Medicines & Healthcare products Regulatory Agency

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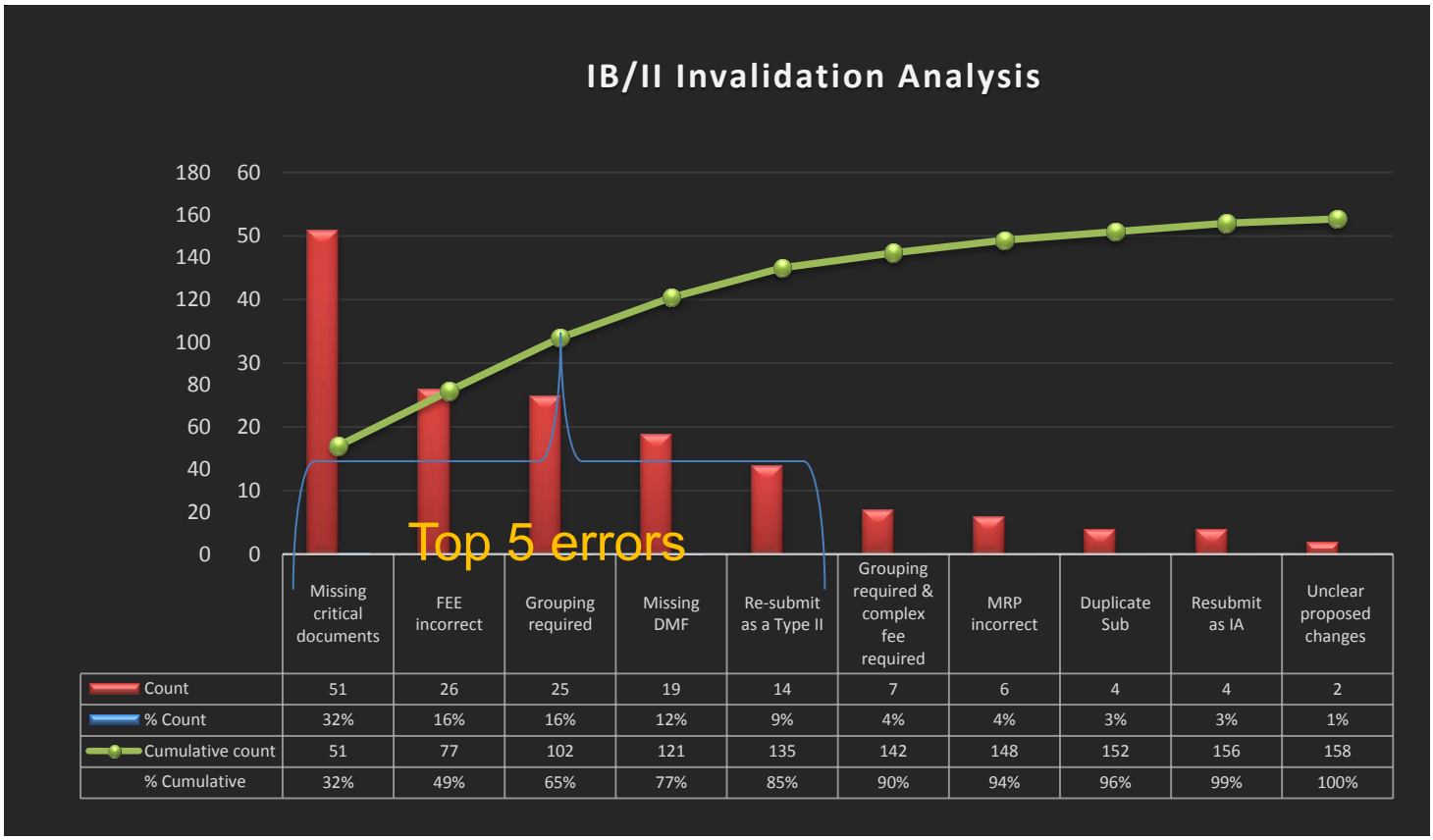
www.gov.uk/mhra

For Type IB & Type II variations a recent project has analysed the top 5 most common invalidation issues, see link for further information

For Type IA a recent project has analysed the top 5 most common rejection issues, see link for further information

Applicants are strongly advised to use the pre-submission checklist which will reduce likelihood of the submitted application being invalidated or rejected.

