KPIs Centralised Procedure:

Initial marketing authorization application and use of checklist

EMA/Industry Platform meeting on Centralised Procedure. 3 December 2020

Presented by Caroline Blanc
Team lead – Administrative procedures and Validations Centre Team
European Medicines Agency

Agenda

- Use of Initial marketing authorization application (MAA) Validation Checklist
- Some statistics on Validation Issues (VSI)
- Key Recommendations

Use of Initial marketing authorization application Validation Checklist

Key conclusions from EMA survey on centralised initial marketing authorisation procedure 2016/2017 from Industry:

Validation issues occur in 90% of initial marketing authorisation applications (iMAAs).

They create additional workload for companies at a critical moment for the timely start of the procedure.

News 08/02/2019

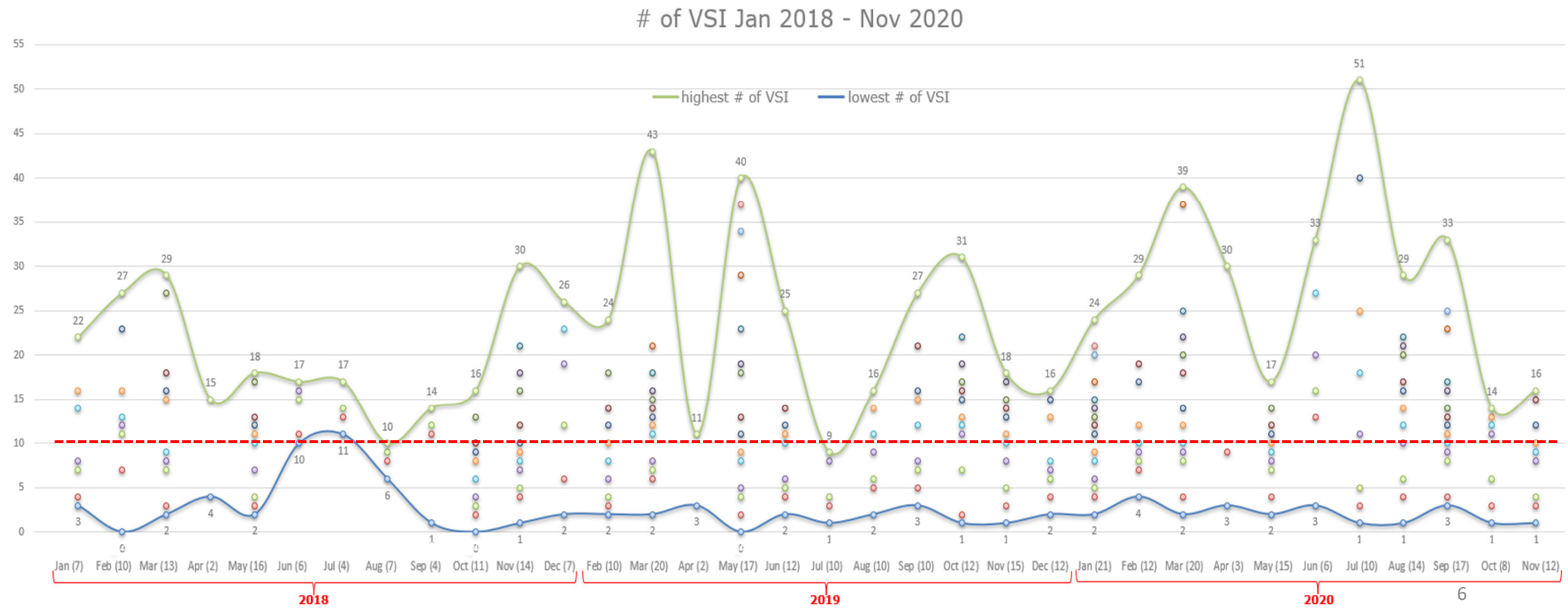
EMA launches checklist to facilitate validation of initial marketing authorisation applications

The initiative is expected to increase the number of ‘first time right’ submissions significantly.

EMA will use this feedback and the information collected on the quality of submissions using the new checklist to improve the validation process itself.

1.5 years later:

Still a high number of iMAAs with >10 validation issues (VSI)



% MAAs using the checklist

Applicants have started using the checklist more in 2020

2019 % OF CHECKLIST USED vs # OF IMAAs

	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
# of IMAAs	10	20	2	17	12	10	10	10	12	15	12
# of IMAAs with checklist	0	0	1	4	8	3	2	2	0	1	7
%	0%	0%	50%	24%	67%	30%	20%	20%	0%	7%	58%

2020 % OF CHECKLIST USED vs # OF IMAAs

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
# of IMAAs	21	12	20	3	15	7	10	14	17	8	13	5
# of IMAAs with checklist	18	8	14	2	12	3	7	8	6	6	8	0
%	86%	67%	70%	67%	80%	43%	70%	57%	35%	75%	62%	0%

