The ideal clinical submission

Structure of presentation

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  - Transitional period
  - Type / category of submission
  - Assigned processes

* **The ideal clinical submission (ICS)**
  - Main documentation
  - Package insert (pi)
  - Patient information leaflet (PIL)

* **The not ideal CS / flawed CS**
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    General
    Pre clinical
    Pi
    PIL
  - Multisource medicines (generics / biosimilars)
  - Line extensions of registered medicines

* **Conclusion**
  - How to prepare / compile an ICS

Transitional period

Paper (MRF based) vs Electronic (CTD based)

Type / category of submission

* New medicines already registered by other medicine regulatory authorities (MRAs) (new chemical entities / biologicals)
* New medicines not yet registered by any other MRA
* Multisource medicines (generics / biosimilars)
* Line extensions of registered medicines
* Package insert / patient information leaflet amendments of registered medicines
* Responses of applicants to Clinical Committee recommendations / Council resolutions
* Other: appeals, referrals, requests, opinions etc

Assigned processes

**** Submissions may be processed by***

- Routine / “slow track”
- Fast track (Expedited)
- Abbreviated medicines registration process (AMRP)
- Urgent Safety Restriction Notice (USRN) process (package inserts)
- Safety Related Package Insert Notifications (SRPINs)

What is an ideal clinical submission?

An ICS is a well structured submission that moves through all stages of the regulatory system without undue delays and / or queries to achieve the intended / desired outcome

The ICS is focussed to match the particular regulatory requirements of the relevant type / category of submission and the assigned process that the submission will follow at the MRA

The ICS

Main documentation

- Is well structured with a logic layout
- Is in line with the general, administrative, format and content requirements per category of submission and assigned processes to be followed in the MRA system (paper or electronic)
- Is in line with the guideline(s) relevant to the submission / application
- Contains quality and well presented preclinical and clinical data
- Checked / scrutinised by quality control / assurance official(s) before it is submitted

Package insert (pi)

- Format (Regulation 9)
- In line with relevant guideline(s)
- Content should be an objective reflection of the current scientific information regarding the use of the medicine and its limitations
- Checked / scrutinised by quality control / assurance official(s) before it is submitted

Patient information leaflet (PIL)

- Format (Regulation 10)
- In line with relevant guideline(s)
- Content should reflect the package insert information using terminology language understandable for the patient
- Checked / scrutinised by quality control / assurance official(s)

The not ideal / flawed CS

Documentation deficiencies

1. General

* Incomplete MRF 1 and SBRA / SA Common Technical Document (CTD)
* Orientation confusion: Poor layout, not well structured, index page mistakes, inaccurate cross referencing, page number confusion (Volume, section paragraph, page number)
* Document binding: flimsy, falls apart, exceeds 4cm / unit missing sections / pages
* Legibility: Poor quality printing / photocopying / scanning, shading of text, high lighting using colour
* Content: Not according to MRF 1 / eCTD and relevant guideline(s)
* Volume overload: raw data included, other

* Duplicate submission in the system

* Response to CC recommendation does not contain one or more of: CC recommendation, CC amended pi, approved pi, or annotated proposed pi

* Flaws in covering letter when addressing CC recommendations eg. compliant response per covering letter but p.i. not compliant

2. Pre-clinical documentation

* Not all sections included. No explanation / reason(s) why a section is omitted
* No effort to reflect on the possible relevance of preclinical findings to humans eg. target organs of toxicity, animal dose vs human dose, pregnancy etc.
* No conclusion on animal findings
* No preclinical expert report

3. Clinical documentation

* Missing sections. No explanation / reason(s) why a section is omitted
* No indication whether a study is pivotal or supportive
* No indication whether clinical trial results were published or presented
* No motivation for using a placebo
* Flaws in study design and methodology
* Studies not powered to get valid conclusive answers on outcomes, small patient numbers
* Questionable statistics used for analysis of results
* No inclusion and exclusion criteria
* Poor presenting of results eg. No confidence intervals, relative risk but not absolute risk, no tables or graphs, etc.
* Duration of studies not relevant to the disease / condition to be treated eg. shortterm studies for diseases / conditions requiring longterm treatment

