EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Analysis on common issues raised during Validation of Type IB and Type II Variations

11th Industry stakeholder platform meeting on the centralised procedure. 24th November 2023

Presented by Elsie Merken, Procedures Office, EMA and Sara Pulido Sanchez, Therapeutic Areas Department, EMA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

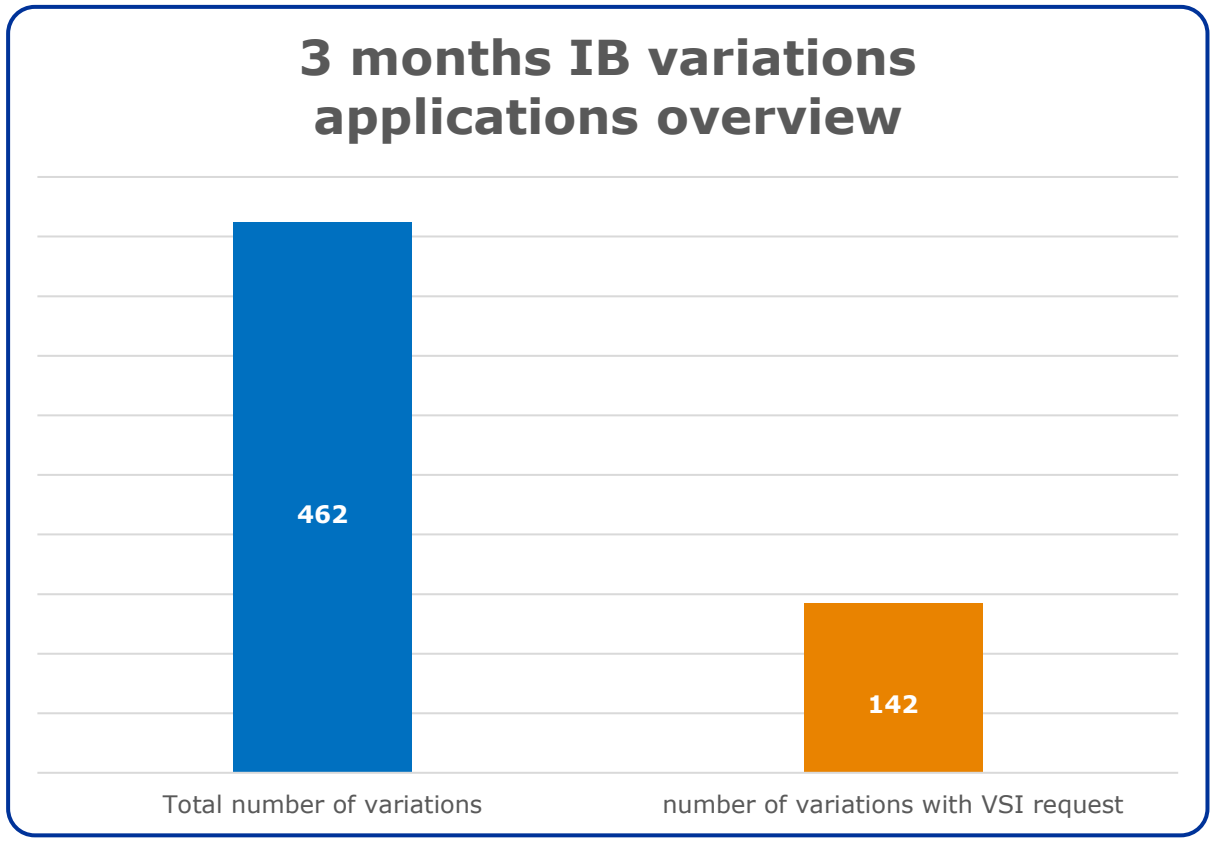
Type IB Variations

We intend to:

- Provide an overview of the validation issues identified during validation of IB variations
- Increase awareness of the guidance documents and tools that could be used in the preparation of the submissions.

… with the ultimate target of reducing the number of issues raised during validation

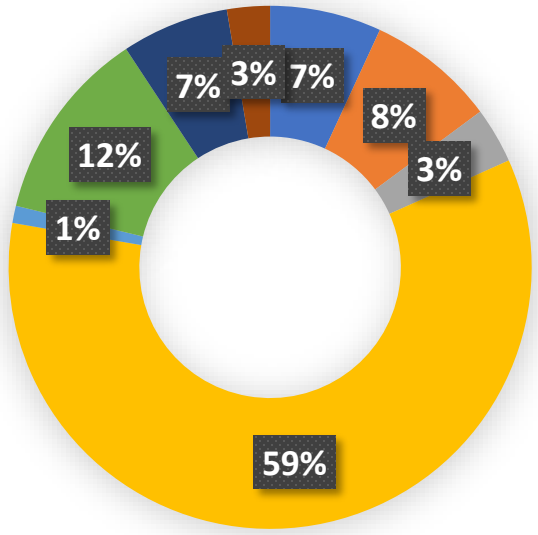
Overview of Type IB variations received during 3 months



30% of the variations submitted led to a VSI request

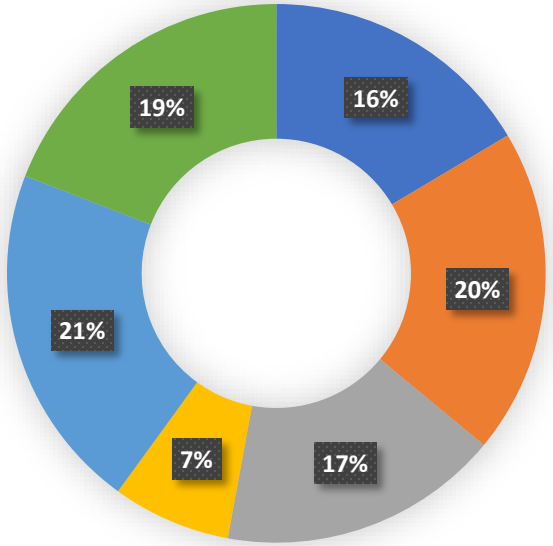
Most common IB validation issues

VSI issues per area



- Annexes
- Checklist
- Documentation
- eAF
- eCTD
- Editorial changes
- Generic/Biosimilar
- Other

VSI issues in the eAF



- Contact details
- Precise scope
- Present/Proposed table
- Procedure type
- Incorrect scope / number of scopes
- Other

Most Common IB Validation Issues

Inaccuracy of the Variation Classification – Variation Type – Precise Scope

- Incorrect classification, scopes missing to cover additional changes, missing upgrade to type IB by default when conditions are not met for IA variations grouped with IB.
- Precise scope incomplete or unclear, or missing reference to previous procedure number (when relevant)

Inaccuracy of the Present/Proposed table

- Not reflecting all changes applied for or missing the precise wording
- Missing site details autofilled via SPOR/OMS
- Missing EU or EMEA ASMF number and version
- Not reflecting all changes applied for in the annexes (expected to include changes introduced in all languages, not only EN)

Most common IB validation issues

Contact Details

- Contact details inconsistent with information notified to EMA
- Letter of Authorisation missing, when applicable

Other VSI issues

- Presentations or Annexes affected incorrectly completed in the eAF
- Checklist related to product information annexes missing

Editorial changes

- Editorial changes missing in the precise scope and/or in the present/proposed table
- Justification missing as to why the change is considered editorial
- Declaration missing - 'The changes do not change the content of the dossier beyond the scope applied for'