Ratio checklist used versus number of validation issues

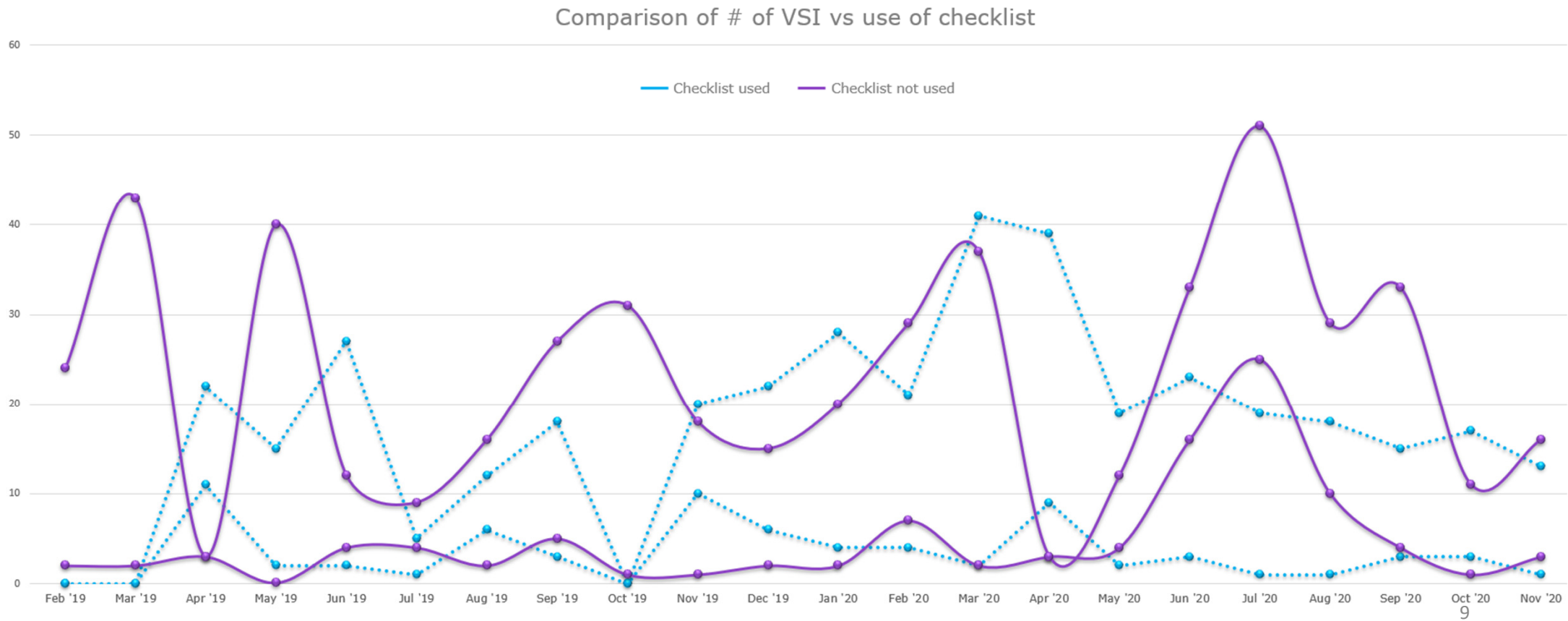
Less validation issues when the checklist is used.

Since May 2020:

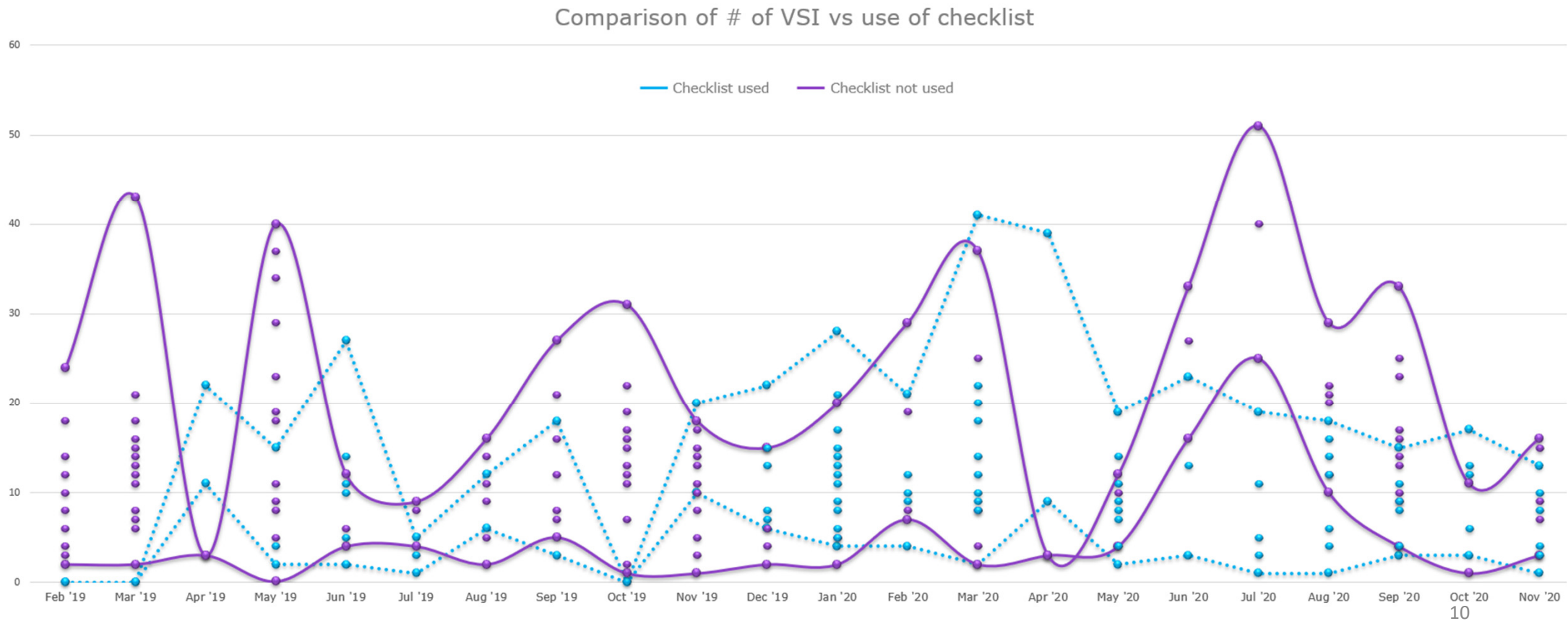
	2019	2020	> May 2020
Checklist used:			
#VSI	244	947	431
#MA	28	92	50
Ratio	9	10	9
Checklist not used:			
#VSI no ckl	1240	742	571
#MA no ckl	102	48	34
Ratio	12	15	17

