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Introduction to ISS/ISE

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Outline

- Common Technical Document
- ISS/ISE guidelines and location within CTD
- How to develop pooling strategy & ISS/ISE SAPs
    - Efficacy considerations (ISE/SCE)
    - Safety considerations (ISS/SCS)
- Concluding remarks

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Common Technical Document

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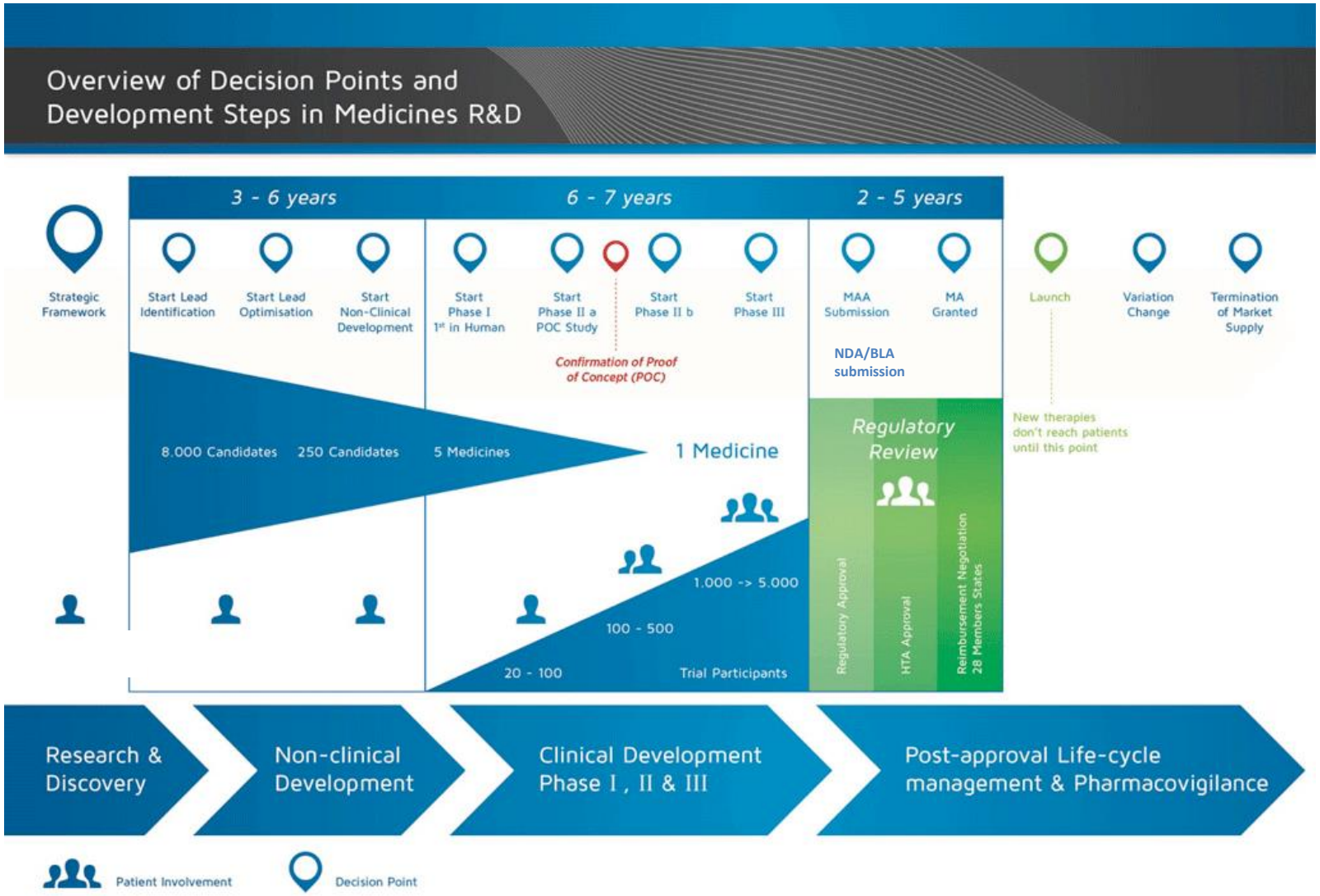
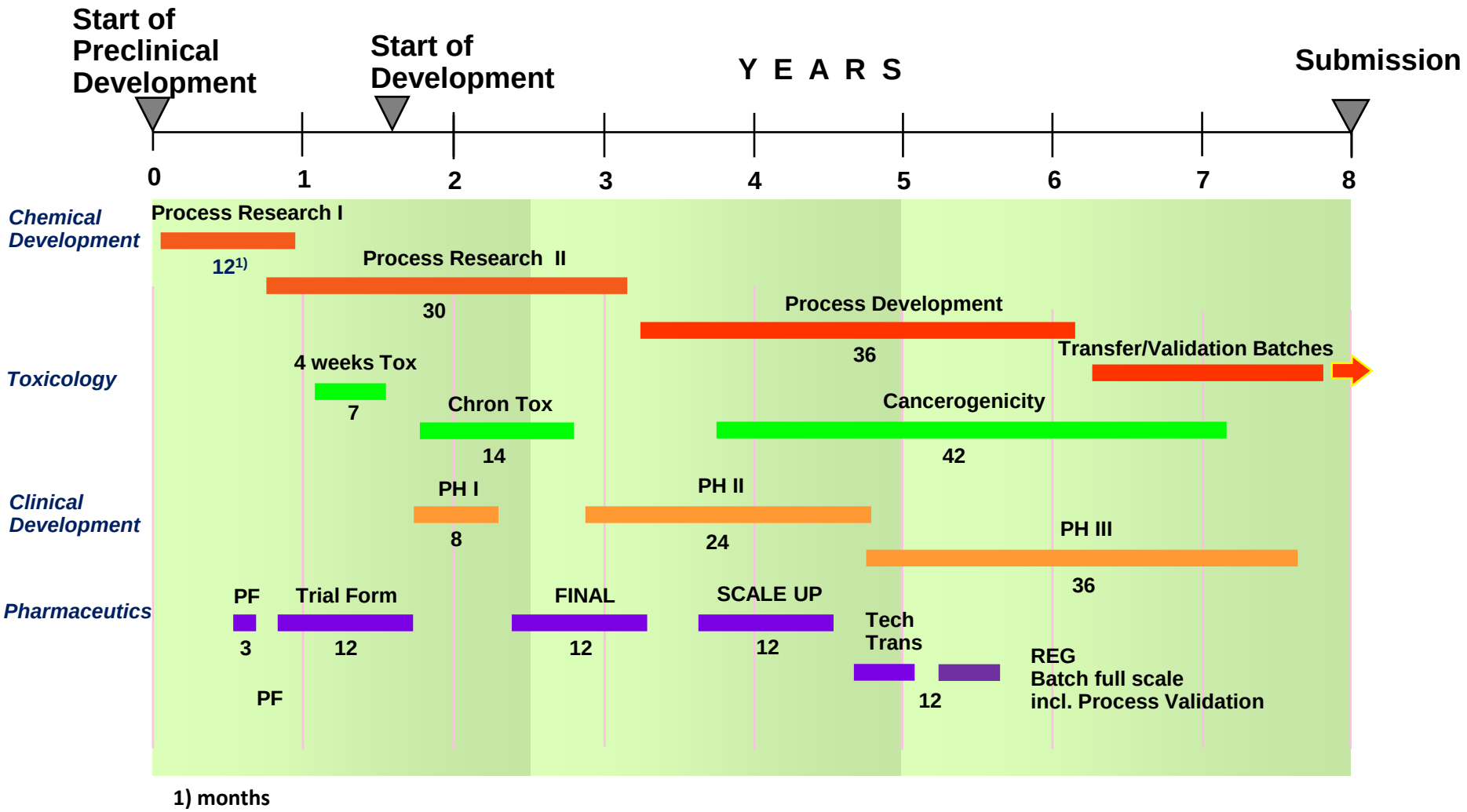
Drug Development Process