Most common IB validation issues – C Scopes

C.I.2.a

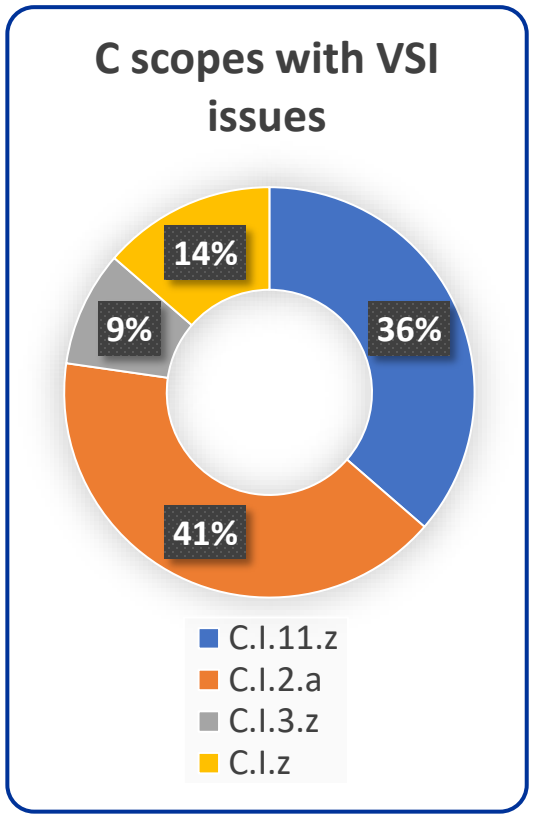
Changes in the annexes of a Generic/Hybrid/Biosimilar
- Changes not aligned with the reference product (all languages)
- The word PI (track changes) of originator
- Incorrect number of scopes applied for (to be aligned with originator)

C.I.3.z

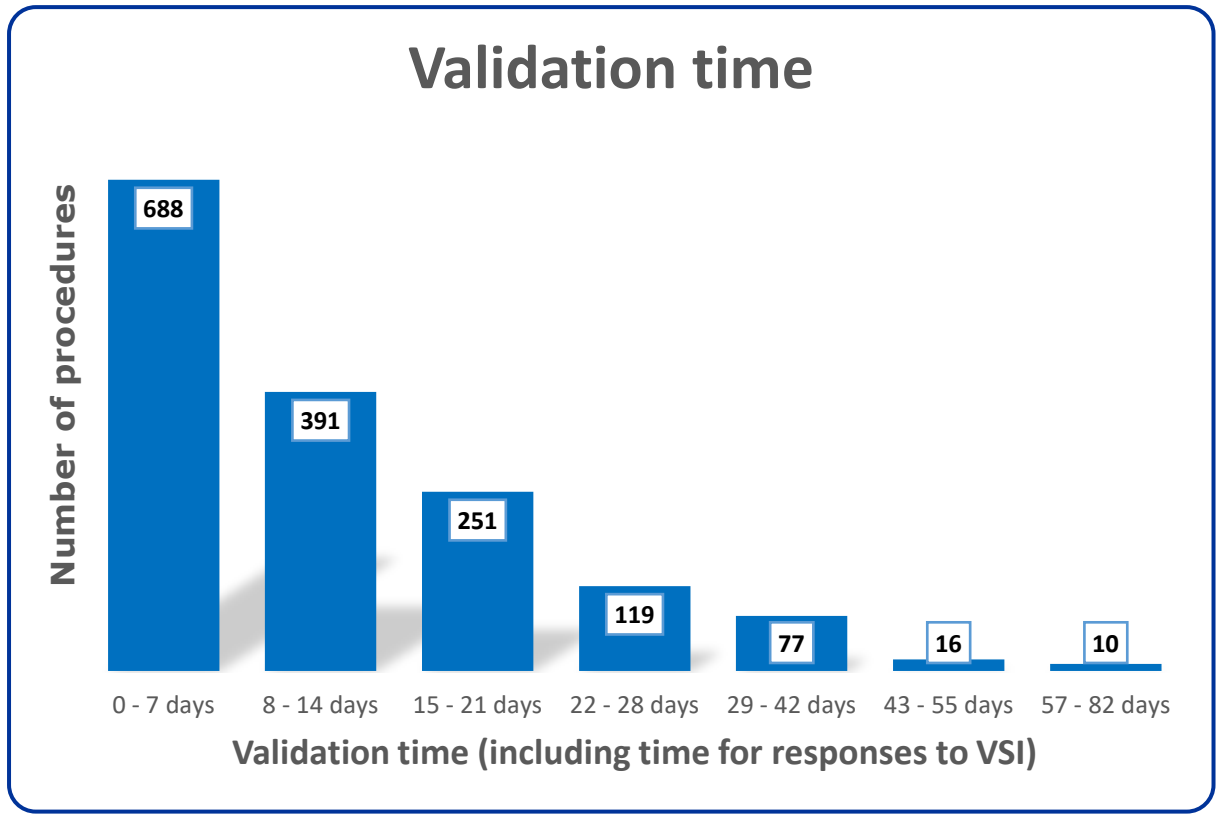
Changes in the annexes to implement outcome of PSUR/PASS
- The precise scope is missing the details of the change applied for
- Changes are not aligned with the requested update

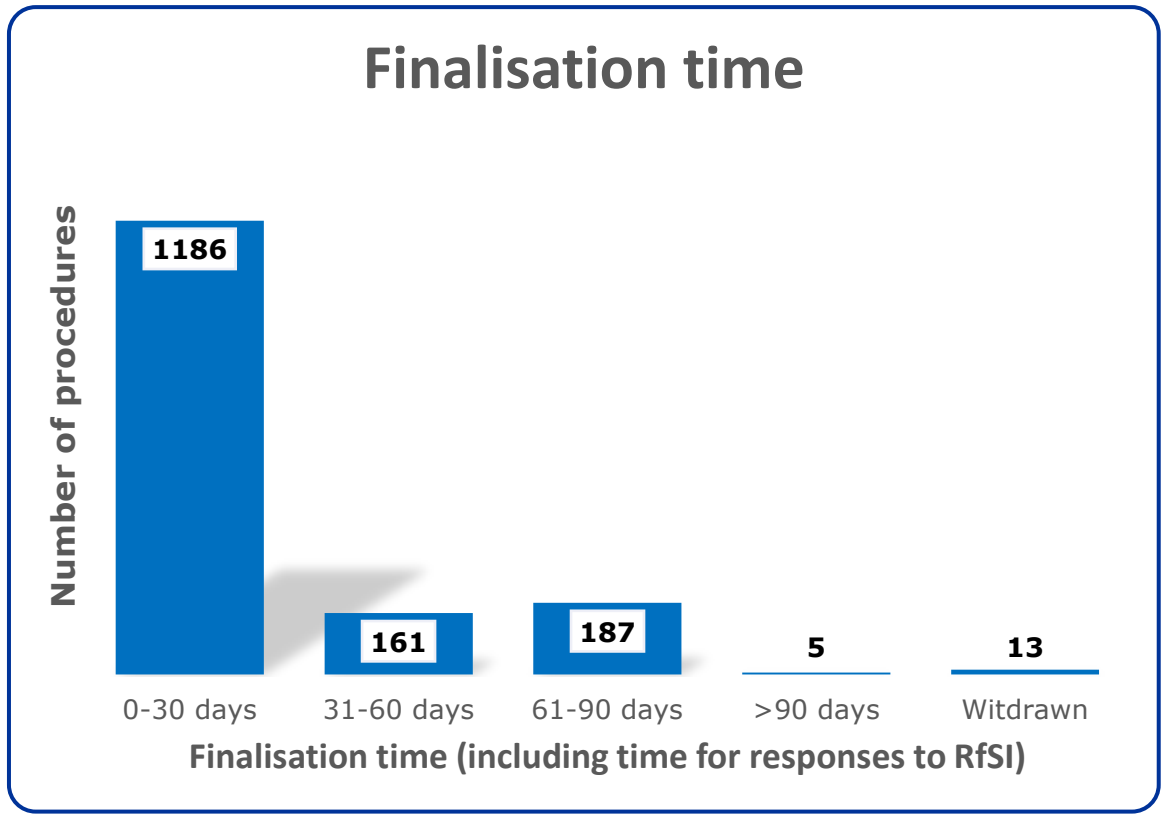
C.I.11.z

Changes to the obligations and conditions, including RMP
- The precise scope is missing the details of the change applied for
- Procedure number and assessment report requesting the change missing
- Missing documentation (RMP, RMP track changes, or summary of changes)



Validation and finalisation time of IB procedures in 2022





The overall time for IB's can be significantly reduced if attention is given **to the quality of the submission**

Improving quality of type IB variations: How to prevent VSI requests?