Comparison of number of validation issues versus use of checklist

The checklist reduces the number of validation issues



Comparison of number of validation issues versus use of checklist



Validation checklist regularly updated to prompt industry to address recurring issues and new arising regulatory/scientific matters

Latest updates of published checklist in July 2020:

- Orphan Designation

1.2.1 Orphan medicinal product information			Orphan designation: marketing authorisation
Orphan designation has been applied for this medicinal product? ('Yes' is ticked in section 1.2.1 of the AF)		Ensure that the pharmaceutical form indicated on the Orphan designation corresponds to that stated on the eAF.	Orphan designation: Overview
The **Sponsor** of the Orphan designation should be **established in** the Union (**EEA**)			
In case of **OD transfer**: The Commission Implementing Decision concerning the transfer of the designation has been finalized and it should be submitted together with the initial Commission Decision relating to the designation. The name and address of the new Sponsor indicated under Art. 2 of the Decision concerning the transfer should correspond to the details of the proposed applicant under section 2.4.1 of the eAF.		The Decision on the Transfer should be finalized prior to the submission of the dossier. Both the original designation and the Decision on the Transfer should be included.	

- Nitrosamines risk assessment

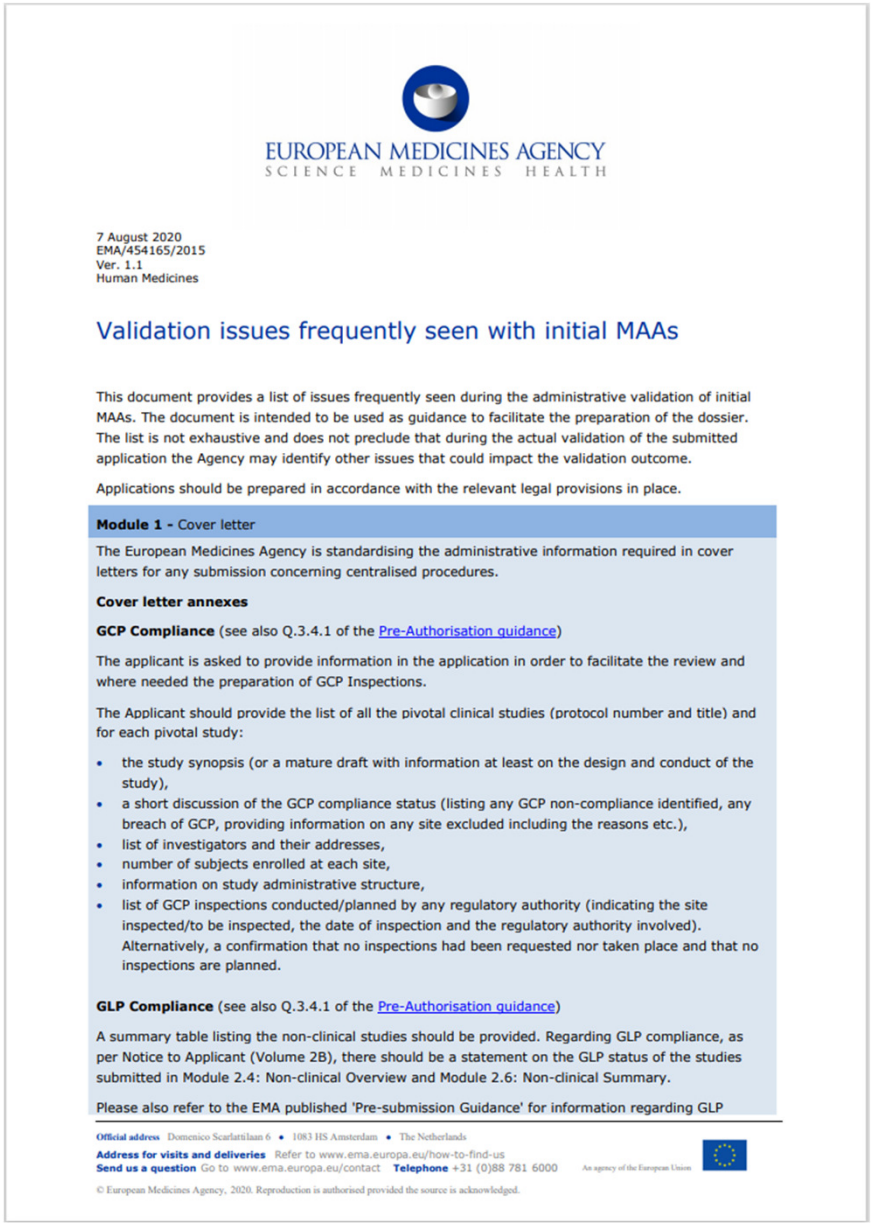
In the context of the on-going review under Article 5(3) of Regulation (EC) No 726/2004 related to the potential presence of nitrosamine impurities in human medicinal products, applicants/MAHs are requested to review their product for potential presence of nitrosamine impurities and to conduct risk evaluations/risk assessments as appropriate. Please confirm that this (marketing authorisation) application includes such risk evaluation/risk assessment as relevant.		This check only applies to Chemical ASs. Information on the risk evaluation/risk assessment should be included in Mod. 1 as an annex to the Cover letter.	Nitrosamines impurities Questions and answers on 'Information on nitrosamines for marketing authorisation holders Information on nitrosamines for marketing authorisation holders