IB/II common errors



	Missing critical documents	FEE incorrect	Grouping required	Missing DMF	Re-submit as a Type II	Grouping required & complex fee required	MRP incorrect	Duplicate Sub	Resubmit as IA	Unclear proposed changes
Count	51	26	25	19	14	7	6	4	4	2
% Count	32%	16%	16%	12%	9%	4%	4%	3%	3%	1%
Cumulative count	51	77	102	121	135	142	148	152	156	158
% Cumulative	32%	49%	65%	77%	85%	90%	94%	96%	99%	100%

1. Missing Critical documents

The most common critical document to be missing from a submission are the SPC fragments. When a submission is made for all National and MRP variations, it is a documentation requirement to provide

individual clean SPC fragments, in a working documents folder. If the submission contains a bulk of licences it can be helpful to provide separate working document folders (one for each licence/bulk member, named appropriately) or the SPC fragments are collated in one working documents folder but each document named appropriately e.g. Section 2 – PL 0001 and Section 2- PL 0002 **or** Section 2- 10mg, Section 2- 20mg.

Other critical documents where applicable should also be provided according the guideline requirements of individual change codes. These documents may be updated sections of dossier or just supporting documents provided as evidence to support the proposed changes. If any documentation requirements cannot be met for whatever reason a justification statement should be provided with the guidelines page.

2. Missing or insufficient POP

Missing or insufficient POP is covered on the website.
https://www.gov.uk/medicines-apply-for-a-variation-to-your-marketing-authorisation#fees

Insufficient proof of payments are often provided due to the misconception of bulked fees. Refer to link which will guide applicants on providing the correct proof of payment.
Found in 33.1 Bulk fee reductions at https://www.gov.uk/government/publications/mhra-fees/current-mhra-fees#variations-licence-variations-application-fees

3. Grouping required

The applicant should review the MHRA published guidance on examples of acceptable groupings at the link below.
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/369000/Examples_of_groupings.pdf
and additionally review the CMD(h) website for acceptable groupings
http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/Variations/CMDh_296_2013_Rev20_2014_07_-_clean.pdf

If the proposed grouping has not been covered from one of these sources then it is likely the Grouping will require approval from Regulatory information Service at Variation Queries. Send the filled out grouping template to Variations@mhra.gsi.gov.uk

Additionally it is a requirement when submitting a Grouping that the source of grouping approval is provided with the dossier and reference is made to it in the cover letter and application form.

4. Missing DMF

Active substance master files (ASMFs)

ASMFs holders must submit their dossier to MHRA. It is your responsibility to make sure that the ASMF is submitted either before you submit your application or at the same time, as your application will not be valid without it.

The ASMF holder will need to register with the Common European Submission Platform (CESP) and then make their application through CESP.

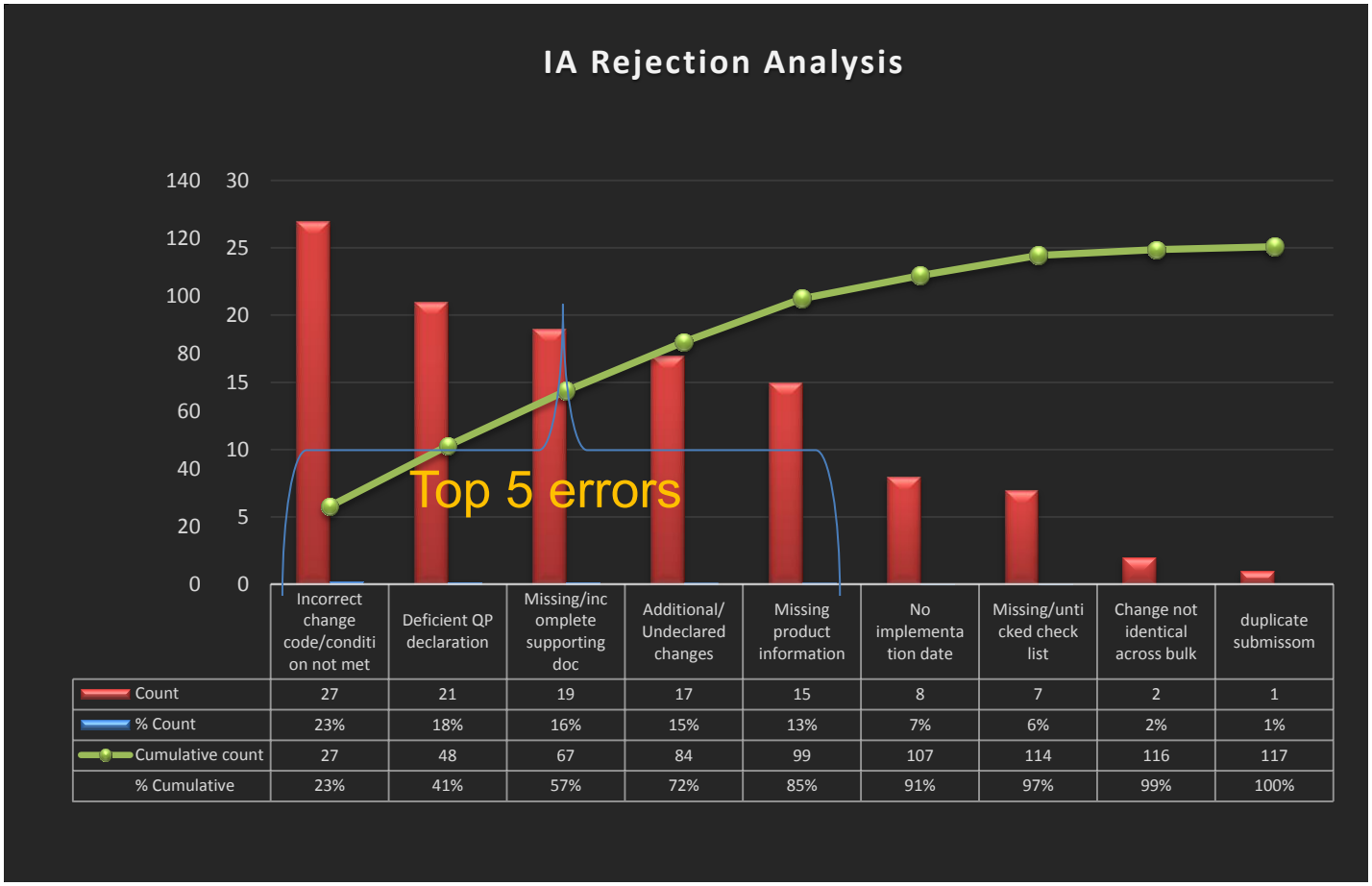
We have produced guidance on submitting an ASMF (PDF, 74.7KB, 2 pages) to help the ASMF holder prepare their dossier.