- Please consult EMA's webpage dedicated to Improving quality of submissions, where applicants can find:
  - Practical guidance on the completion of the application form
  - Guidance for the preparation of the precise scope section of the application form
  - Checklist for product information annexes for type IA/IB variations without linguistic review
  - Pre-notification checklist for type IB variations
- Additional guidance can be found in Classification of changes: questions & answers and in Quality of medicines: questions and answers: Part 1 and Part 2
- If the answer cannot be found on our website, a query can be raised via EMA Service Desk

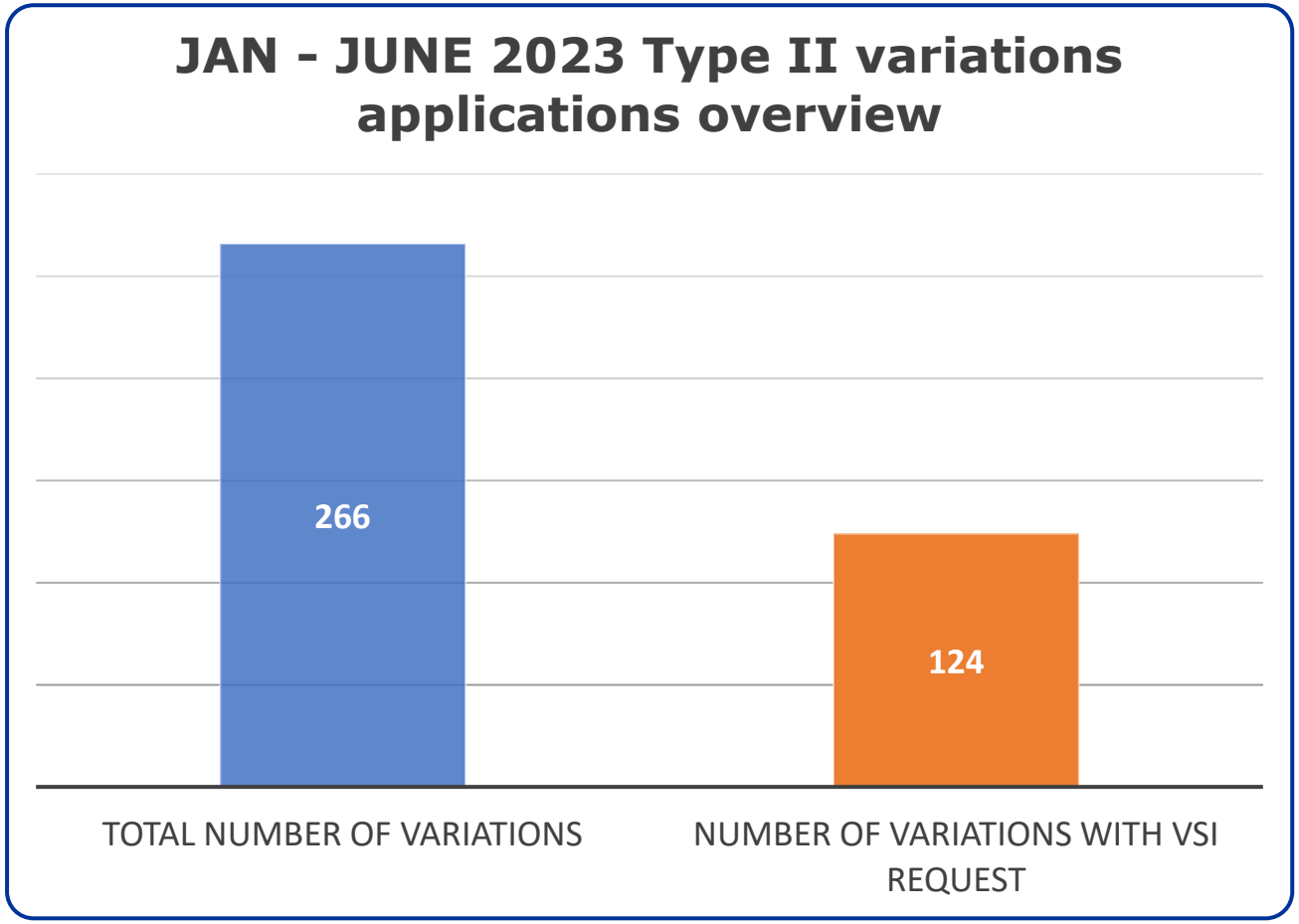
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Type II Variations (Non-clinical/Clinical/RMP)

Agenda:

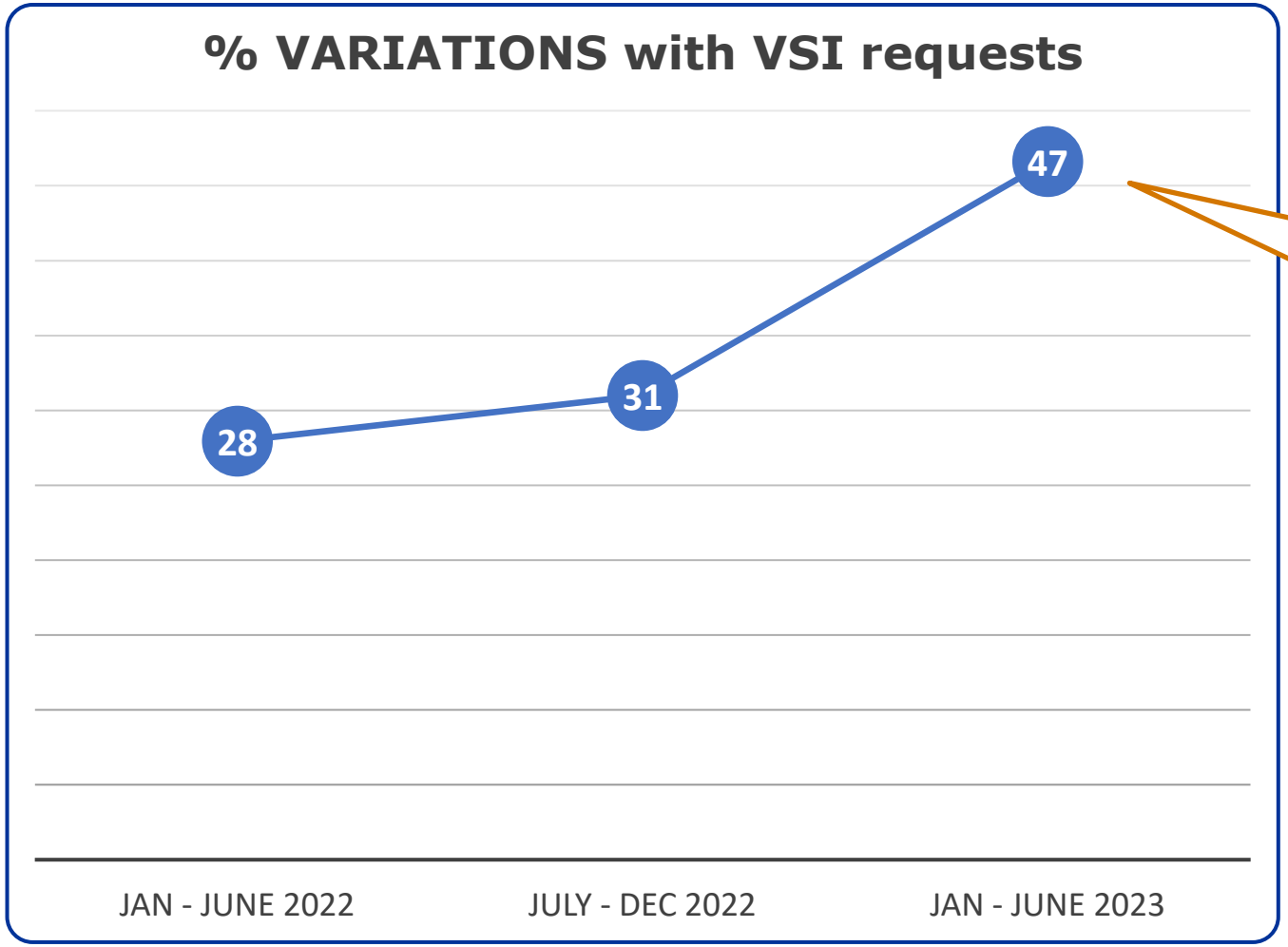
- Overview of the type II (Non-clinical/Clinical/RMP) variations received in the first half of 2023
- Examples of the most common validation issues identified
- Usage of the Validation Checklist and the reduction in VSI (Validation Supplementary Information) requests
- Improving the Quality of the Variation Applications: How to prevent VSI requests?