* Gender issues
* No dose ranging studies (dose response)
* No age or dose stratification
* Unsuitable comparator, or dose / dosing frequency of comparator is less than recommended for the indication
* Formulation and / or strength and / or dose used in the clinical studies different from that in the pi.
* Formulation and / or strength inappropriate for a particular population eg. children
* Study results not presented in terms of ITT and PP
* Relevant tables and / or graphs not attached
* Drop out rate or deaths not stated or explained
* Reference to ongoing studies without indication when results are to be expected
* Pooling of clinical study results where study designs and outcomes are not similar
* Borderline / marginal efficacy

* Borderline / marginal efficacy but major side effects
* No reflection on the clinical relevance of certain statistical significant findings
* No summary reflecting on all the study results in terms of efficacy and safety
* No benefit risk profile of the medicine in terms of the proposed indication at the proposed dose in the proposed population
* Biased expert report (company employee) or no clinical expert report
* Negative correspondence with other MRA's not included
* Package insert of a MRA with which Council aligns itself, not included

4. Package insert deficiencies

* Not in line with Regulation 9 and the package insert guideline
* Pi not submitted, pages missing, text printed on both sides of page
* Mini text book / guidelines / manual
* Use of shading or colours to highlight text
* Spacing of text and letter size not according to guideline
* Grammar and spelling errors
* Statements without references or incorrectly referenced or cross referenced
* No annotated pi
* Pi not marked “proposed”, “approved” no date on pi, pages without initials
* Contains promotional statements (advertising) or hidden claims

* Contains comparisons with other medicines or statements suggestive of a potential advantage over competitors
* Contain statements / words to detract from / soften the seriousness of the reported side effects
* Contains statements / words not allowed eg. like all medicines, drugs, novel agent
* Confusion when to use generic name (INN) and when to use proprietary name
* Confusion how to present side effects
* Paediatric use: formulation and / or dose inappropriate, tablets not dividable
* Inconsistencies in pi. eg. impairment of hepatic function is a contra indication but dosage and directions for use reflect a dose for use in severe hepatic impairment

* Does not contain the standarised information / text approved by Council for certain categories of medicines eg. text relating to non selective NSAIDs and COX2 inhibitors.

* Package insert amendments based on CCDS / SPC without the refences on which the CCDS / SPC amendments were based

PIL deficiencies

* Not in line with Regulation 10 and PIL guideline
* Not based on the pi and not cross referenced to pi
* No date on PIL. No indication whether it is a proposed or an approved PIL.
* Grammar and spelling errors
* Not understandable for patient / consumer
* No changes to headings and text to accommodate parenteral formulations eg " Before you (take) (use) T/N" is applicable to oral formulation but not for I.V. formulation. For I.V. formulation it should be "Before you (are given) (receive) T/N"
* PIL submitted without a pi.
* Contains lengthy description of diseases / conditions

Deficiencies: multisource (generic/biosimilar medicines)

* Deficiencies regarding main documentation, p.i. and PIL, where relevant, are applicable
* Not in line with relevant (guideline(s)
* Formulation not identical to that of the innovator
* No clinical studies (safety and efficacy) are included (where bio equivalence data are not available) Clinical data always required for biosimilars
* Most recent innovator pi. and / or standarised package inserts (when available) are not included
* No references are included
* Indications / dosages applied for not in line with innovator pi.

Deficiencies: Line extensions of registered medicines

* Deficiencies regarding main documentation, pi and PIL, where relevant, are applicable

* Not a direct proportional up-or down scaling of the registered medicine formulation

* The strength does not fit into the already approved dosage range for the indication(s)

Conclusion

* To prepare / compile an ICS, attention should be given to the deficiencies that have been identified

Deficiencies identified

Flaws relating to preparing / compiling the submission

* Main documentation: not fully compliant with regulatory document and guideline requirements (general, administrative, format and content) relating to type of submission and process to be followed
* Pi and PIL not fully compliant with relevant regulations and guidelines
* Layout, structure, indexing, referencing, cross referencing, grammar, spelling, printing photocopying / scanning quality, covering letter, leave much to be desired

Flaws in quality of safety and efficacy data

* Not all data required are included eg. benefit risk profile
* No expert reports, biased expert reports
* Flaws in clinical studies eg. design, methodology, patient numbers, duration, analysis and presentation of results. etc

Flaws in quality control / assurance of submissions

* Submissions reflect negatively on current quality control / assurance measures that are in place to check submissions before being submitted

THE END