selected the quality assessment can not be completed

Q11 outlines a number of principles that should be considered when selecting an API SM. However[6]:

Starting materials: Guidance

- ICH Q11: Development and manufacture of drug substances (May 2012)
- EU reflection paper on API Starting Materials (October 2014)
- ICH Q&A document for Q11.

Both provide guidance on what issues should be considered when selecting a starting material.

It is critical that a justification for the starting material is included in the section 3.2.S.2.3 that covers all the principles outlined in Q11.

Impurities

Lack of an in-depth comprehensive analysis of all potential impurities.

Over-reliance on Pharmacopoeia monographs.

Absence of a rational control of solvents.

Inattention to the presence of potential genotoxins.

- VALSARTAN is case in hand

The discussion in 3.2.S.3.2 should include the following broad steps:

What are the potential impurities?

What are the actual amounts present?

What is the rationale for control of these impurities?

This process needs to be followed for every impurity.

Impurities

Have all impurities been considered?

Organic impurities – synthetic, introduced from SMs, degradation

Inorganic – reagents; metals

Solvents

Genotoxins -Potentially genotoxic impurity:
compound with structural alert

To make such an analysis, you need to know

- How the SMs are prepared
- How the API is prepared in detail

Impurities: API Monograph

Often a discussion is simply replaced by a table listing the organic impurities from a suitable API monograph.

Monographs are developed based upon specific methods of preparation and are not comprehensive.

Therefore
what if it is the same synthesis but using different reagents? or
the SMs are the same, but assembled in a different order?
a different route of synthesis with different intermediates is used.

These factors will affect the type of impurities and/or the amount of impurity observed.

Manufacture (3.2.S.2)

Intermediate specification limits not justified

Batch sizes at each step not defined

Insufficiently detailed process descriptions

reprocessing/reworking not stated

Use of recovered solvents not stated

Full disclosure of information from external intermediate suppliers not provided

Intermediate manufacturing

It is increasingly common for an APIMF to include one or more intermediate sites. This makes assessment more complex.

It makes the control of the overall manufacturing process more difficult to judge. And, intermediate sites are rarely inspected.

It is often clear from the documents provided that the API manufacturer is only considering the steps they undertake as important and part of the manufacturing process

The quality of the API is confirmed, but not ensured, by the API specifications. Controls throughout the manufacturing process are important to obtain API of the required quality.
These include specifications for the isolated intermediates and in-process controls.

The setting of intermediate controls and in-process controls can only make sense if the applicant has provided a good discussion on the origin and fate of impurities

Final Pharmaceutical Product (FPP)- Biobatch

The generic **quality** dossier is supported by a BE study.

This BE study uses a **single biobatch** to support the safety and efficacy (S/E) of the product.

The **quality** review must also start from the **S/E** point.

What does this mean?

- The **biobatch** becomes the reference for the **quality** assessment.

Biobatch as quality reference

Full characterization includes	A Certificate of Analysis /batch analysis (according to **acceptable** specifications If the API is not soluble, Particles Size Distribution (PDS) Polymorphism- control of polymorphism is critical
API Biobatch Specification	PDS and Polymorphism should be bases on biobatch results
Full Characterisation of FPP	A Certificate of Analysis (batch analysis), according to **acceptable** specifications Ensure that the COA covers any elements that were deficient in the FPP specifications.
FPP Biobatch specifications	The dissolution and impurities limits are set based on the biobatch results.