Overview of Type II (Non-clinical/Clinical/RMP) variations received in the first half of 2023



47 % of the variations submitted led to a VSI request

% Variations with VSI requests from Jan 2022 – June 2023



A new request, word version of the M2 documents, was introduced in January 2023

Most Common Validation Issues

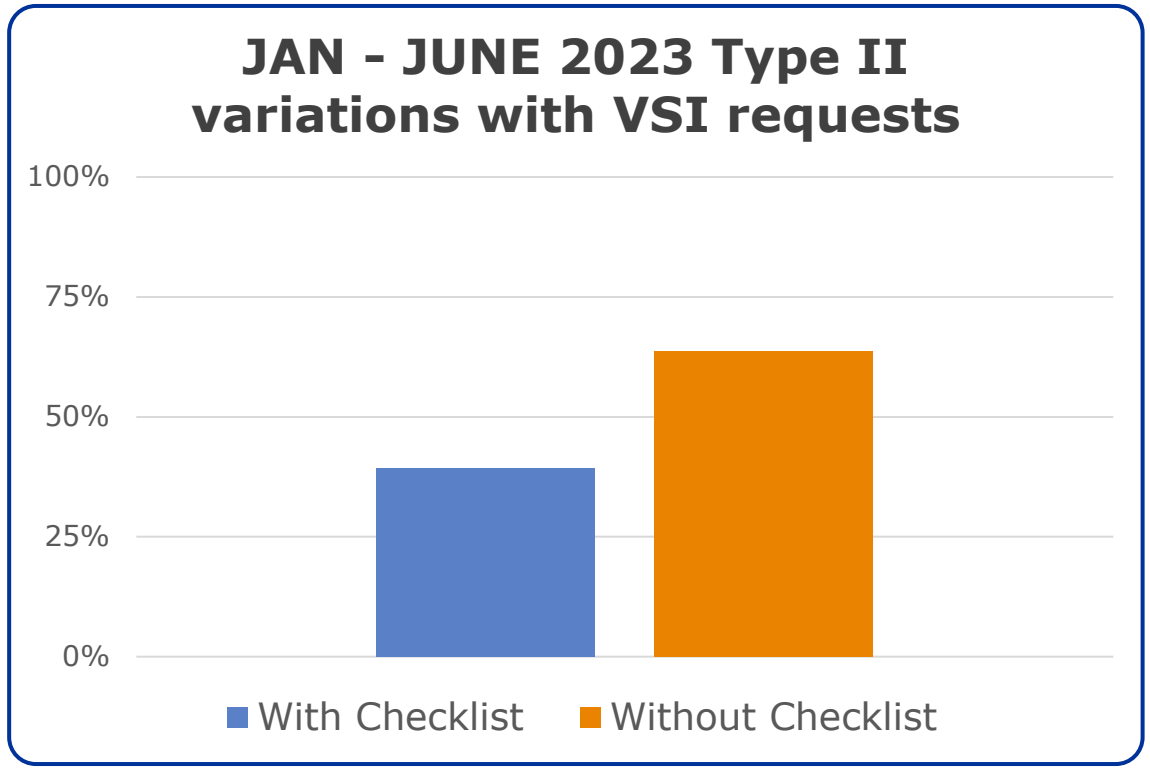
Inaccuracy of the Variation Classification chosen

- Choosing the incorrect Variation Classification for the proposed change
- Submitting a variation application with multiple scopes as a single application instead of grouped

Missing or Incorrectly submitted documents

- Module 2 Documents not provided in Word format as part of the Working documents (recent update)
- Missing Present/Proposed Table in Module 1.2: Application Form (should reflect all proposed changes to the PI)
- Missing or Incomplete Module 1.4: (Non-)Clinical Expert Statement (should be signed and dated + CV included)
- Missing Module 1.9: Information relating to Clinical Trials (required for interventional clinical studies that included at least one study centre outside of the EU)

Usage of the Validation Checklist and the reduction of VSI (Validation Supplementary Information) requests



39 % of the variations submitted with checklist led to a VSI request, compared to the **64%** of the variations without checklist

Variation applications that provide a checklist upfront result in **less VSI requests**.

Improving quality of type II variations: How to prevent VSI requests?

- Using the Validation Checklist helps in preventing validation issues (make sure to use the latest version)
- Reviewing the Post-Authorisation Guidance and Q&A on the EMA Website when preparing your submission
- If you cannot find the answer to your question on the EMA website, you can send your type II variation (Clinical/Non-Clinical/RMP) query to: IIquery@ema.europa.eu

To conclude:

Many of the validation issues for Type IB and Type II variation applications can be easily avoided if the available guidance is taken into account.

Questions and Suggestions

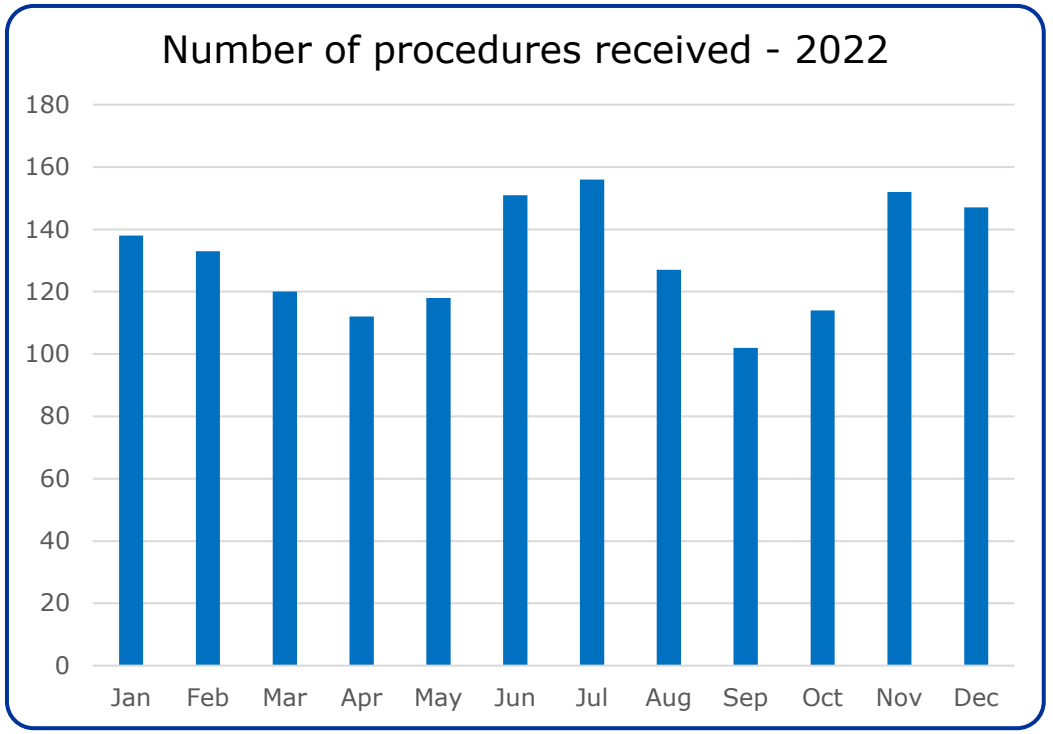
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Type IB Variations – Back-up slides