https://toolbox.eupati.eu/resources/discovery-and-development-of-medicines/

Drug Development – A lot of data to submit

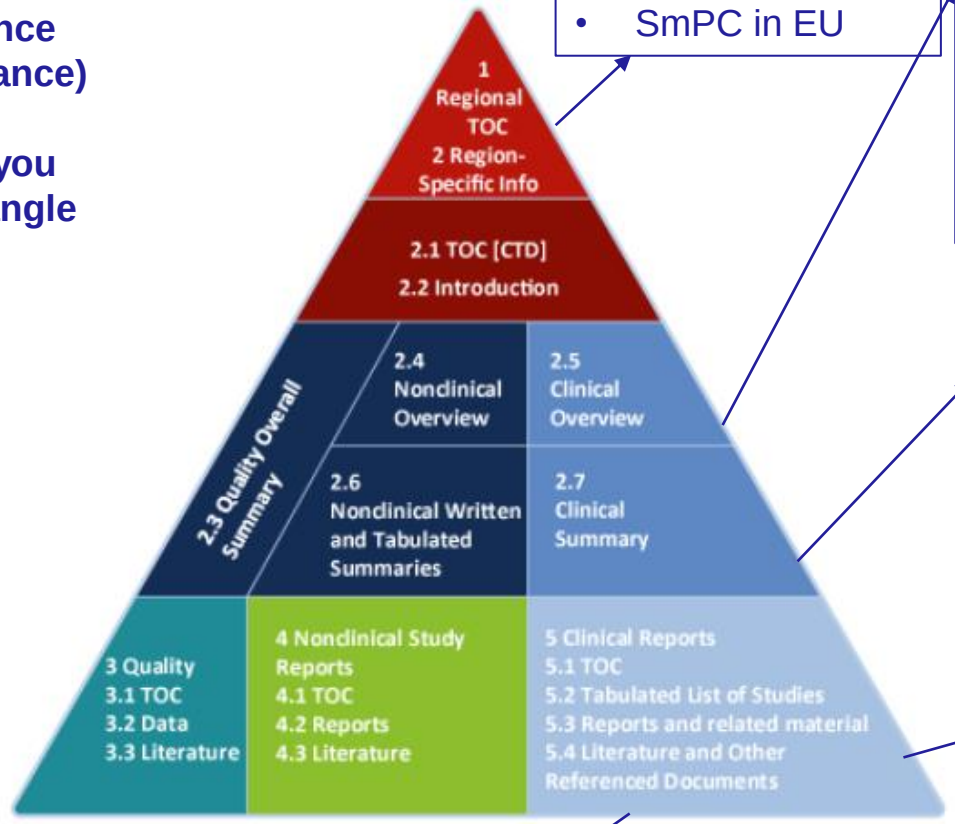


1) months

Submission to Which Regulators?

The Common Technical Document - Content

- **CTD format is defined in ICH M4 guidance (full TOC + guidance)**
- **More details as you go down the triangle**



Drug label
- USPI in US
- SmPC in EU

2.5 - Clinical Overview (CO)
- Critical summary of clinical data
- Succinct discussion and interpretation of clinical findings
- Strength and limitations
- Benefits and Risks of new drug
- Can be as small as 30 pages depending on size of drug development

2.7.2 - Summary of Clinical Pharmacology Studies
2.7.3 - Summary of Clinical Efficacy
2.7.4 - Summary of Clinical Safety
- Detailed factual summary of all the clinical information in the CTD (from individual reports or pooled/integrated analyses)
- Factual rather than interpretation/discussion (covered in CO)

5.3.5 Reports of Efficacy and Safety Studies
5.3.5.1 Study reports of controlled clinical studies pertinent to the indication
5.3.5.2 Study reports of uncontrolled clinical studies
5.3.5.3 Reports of Analyses for more than one Study
→ This is where the Integrated Summary of Efficacy (ISE) and the Integrated Summary of Safety (ISS) can be placed if they are produced

This is also where supporting SDTM and ADaM datasets are placed, if submitted

USPI: United States Prescribing Information
SmPC: Summary of Product characteristics

ISS/ISE guidelines and location within CTD

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Summary of FDA Guidelines

*"**ISE and ISS are required** in applications submitted to the FDA in accordance with the regulations **for NDA submissions** (21 CFR 314.50(d)(5)(v) and 21 CFR 314.50(d)(5)(vi)(a), respectively)"*

1. **Integrated analysis** that offers insights beyond those observable in individual clinical trials
2. Relevant data from **controlled trials**, as well as other sources (i.e., clinical pharmacology studies)
3. Format is **flexible** (case-by-case) and should be discussed with FDA ahead of submission