Every time there's a new release, a mass mailing is sent to all contacts for upcoming IMAAs for awareness.

Next release foreseen in December (to include new BREXIT rules).

Publication of document listing Validation issues frequently seen with initial MAAs

Document regularly updated (last version 07.08.20)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

7 August 2020
EMA/454165/2015
Ver. 1.1
Human Medicines

Validation issues frequently seen with initial MAAs

This document provides a list of issues frequently seen during the administrative validation of initial MAAs. The document is intended to be used as guidance to facilitate the preparation of the dossier. The list is not exhaustive and does not preclude that during the actual validation of the submitted application the Agency may identify other issues that could impact the validation outcome.

Applications should be prepared in accordance with the relevant legal provisions in place.

Module 1 - Cover letter

The European Medicines Agency is standardising the administrative information required in cover letters for any submission concerning centralised procedures.

Cover letter annexes

GCP Compliance (see also Q.3.4.1 of the Pre-Authorisation guidance)

The applicant is asked to provide information in the application in order to facilitate the review and where needed the preparation of GCP Inspections.

The Applicant should provide the list of all the pivotal clinical studies (protocol number and title) and for each pivotal study:

- the study synopsis (or a mature draft with information at least on the design and conduct of the study),
- a short discussion of the GCP compliance status (listing any GCP non-compliance identified, any breach of GCP, providing information on any site excluded including the reasons etc.),
- list of investigators and their addresses,
- number of subjects enrolled at each site,
- information on study administrative structure,
- list of GCP inspections conducted/planned by any regulatory authority (indicating the site inspected/to be inspected, the date of inspection and the regulatory authority involved). Alternatively, a confirmation that no inspections had been requested nor taken place and that no inspections are planned.

GLP Compliance (see also Q.3.4.1 of the Pre-Authorisation guidance)

A summary table listing the non-clinical studies should be provided. Regarding GLP compliance, as per Notice to Applicant (Volume 2B), there should be a statement on the GLP status of the studies submitted in Module 2.4: Non-clinical Overview and Module 2.6: Non-clinical Summary.

Please also refer to the EMA published 'Pre-submission Guidance' for information regarding GLP

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Conclusion:

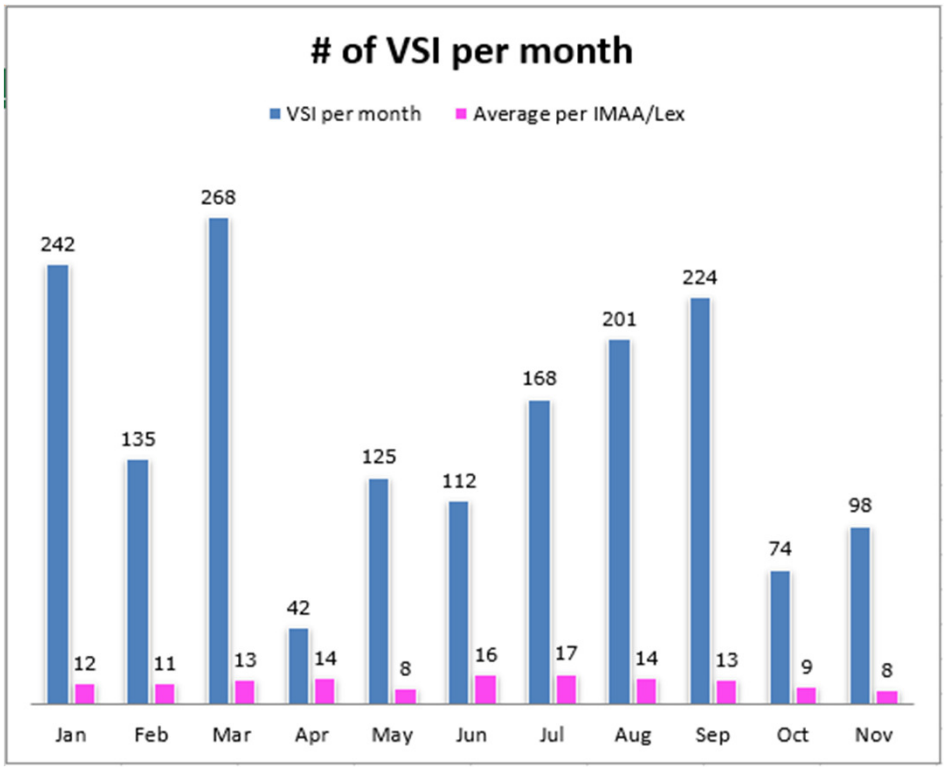
- The number of validation issues is still high
  - Validation issues occur in 99.5% of iMAAs
- When the checklist is used, the number of validation issues is reduced
- Need for industry to increase systematic use / submission of the validation checklist