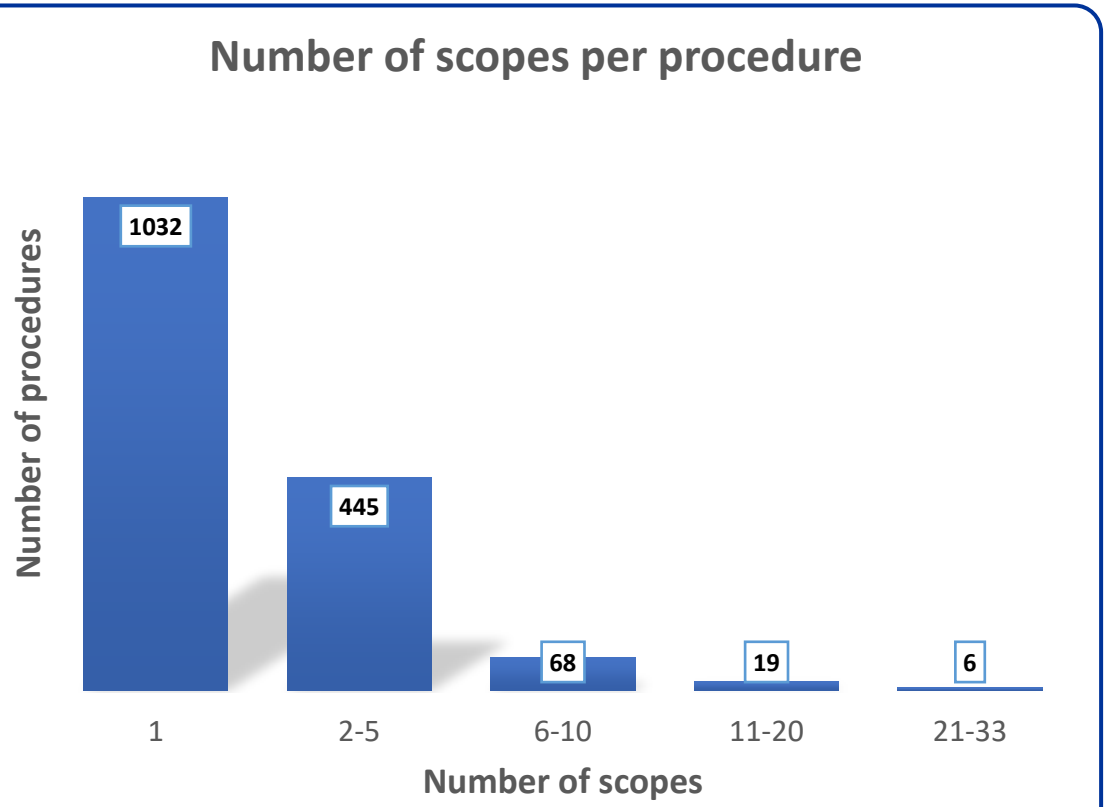
Overview of type IB variations received (2022)

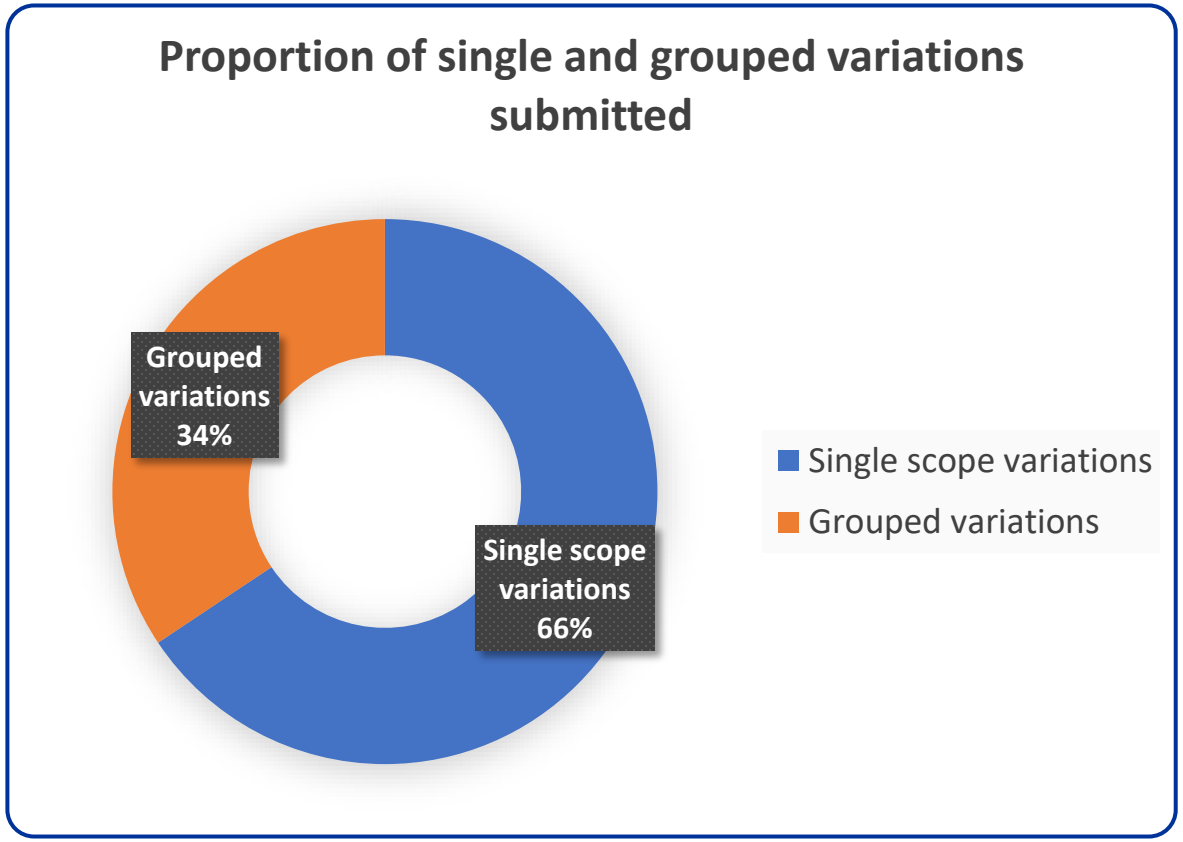
1570 type IB variations

- ✓ 1539 notifications (98%)
  - 1537: final acceptance (99,9%)
  - 2: non-acceptance (0,1%)
- ✓ 31 procedures withdrawn (2%) :
  - 18: during validation (58%)
  - 13: during the procedure (42%)