FDA Guidance on Format of ISE/ISS

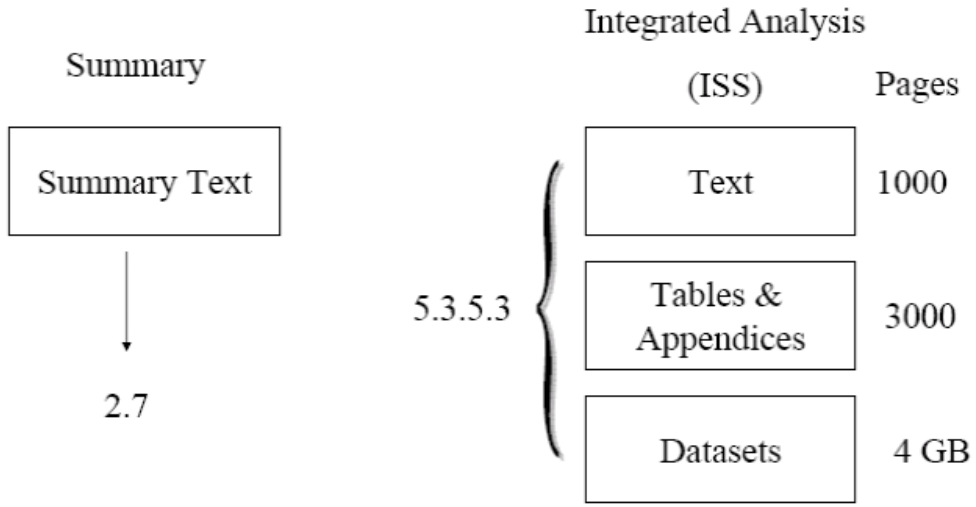
1. *"A common problem with the CTD-formatted applications is that **applicants incorrectly assume that the clinical summary sections satisfy the regulatory requirement for the ISE and ISS**. This assumption can result in a determination by the FDA that an application is incomplete and may result in a **refusal-to-file action** for the application".*
2. **Exceptions exist** where the clinical summaries alone can satisfy the requirements of the ISE/ISS (i.e., one pivotal study)

ISS/ISE location within CTD

A. Example 1: Large ISS Placed in Module 5

An applicant submits a BLA or BLA supplement with an ISS consisting of 1,000 pages of text (with incorporated tables and figures), 3,000 pages of appendices of supporting tables and figures, and 4 gigabytes (GB) of datasets used in the integrated safety analyses. The full ISS is placed in Module 5 (section 5.3.5.3). The text portion is summarized in a smaller 100-page document and placed in Module 2 (section 2.7.4) as the Summary of Clinical Safety. Figure 1 illustrates this example.

Figure 1

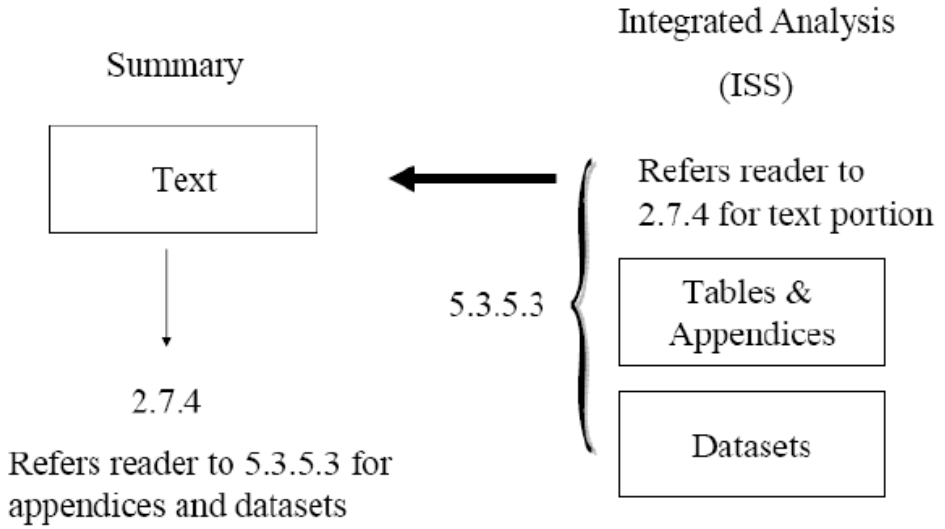


This submission is acceptable. The ISS is appropriately located in section 5.3.5.3. The text portion is too large for Module 2 and is appropriately summarized for section 2.7.4.