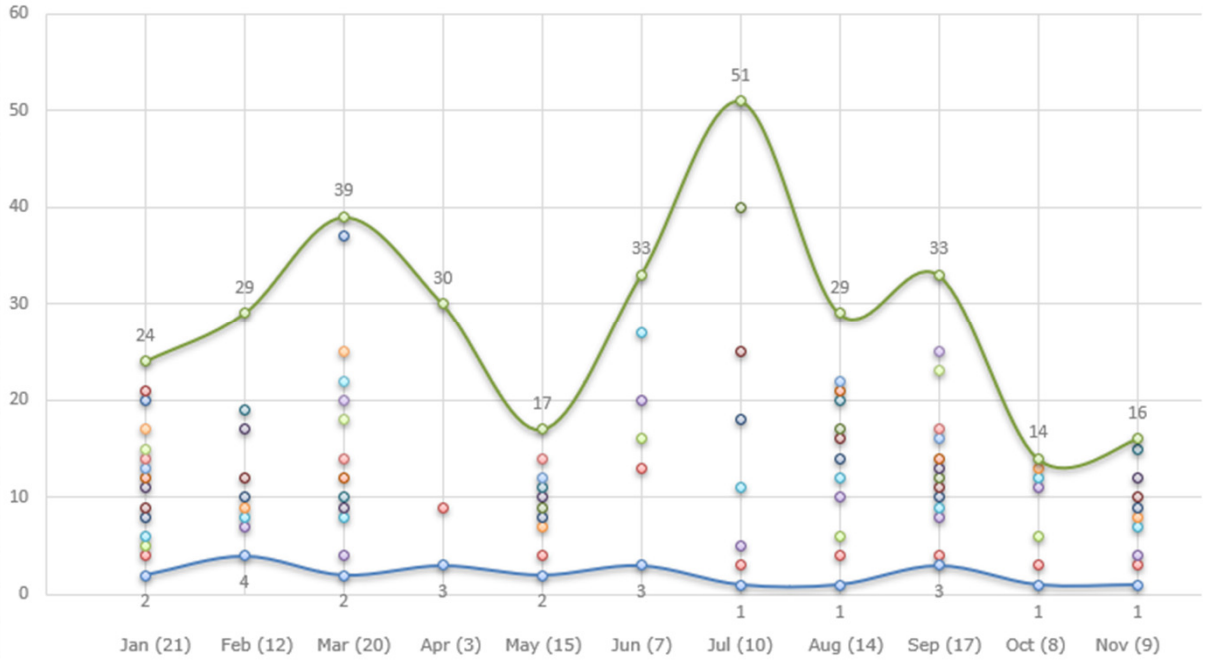
Some statistics on Validation Issues

VSI raised in 2020

No first time right iMAA submissions

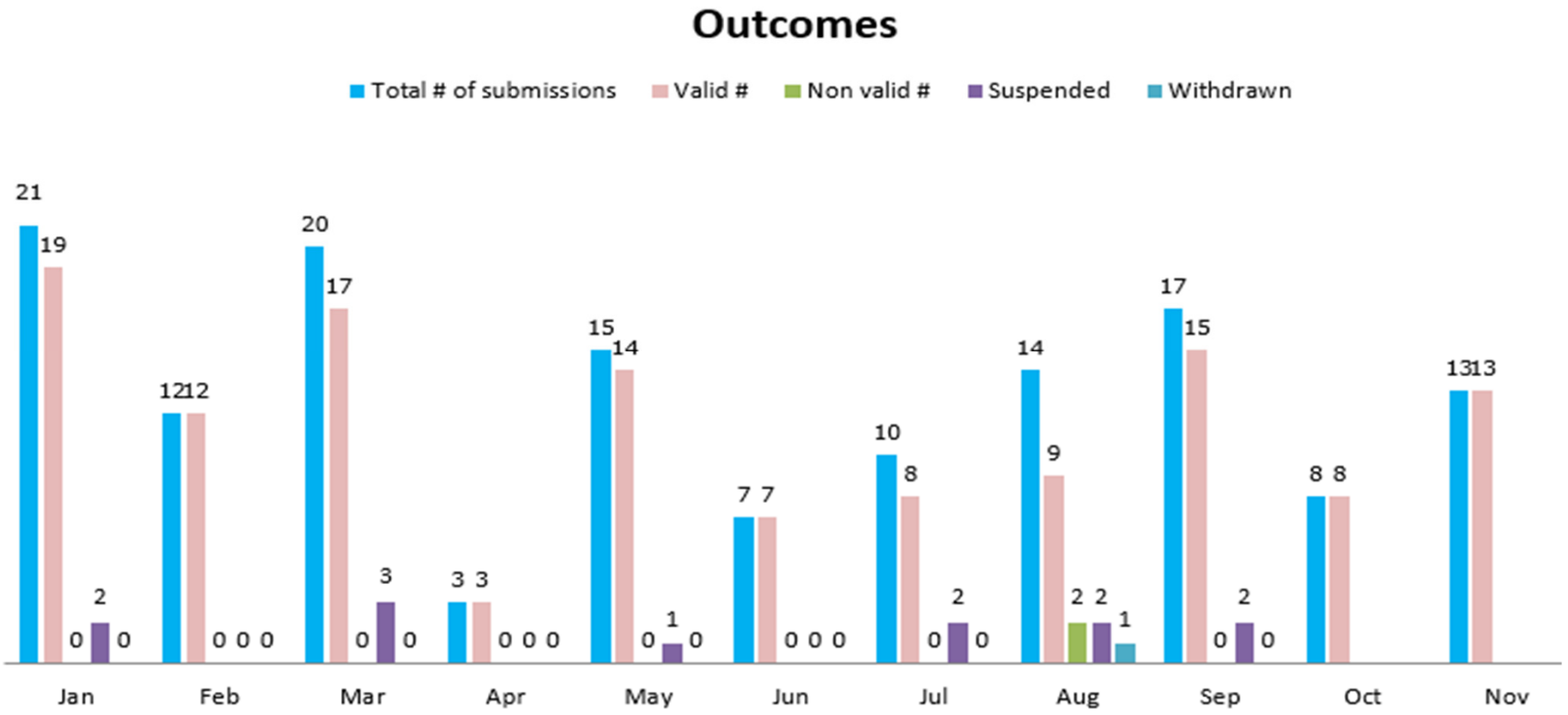
Some iMAAs have a very high number of validation issues (premature application?)