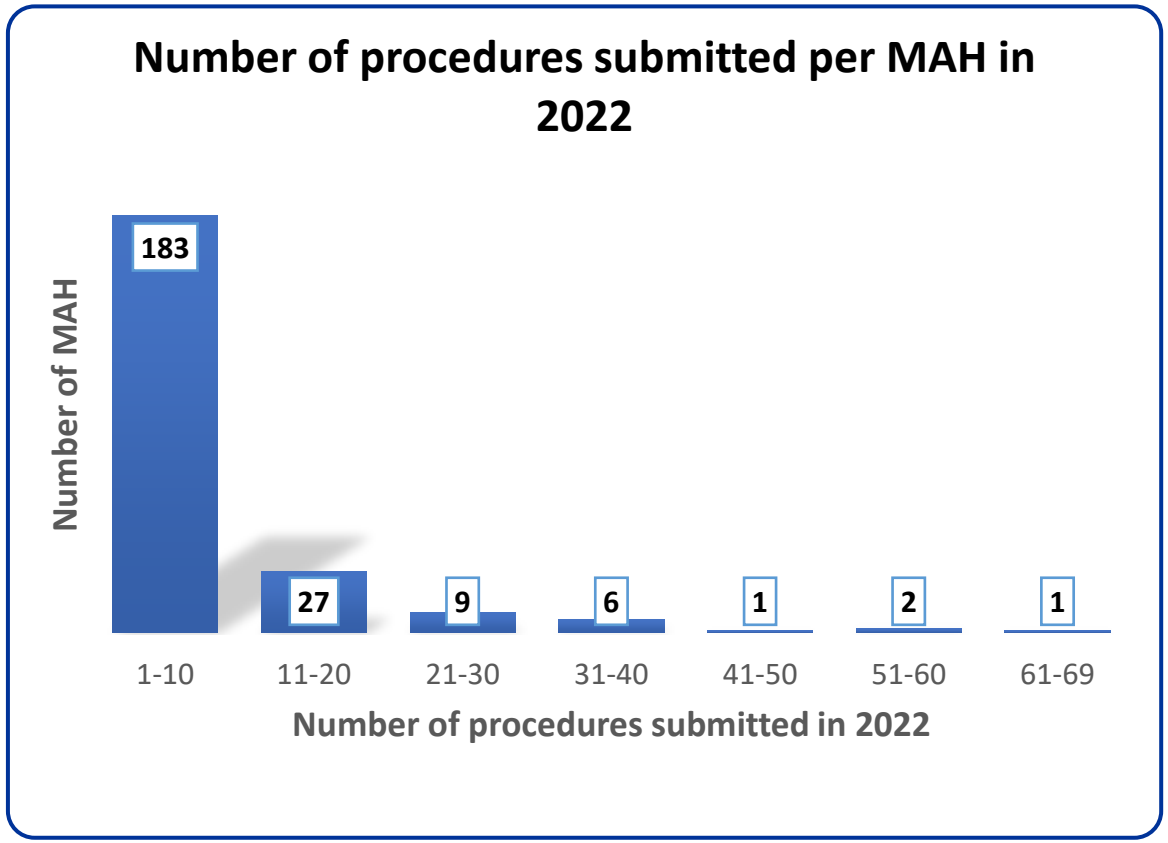
Number of scopes per IB variation procedure (2022)