D. Example 4: Small ISS Split Between Module 2 and Module 5

An applicant submits an NDA supplement. The ISS contains 100 pages of text (with incorporated tables and figures), 1,000 pages of appendices of supporting tables and figures, and 1 GB of datasets used in the integrated safety analyses. The ISS is split: the text portion is placed in Module 2 (section 2.7.4), and the appendices and datasets are placed in Module 5 (section 5.3.5.3). Section 2.7.4 refers the reader to section 5.3.5.3 for the appendices and datasets. Section 5.3.5.3 refers the reader to section 2.7.4 for the text portion of the ISS. Figure 4 illustrates this example.

Figure 4



This submission is acceptable. The ISS is small, allowing the text portion of the ISS to also function as the Summary of Clinical Safety in Module 2. Each section of the split ISS refers the reader to the appropriate section where the remainder of the ISS is located.

Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), April 2009

Integration vs Pooling

- **Does integration mean pooling data?**
- **Integrated Summary of Safety/ Efficacy** brings together in one place in the review all data and analyses pertinent to a particular safety/efficacy issue or question
  - Looking primarily at data from **individual studies** or at datasets resulting from **pooled data/results from several** studies is not critical to the concept of an integrated review.
  - Either approach, or both approaches, can be used in an integrated review
- **Considerations for pooling**
  - Study design (blinding, control group)
  - Study duration
  - Patient population
  - Dosing schema
  - Method of AE reporting (e.g., eliciting)
  - Inconsistent definitions and/or convention

→ **Pooling depends on objectives of analysis**

Summary of guidelines inc. ICH M4E

- ICH M4E guideline describes the topics to be covered in CTD (e.g., for clinical SCE/SCS and if needed and appropriate ISE/ISS).
  - Important to **plan in advance** which study results will be used in which section of the SCE/SCS and to support which claims of the risk/benefit assessment.
  - **Pooled analyses are not mandatory** and are generally done only if required to support the evidence available from the pivotal(s) trial(s), and if appropriate.
  - **If pooled analyses are done, the objective/reason for pooling needs to be explained and the validity of the pooling has to be justified.**
- Separate ISE/ISS texts in Module 5.3.5.3 are not required if the efficacy/safety evidence can be described within the maximum page number expected for SCE/SCS
- **Not necessary to re-program individual study results** to present individual study data in the ISS/ISE; the SCE/SCS can refer to individual CSR outputs instead

How to develop pooling strategy and ISS/ISE SAPs

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Pooling strategy and ISS/ISE SAP Preparation

In depth review of all study protocols, analysis plans/ TFL shells, CRFs and other data specs

- Gather all documents very early on in the project
- Any interactions with regulatory authorities about submission/ pooling strategy yet?

Tabular summary of key aspects of studies

- Population
- Sample size by dose level
- Design highlights
- Phase
- Efficacy endpoints
- Safety endpoints

Development of pooling strategy

- Need to understand the aim of ISE-ISS,
- Understand how integrated/pooled analyses fit into overall submission and planned label claims

ISS/ISE analysis plan text document

- Need input/review also from other functions e.g. Clinical, regulatory, medical writing…
- Need to plan for agreement of pooling strategy /data presentation in dossier with regulatory authorities

All based on ICH M4E Guidelines about CTD, Modules 2 and 5

ISE / SCE ANALYSIS – ICH M4E guideline

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SCE and ISE

2.7.3 Summary of Clinical Efficacy

2.7.3.1 Background and Overview of Clinical Efficacy

2.7.3.2 Summary of Results of Individual Studies

2.7.3.3 Comparison and Analyses of Results Across Studies

2.7.3.3.1 Study Populations

2.7.3.3.2 Comparison of Efficacy Results of all Studies

2.7.3.3.3 Comparison of Results in Sub-populations

2.7.3.4 Analysis of Clinical Information Relevant to Dosing Recommendations

2.7.3.5 Persistence of Efficacy and/or Tolerance Effects

2.7.3.6 Appendix

Data presented can come from from individual CSR and/or from integrated/pooled analyses, if appropriate, presented in ISE