Biobatch should fully represent the intended production batches

Setting dissolution limits is on case-by-case,

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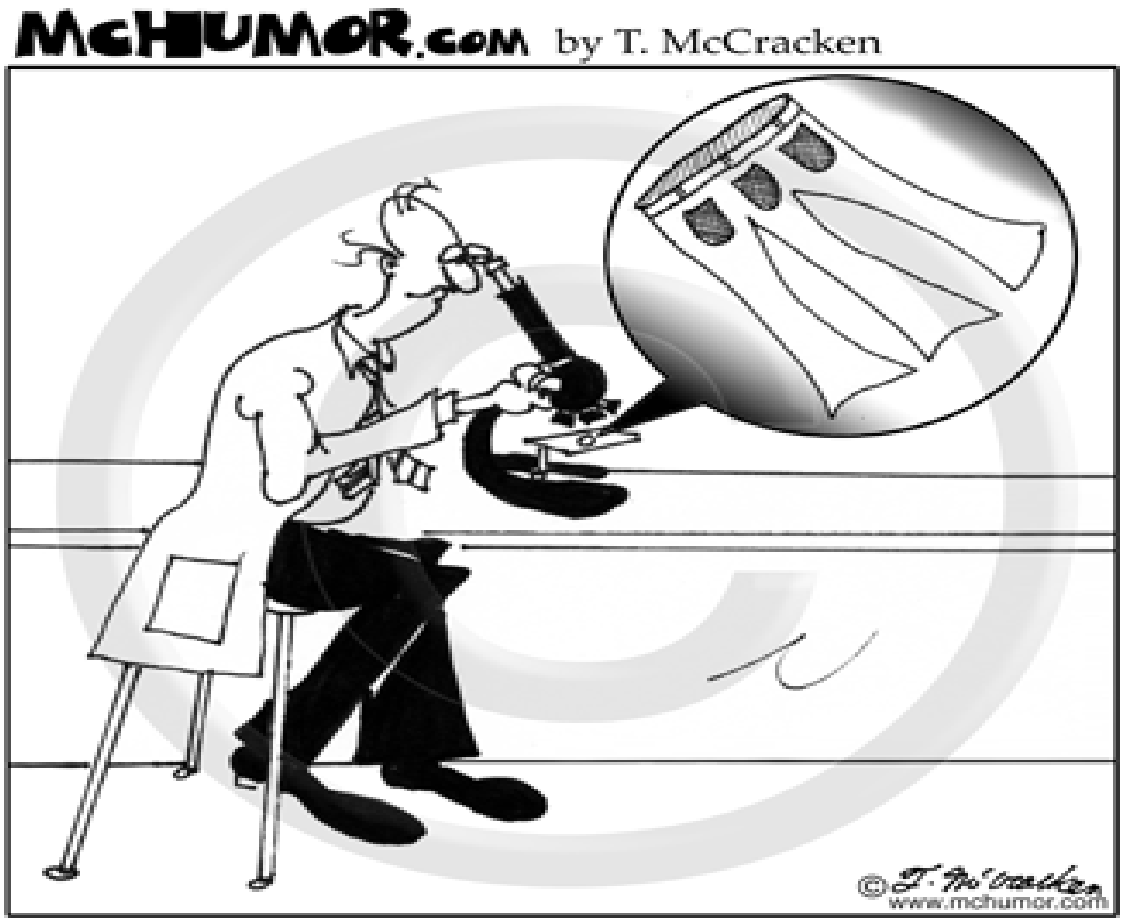
What is the solubility?

The solubility of the API
is determined over the physiological pH range: (for pH 1.2, 4.5, 6.8).

DSV = $\frac{\text{largest dosage strength (mg)}}{\text{Minimum concentration of API (mg/mL)}}$

DSV > 250 mL is a low solubility API



Mutant Jeans

What is a specification?

- A specification is a list of tests, references to analytical procedures (validated), and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. (ICH Q6A)
- ICH Q3A - Q3D: Impurities
- Take into account primary batches/biobatch release/stability results
- All stability indicating parameters should be in the shelf life specifications
- FPP manufacturer's API specifications should be one set ideally, regardless of number of suppliers (any differences e.g. solvents may be stated.

Example of specifications

- Description should include colour of tablets (full description of tablet appearance)
- Impurities: legend identifying impurities by chemical names or by compendial names (e.g. Ph.Eur. impurity A) should be added,
- Dissolution limits should be expressed in terms of 'Q' i.e. Not less than (NLT) 70% (Q) in 60 minutes. The limits may need to be tightened based on biobatch dissolution profile results.
- Assay limits should be 95.0-105.0%
- A test for uniformity of dosage units should be added
- Disintegration limits
- Include 2 identification tests (however, one identification test by IR sufficient)
- A test for fineness of dispersion
- Microbial limits should be in line with harmonized pharmacopoeial requirements

More Common Deficiencies

- Specification not version-controlled,
- Critical test parameters not included e.g. missing PSD limits for low solubility API etc.
- Proposed limits not considered appropriate e.g. assay limits too wide
- Officially recognized pharmacopoeial monograph exists and the proposed In House tests/limits do not meet minimum pharmacopoeial requirements
- Pharmacopoeial standard claimed not met by proposed tests/limits or equivalence of proposed In House test methods is not demonstrated
- References to test methods missing from the specifications
- Limits for specified impurities above QT not qualified
- Discriminating ability of the dissolution medium not demonstrated
- Use of wrong reference product
- Unjustified use of surfactant in quality control medium and comparative dissolution

SAHPRA will use WHO PQ's stringent regulatory authorities (SRA) as a basis for regulators to recognise

SAHPRA will recognise a regulatory authority that:

- *Was a member of ICH prior to 23 October 2015: US FDA; EMA, Japan MHLW*
- *Was an ICH observer prior to 23 October 2015: Swissmedic; Health Canada*
- *SAHPRA has had significant previous engagement: Australia TGA; United Kingdom MHRA; Zazibona; WHO PQ*

Note: FDA = Food and Drug Administration; EMA = European Medicines Agency; MHLW = Ministry of Health, Labour and Welfare
Source: WHO/PQT Guidance Document 15 February 2017

"People who live in glass houses shouldn't throw stones"

Regulatory agencies criticise industry for the deficiencies in their dossiers, but what about the reports generated?

- Insufficient backgrounds to the recommendations
- Ambiguous or imprecise recommendations

Risk based balancing act of regulatory function

Acknowledgement

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