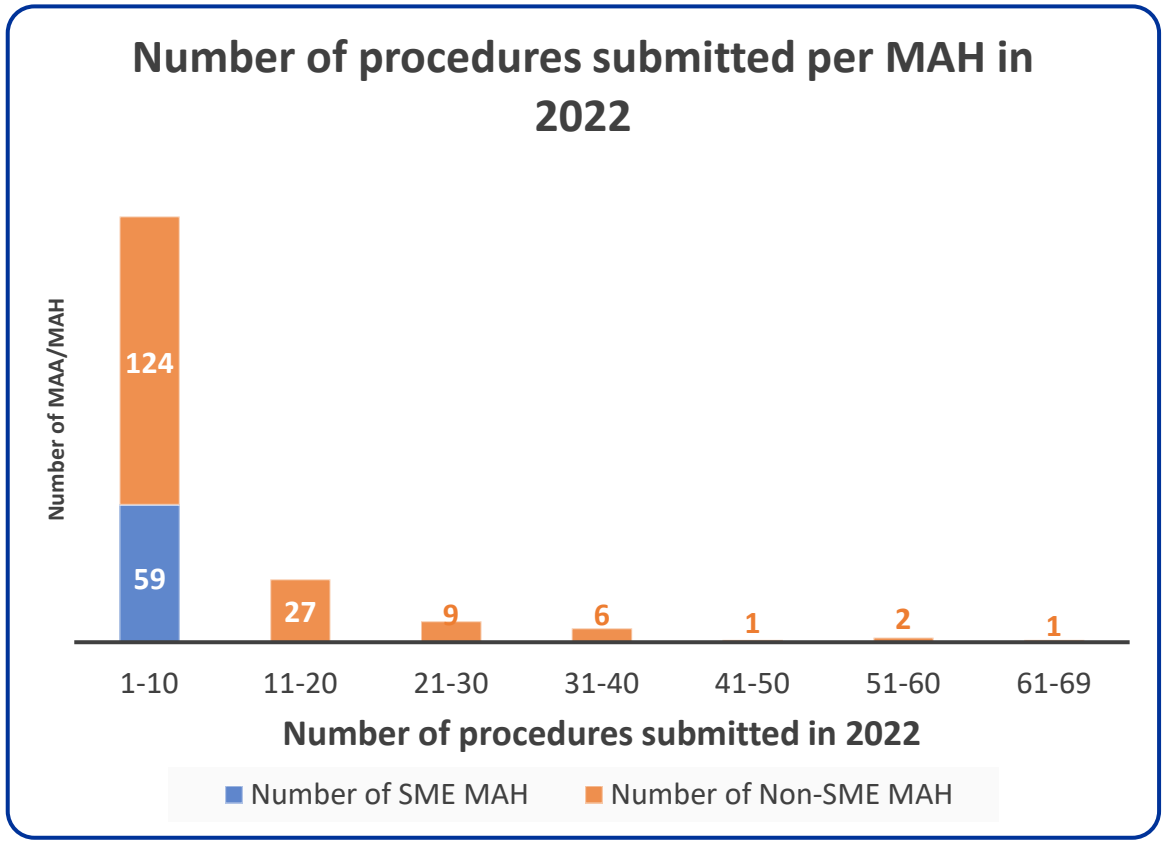




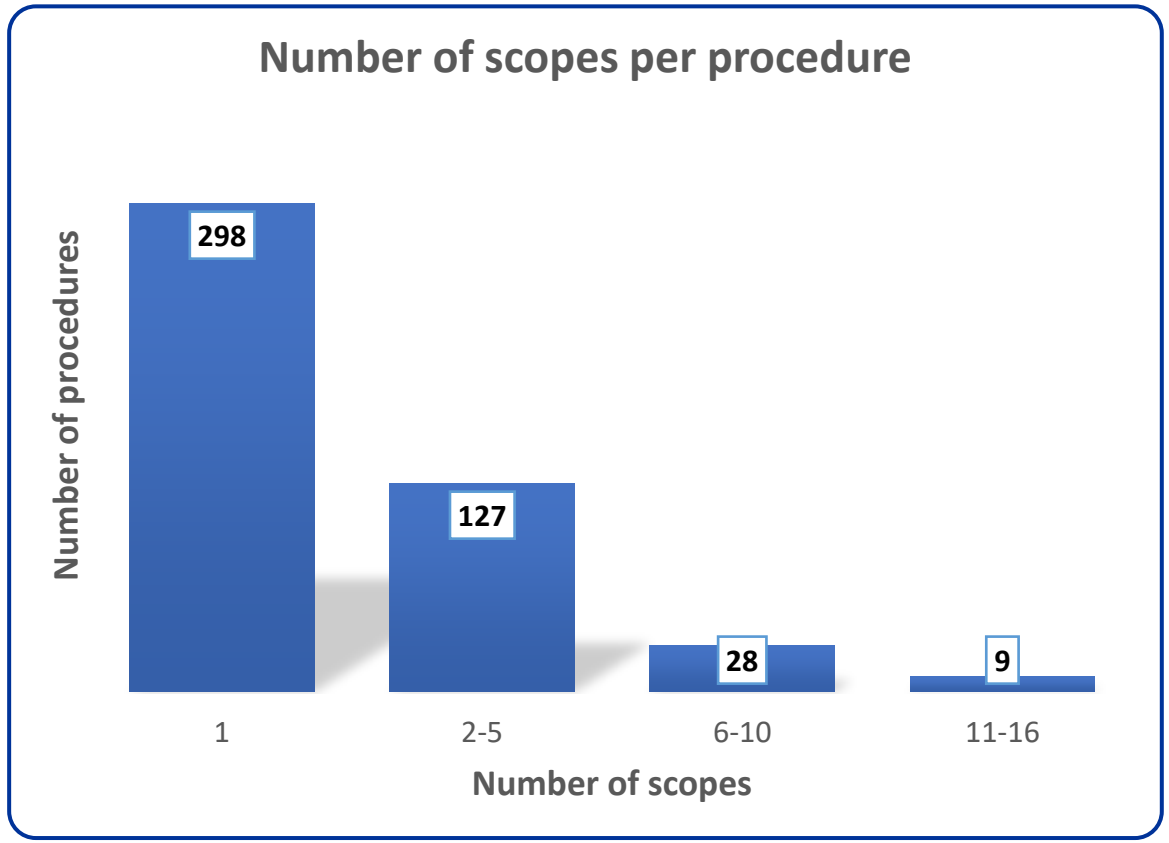
Number of procedures per MAH (2022)

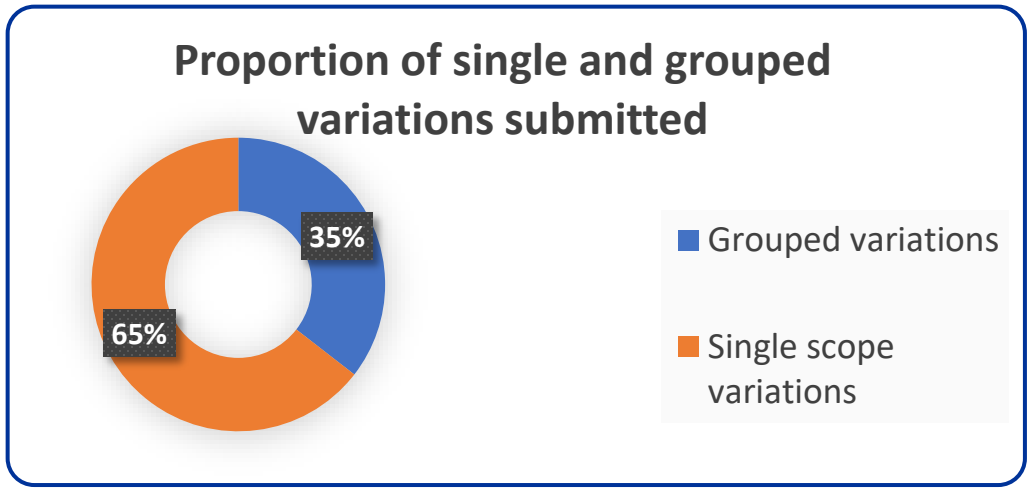
229 MAHs submitted type IB variation procedures in 2022.

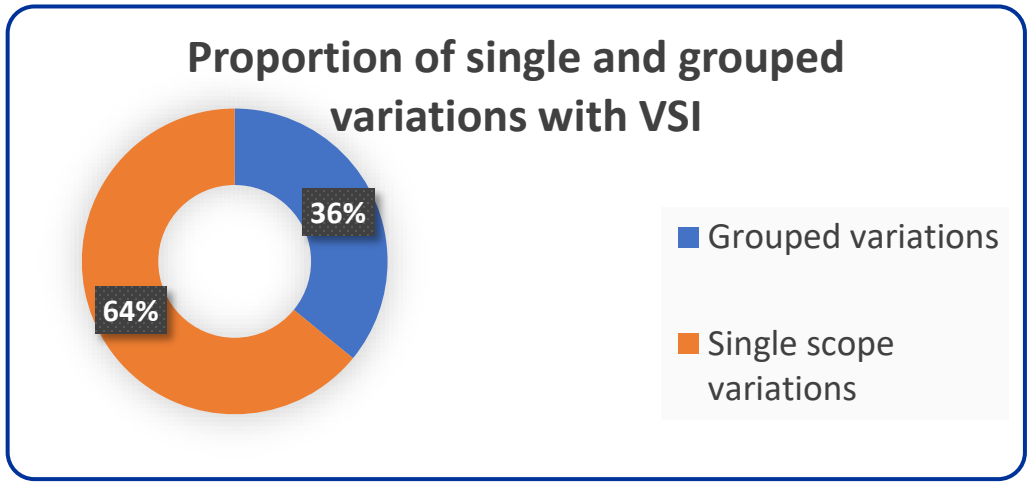




Number of scopes per IB variation procedure (3 months)