ISE=Integrated Summary of Efficacy located in Module 5

5.3.5 Reports of Efficacy and Safety Studies

5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

5.3.5.2 Study Reports of Uncontrolled Clinical Studies

5.3.5.3 Reports of Analyses of Data from More than One Study

5.3.5.4 Other Study Reports

Guidance for pooled efficacy analyses

The section should begin with a brief overview of the design of the controlled studies that were conducted to evaluate efficacy. These studies include dose-response, comparative efficacy, long-term efficacy, and efficacy studies in population subsets. Critical features of study design should be discussed, e.g., randomisation, blinding, choices of control treatment, choice of patient population, unusual design features such as crossover or randomised withdrawal designs, use of run-in periods, other methods of "enrichment", study endpoints, study duration, and prespecified plans for analysis of the study results.

For pooled efficacy analyses, it is assumed and expected throughout the CTD and various regulatory guidelines that **only controlled studies would be pooled** e.g., the PhIII or pivotal trials, potentially with the PhII trial(s) if also controlled and of the same design and duration as PhIII.

Pooling generally done only **to improve precision of the estimates** or **to provide a larger database to assess subgroups**.

Justification to be provided for efficacy pooling

- Same study design (e.g. control, duration, blinding…)
- Same population, inclusion and exclusion criteria, actual demog/patient characteristics
- Same endpoints (exact definitions/methods)
- Same stats methods especially on calculation of p-values/confidence intervals
- Consistent individual study results

All to be documented in ISE SAP:

- If pooling done, need to present info on which variables will be pooled, how the data was collected in individual trials, how the endpoints were derived and if new mapped or pooled derivations need to be defined.
- Plans for testing heterogeneity of results between studies, performing sensitivity analysis for the pooled analysis…

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ISS / SCS ANALYSIS – ICH M4E guideline

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SCS and ISS

SCS= Summary of Safety in Module 2

Data presented can come from from individual CSR and/or from integrated/ pooled analyses, if appropriate, presented in ISS

Exposure

2.7.4.1.2 Overall Extent of Exposure

A table (see example provided in the section 2.7.4.7 Appendix) and appropriate text should be generated to summarise the overall extent of drug exposure from all phases of the clinical study development programme. The table should indicate the numbers of subjects exposed in studies of different types and at various doses, routes, and durations.

- This can be done by adding up the info on exposure from individual CSRs or by pooling the exposure data from all trials.
- **Recommended to pool data for exposure to support this part of the SCS** ; this will enable presentation of the data in several ways + by relevant subgroups.

Table 1.1.4 Total Number of Subjects Exposed

Phase/Studies	Drug x Dose 1	Drug x Dose 2	Drug x Dose 3	Drug x Any dose	Placebo
Total number of subjects exposed	xxx	Xxx	xxx	xxx	xxx
Phase 1 studies total	xxx	Xxx	xxx	xxx	xxx
xxx-001	xxx	Xxx	xxx	xxx	xxx
xxx-005	xxx	Xxx	xxx	xxx	xxx
Phase 3 studies total	xxx	Xxx	xxx	xxx	xxx
xxx-002	xxx	Xxx	xxx	xxx	xxx
xxx-003	xxx	Xxx	xxx	xxx	xxx
xxx-012	xxx	Xxx	xxx	xxx	xxx

- *Additional exposure summaries will cover:*
  - *total number of patients who received study drug for different durations (≤1 day, 2 days- 1 week, 1 week – 1 month, 1 month – 6 months, 6 months – 1 year, ≥1 year)*
  - *by relevant demographic characteristics*
    - *age category*
    - *race*
    - *gender*

Adverse Events

When most of the relevant safety data are derived from a small number of studies (e.g., one or two studies), or when very different study subject populations were enrolled in the studies that were performed, presentation of data by study will often be appropriate. When the relevant exposure data is not concentrated in a small number of studies, however, grouping the studies and pooling the results to improve precision of estimates and sensitivity to differences should generally be considered.