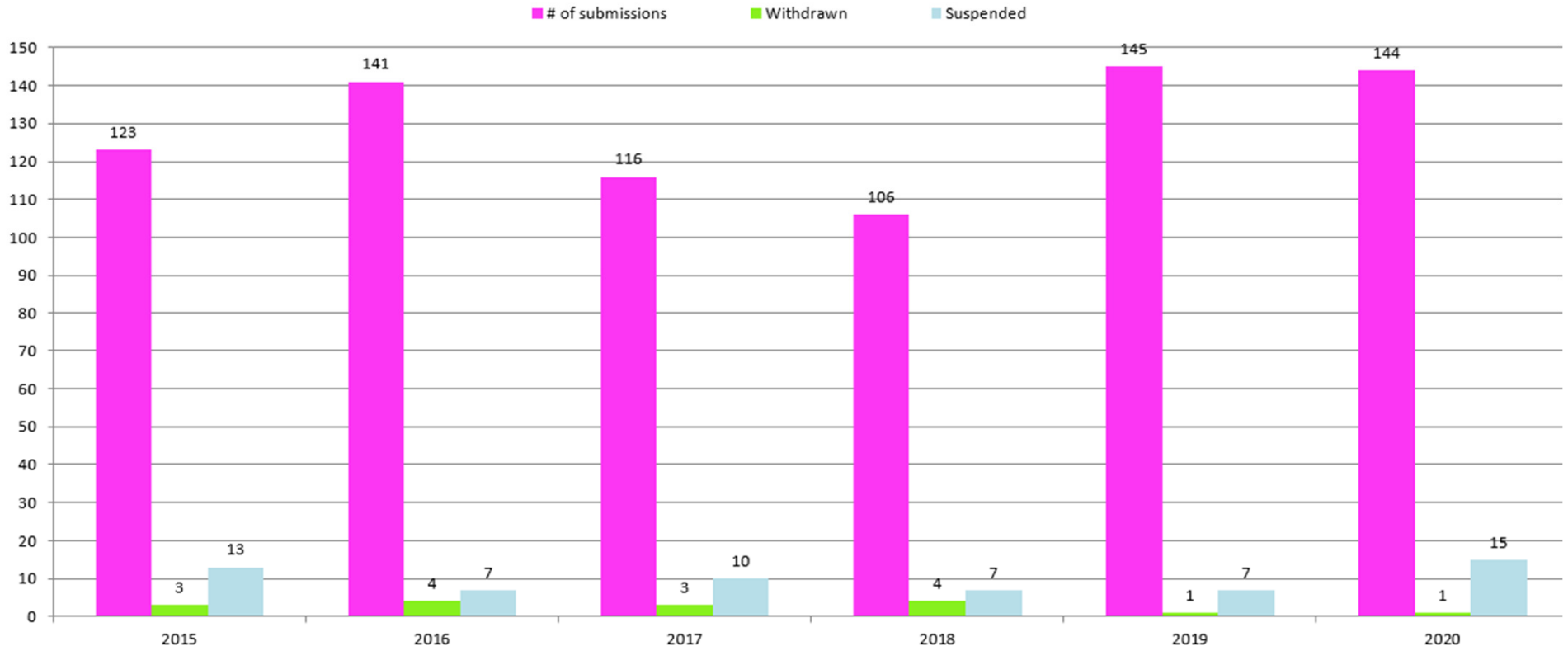
Validation outcomes in 2020

98% of iMAAs submitted are starting
(only 1 withdrawal and 2 negative validations in 2020)