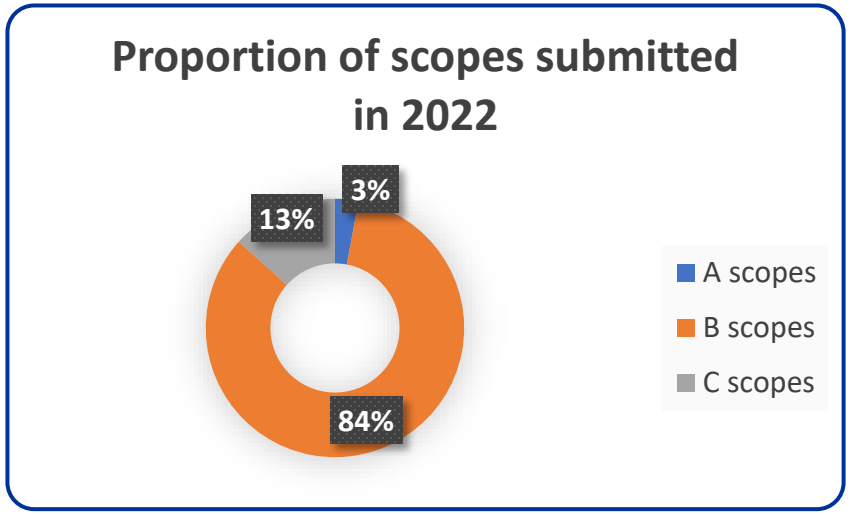


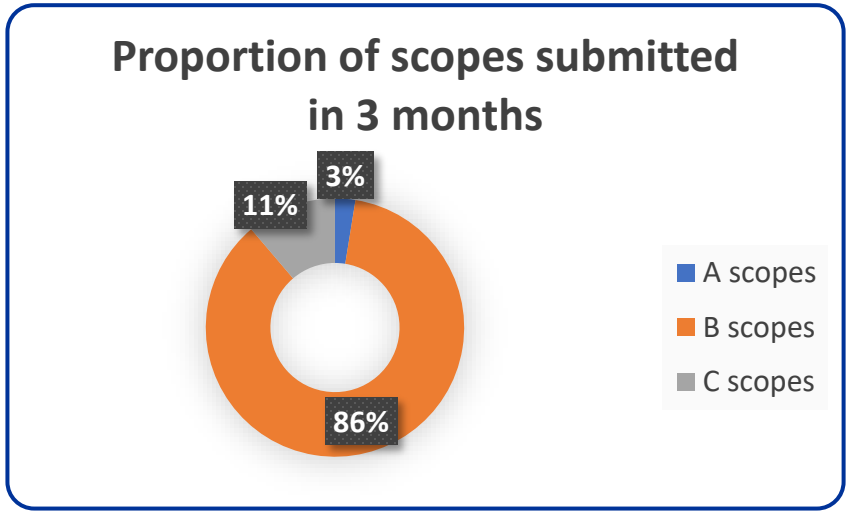




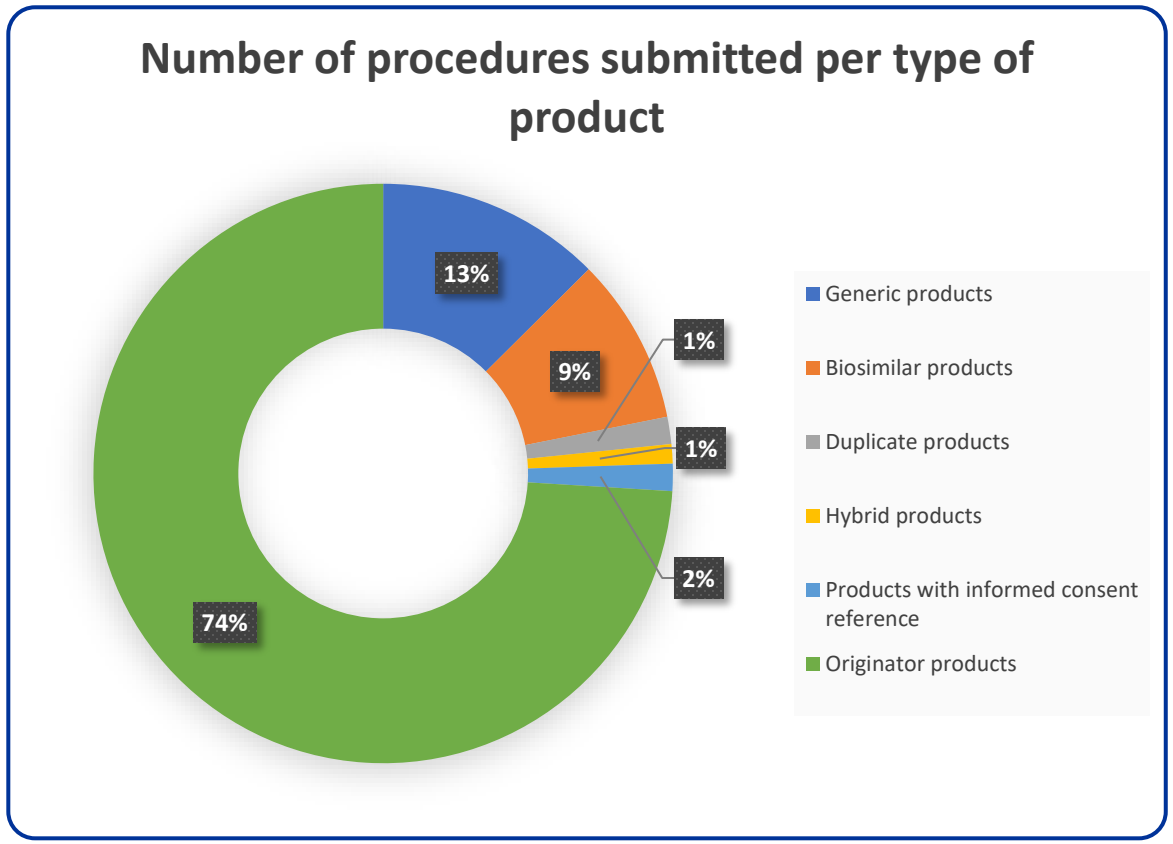
Type of variation scopes submitted

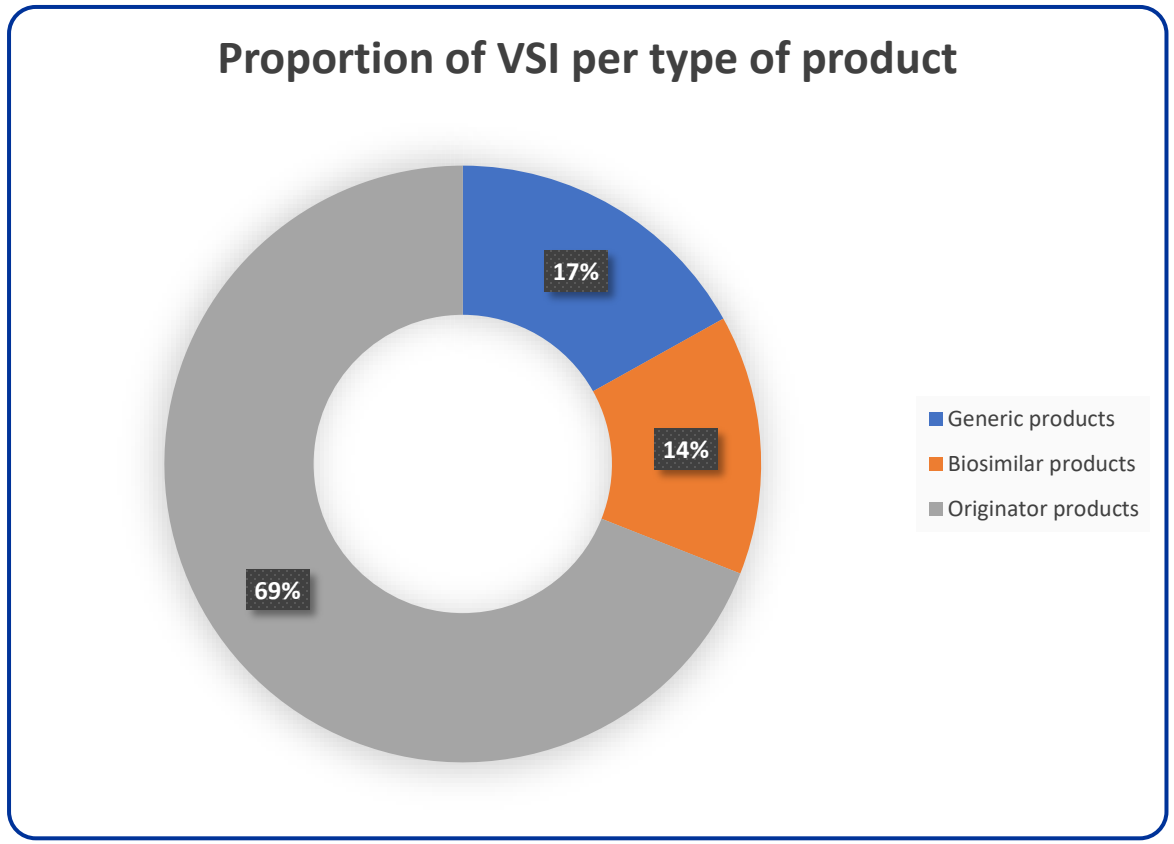
SCOPES	2022	3 months
A – Administrative changes	93	24
B – Quality changes	2655	814
C – Safety, efficiacy, Pharmacovigilance	424	106
Post consulation for ancillary medicinal substance, equivalent to IB	9	2
TOTAL	**3181**	**946**





Proportion of VSI per type of product (3 months)





Proportion of A, B, C scopes with VSI (3 months)