Groups of studies that could be used in pooled safety analyses include the following:

- **All controlled studies** or subsets of controlled studies, such as all placebo-controlled studies, studies with any positive control, studies with a particular positive control, or studies of particular indications (and thus carried out in different populations). These groupings are considered the best source of information about the more common adverse events and can distinguish drug-related events from spontaneous events. Rates in control and treatment groups should be compared.
- **All studies, excluding short-term studies in healthy subjects**. This grouping is most useful for evaluating rarer events.
- **All studies using a particular dose** route or regimen, or a particular concomitant therapy
- Studies in which adverse event reports are elicited by checklist or direct questioning, or studies in which events are volunteered
- Pools of studies by region

SCS Requirements: Adverse Events

- Present data from studies individually AND/OR pool some AE data in ISS
- If pooling, need to create meaningful safety groupings to assess safety e.g.
  - By study design
  - By Phase
  - By population (e.g. age groups, disease stage...) and study design
- Then need to decide which variables will be pooled, if some mapping needs to be done for pooling and how the data will be presented, if specific analyses need to be done to adjust for varying exposure durations...
  - **All to be documented in ISS SAP**

Example 1 – Drug developed for rare disease

5 studies in patients:

1 Phase I (study 001), 12 months, open-label, multiple dose groups (dose 1, dose 2, dose 3), no control, Total N=11

1 Long term Phase I extension (study 002), all subjects on dose 1, no control, Total N=9

1 Phase II/III pivotal (study 003), controlled (dose 1, dose 0.5, placebo), 12 months, double-bind, Total N=36

1 methods trial (study 004), no treatment, Total N=28

1 paediatrics trial (study 005) ; single arm then double blind, Total N=15

Only Study 003

Groups of studies that could be used in pooled safety analyses include the following:

- All controlled studies or subsets of controlled studies, such as all placebo-controlled studies, studies with any positive control, studies with a particular positive control, or studies of particular indications (and thus carried out in different populations). These groupings are considered the best source of information about the more common adverse events and can distinguish drug-related events from spontaneous events. Rates in control and treatment groups should be compared.
- All studies, excluding short-term studies in healthy subjects. This grouping is most useful for evaluating rarer events.
- All studies using a particular dose route or regimen, or a particular concomitant therapy
- Studies in which adverse event reports are elicited by checklist or direct questioning, or studies in which events are volunteered
- Pools of studies by region

Study 003 + Studies 001/002 for adult results; not very helpful to pool data instead of looking at separate summaries to find rare events in the context of small Ns per study.

Example 2 – Drug developed for CNS disease

4 studies in patients:

1 Phase II (study 21), 6 months, double blind, placebo-controlled (dose 1, dose 2, dose 3, placebo), no control, N=120 /group

1 Long term Phase II extension (study 22), all former placebo subjects re-randomized to dose 1, dose 2 or dose 3; other subjects remain on intial dose in study 21 for up to 22 months; then all dose 3 subjects re-randomized to dose 1 or dose 2 for up to 4 years then all subjects switched to dose 2 for up to 4 years. Total N= 350 (at the start)

1 Phase III pivotal (study 31), double blind, active-controlled (dose 2, active), 2 years, N=550/group

1 Long term Phase III extension (study 33), all former placebo subjects switched to dose 2 Total N=850

6-Months POOL:
Dose 1, dose 2, dose 3, with indirect comparison to placebo, active; subjects randomized to double blind treatment in studies 21 or 31

2-year POOL:
Dose 1, dose 2, dose 3, with indirect comparison to active; subjects randomized to double blind treatment in studies 21, 22 or 31; data cut-off 2 year after start of study treatment.

Long-term POOL:
Dose 1, dose 2, dose 3; subjects who received study drug as randomized or open-label treatment in studies 21, 22, 31 or 33; for start of study treatment to data cut-off from submission

Concluding Remarks

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Concluding remarks

- **Submissions are very regulated** with specific document formats, many guidelines…
- **Every drug & drug development is different** so the way to present the products story by summarizing the results needs to be adapted for each submission
- Very **important to understand what makes sense and follows the guidelines** in terms of pooling depending on study designs, data collection/derivations…
- Some of the submission strategy can be planned in advance and agreed in principle with authorities but **changes/adaptations are likely** after final results are known (e.g. discordant results between studies due to be pooled…)
- **Submission strategy and planning is key** to get everything ready on time and work done in parallel on the ongoing studies and the submission workstreams

References

- ICH M4E Common technical document for the registration of pharmaceuticals for human use - efficacy - Scientific guideline, 2016
- Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document, Food and Drug Administration, 2009

Thank you.

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