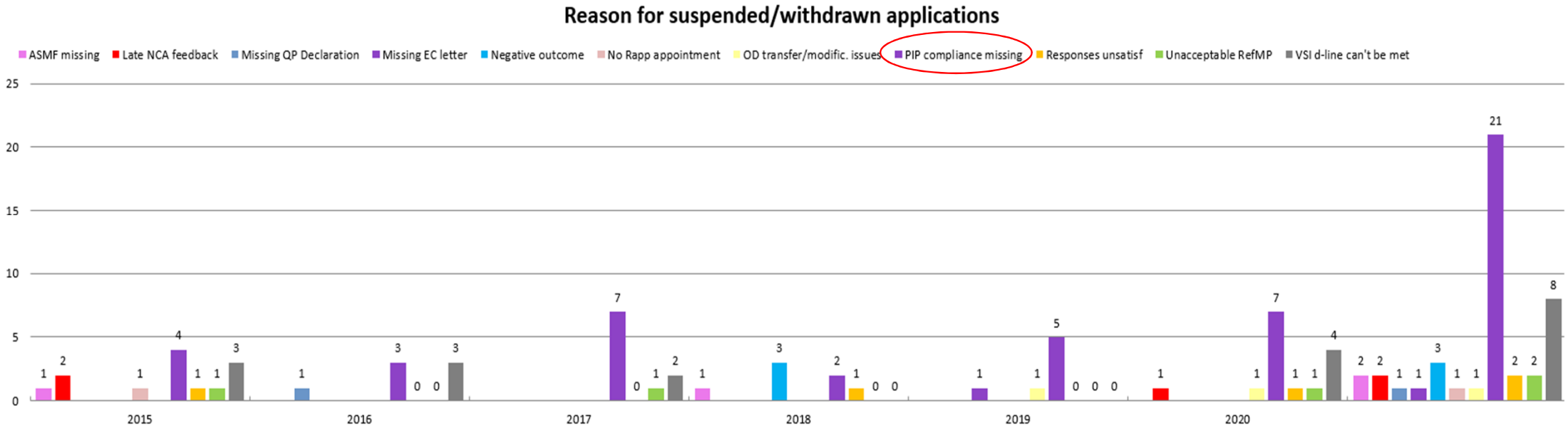
Suspensions and withdrawals since 2015

The number of withdrawals and suspensions is low and stable over the years



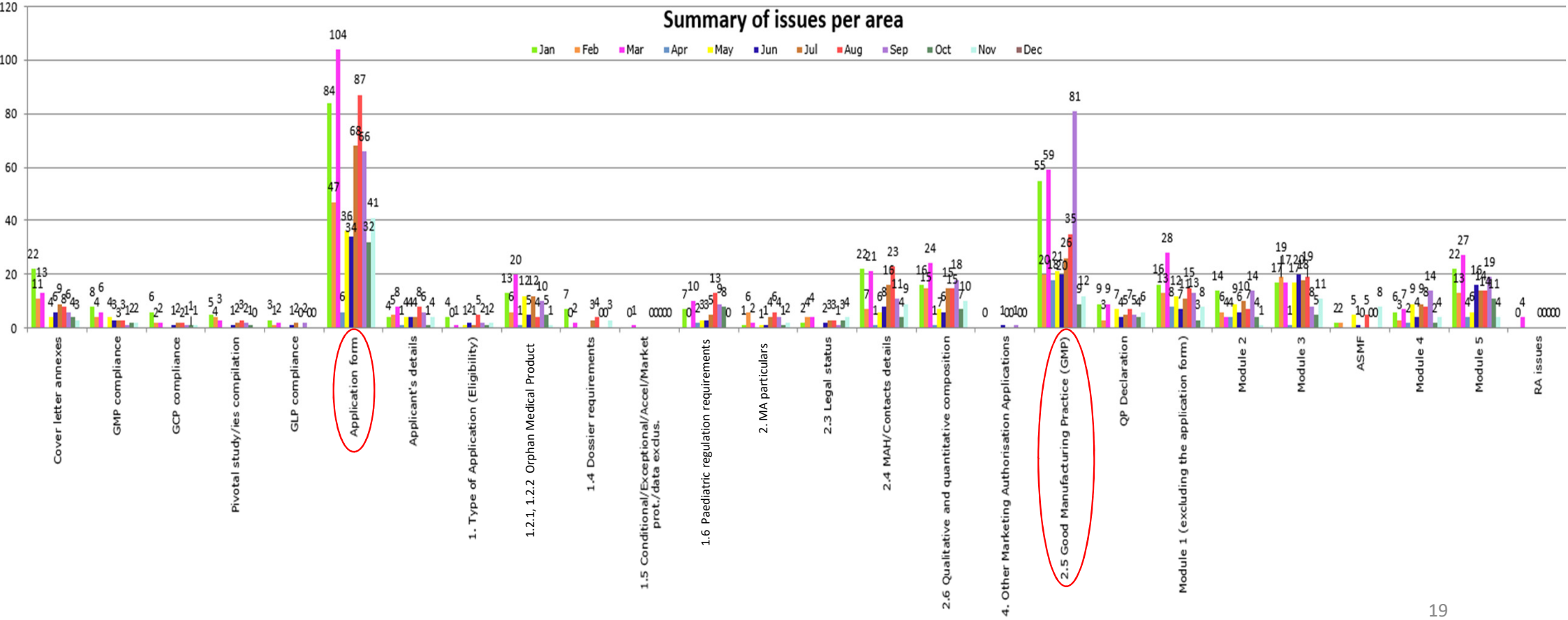
Grounds for suspension and withdrawal

Missing PIP compliance is still the main ground for suspension and withdrawal



Validation issues

A high number of validation issues are raised on the application form and GMP aspects