5. Incorrect Submission Category

MAH should submit applications under the correct category (i.e. TIB or TII). If the applicant is not sure about which category a change should be submitted under, the FAQs should be referred to. If the MAH is still unsure after checking the various FAQs, an email should be sent to variationqueries@mhra.gsi.gov.uk for advice.

Archive of FAQs
http://webarchive.nationalarchives.gov.uk/20141205150130/http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Marketingauthorisations/Variationstolicences/FAQsforvariationssubmittedafter1January2010/Administrativechanges/index.htm#2

IA common errors



	Incorrect change code/condition not met	Deficient QP declaration	Missing/incomplete supporting doc	Additional/ Undeclared changes	Missing product information	No implementation date	Missing/unticked check list	Change not identical across bulk	duplicate submissom
Count	27	21	19	17	15	8	7	2	1
% Count	23%	18%	16%	15%	13%	7%	6%	2%	1%
Cumulative count	27	48	67	84	99	107	114	116	117
% Cumulative	23%	41%	57%	72%	85%	91%	97%	99%	100%

1. Incorrect change code/condition not met

- All conditions and documentation requirements for each change should be met. If a condition or documentation requirement is not applicable an adequate justification should be provided and “NA” should be used instead of a tick when completing the classification guideline check list.

2. Deficient QP declaration

- MAHs are advised to use the published CMDh QP template and ensure all information requested is provided. All relevant registered sites should be covered by the declaration. It is not acceptable to omit a manufacturing site from a QP declaration on the basis that the site is obsolete or it is temporary not in use. Redundant sites should be deleted prior to compiling a QP declaration. Please see the entries under EMA/334808/2014 in the CMDh link below for further guidance
  http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000354.jsp&mid=WC0b01ac0580028bfd

3. Missing/Incomplete supporting document

- MAH should do a appropriate check to ensure all relevant documentation requirement as specified in the classification guideline are included in the dossier. If a condition or documentation requirement is not applicable a suitable justification should be provided and “NA” should be used instead of a tick when completing the classification guideline check list.

4. Additional/Undeclared changes

- All changes should be declared in the application form and the appropriate classification check list should be completed for each change.
- Revised modules of the dossier being submitted should be checked to ensure that only changes that are consequential to the TIA variation are included.

5. Missing Product information

- MAH should ensure that when a TIA affects the product information, revised label, leaflet and SmPC fragments are included in the submission as appropriate. All the revised labels and leaflets for each registered product name and/or own label distributors should be submitted when affected.
- If text version of the label and leaflet is currently registered and a TIA variation affects the livery, revised text versions of the label and leaflet should be provided. However, if mock-ups are currently registered, the expectation is that the MAH provide revised mock-ups. Text versions may only be provided if the MAH have already informed the agency via the appropriate channel that the product is no longer marketed and in these instances a statement to this effect should be included in the application form.