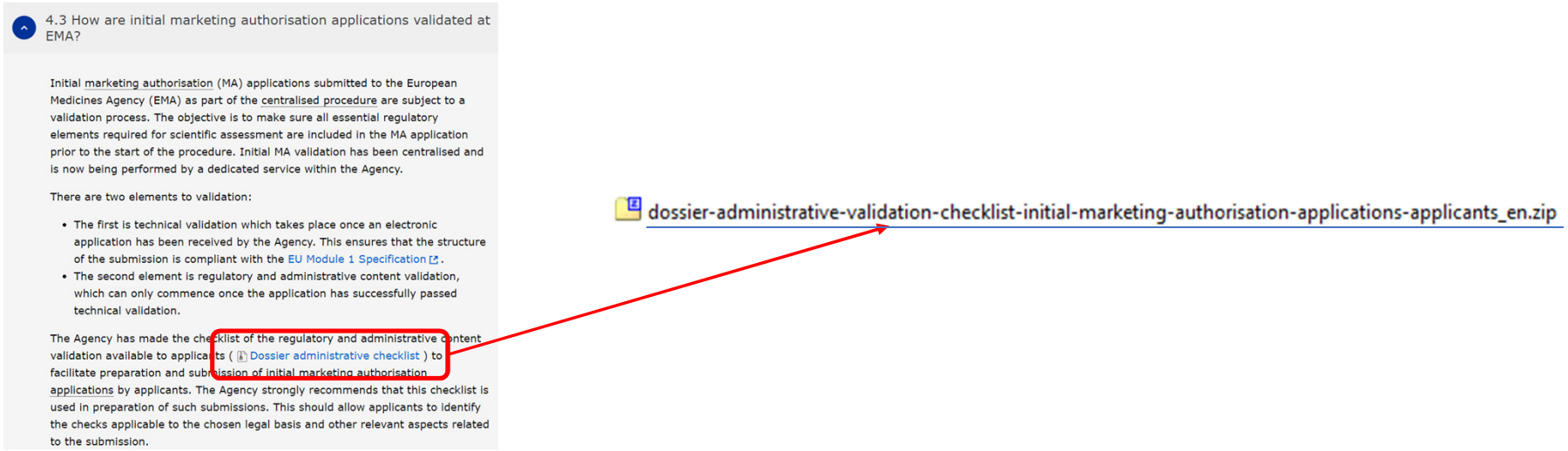
Key Recommendations

- Use the checklist as it reduces the number of validation issues.
- Keep up to date with published guidance, the validation checklist and Q&As as they are updated on regular basis
- Always include the validation checklist in the MAA submission
- To avoid any delay, the PIP compliance should be completed before submission of the iMAA.
- More scrutiny of the GMP related documents is advised (QP declaration not including all necessary information, MIA not covering all activities declared in the dossier,…)
- The Product Lead is available for questions regarding validation of the MAA during the pre-submission meeting and until the submission of the application.
- Corporate/Affiliate cross learning and sharing is important within Industry

Reminder:

Applicants are invited to submit their comments on the checklist to checklist_ima@ema.europa.eu.

The checklist can be downloaded from the EMA Corporate site; it is available under Q. 4.3 of the Pre-authorisation guidance



Useful links:

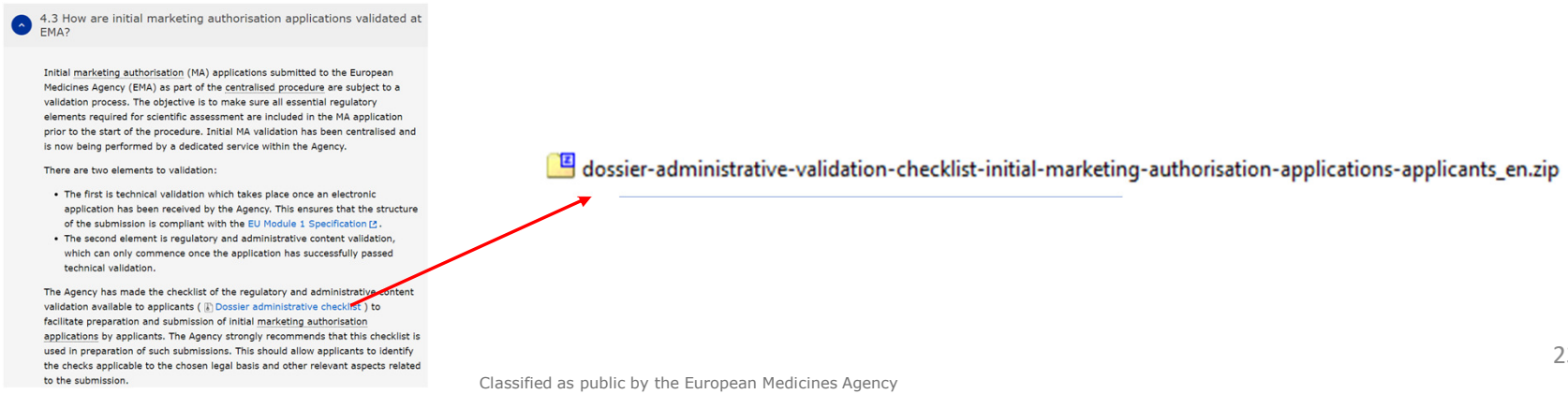
Validation issues frequently seen with initial MAAs

Pre-authorisation guidance: 3.2.1 Do I need to address any paediatric requirements in my application?

QP declaration template

Good manufacturing practice

The checklist can be downloaded from the EMA Corporate site; it is available under Q. 4.3 of the Pre-authorisation guidance



Any questions?

Further information

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