Health and Youth Care Inspectorate
Ministry of Health, Welfare and Sport

Results of the Pharmacovigilance Risk-Based Survey in the Netherlands

Date: 1 July 2018

Inhoud

Introduction

On 1 May 2017, a survey was sent to 811 marketing authorization holders (MAHs) with a marketing authorization of human medicinal products in the Netherlands.

Before the survey was sent to all MAHs, it was tested during two pilot phases in 2016 where 33 MAHs voluntarily participated and completed the survey. The results of the pilot were used to improve the survey. The survey was also discussed with and reviewed by the board members of the Pharmacovigilance Platform Nederland (PPN). A presentation was given in November 2016 to announce the use of the survey by the Health and Youth Care Inspectorate (IGJ). A post meeting with representatives of several MAHs was held to further discuss the questions raised by the field. We received valuable feedback from the MAHs and the board members of the PPN and used this information to further improve the survey.

All MAHs were asked to complete the survey within 3 months. Reminders were sent (letters and e-mails) to MAHs which did not complete the survey before the deadline and a number of MAHs were contacted by telephone.

Altogether, 802 MAHs (98.9%) responded to the request and completed the survey (if applicable) and 9 MAHs did not complete the survey. From the 802 MAHs, 131 MAHs were not required to complete the survey for several reasons:

- They did not have any marketing authorizations (anymore) for products in the Netherlands. The information in the eXtended Eudravigilance Medicinal Product Dictionary (XEVMPD or article 57) database was not up to date.
- They were merged with another company. The information in the XEVMPD database was not up to date.
- They were registered in the XEVMPD database multiple times and therefore received more than one survey for the same MAH. The information in the XEVMPD database was not correct.
- They only had parallel marketing authorizations and no other marketing authorizations (CAPs, NAPs, MRPs or DCPs). MAHs with parallel import marketing authorizations only are required to follow the "MEB 14: Parallel import: marketing authorization and maintenance" guidelines with regard to the pharmacovigilance requirements. These organizations were not within the scope of the survey.

1. General information

This section refers to the registration of the organization in Eudravigilance and the submission and maintenance of product information in the XEVMPD database. Higher scores will be allocated to MAHs without a registration in Eudravigilance, no product information in the XEVMPD database and no procedure which describes the process of submitting and maintaining the product information in the XEVMPD database.

	Yes	No
Registration in Eudravigilance (%)	97.0	3.0
Information in XEVMPD (%)	99.5	0.5
Procedure for submission and maintenance XEVMPD (%)	96.1	3.9

2. Pharmacovigilance System Master File (PSMF)

This section refers to the pharmacovigilance system master file (including location) where the marketing authorization(s) of the organization is covered. Priority will be given to MAHs with a PSMF located in the Netherlands. The number of different MAHs that are covered by one pharmacovigilance system (or PSMF) will be considered when selecting MAHs for the national inspection program.

	Yes	No
Availability PSMF (%)	99.3	0.7
PSMF location in NL (%)	12.0	88.0
PSMF owner (number of surveys completed on PV system level) (%)	71.8	28.2

3. QPPV and national contactperson

This section refers to the EU Qualified Person for Pharmacovigilance (EU-QPPV) and national contact person for pharmacovigilance turnover, within a two year period from 1 January 2015 and 31 December 2016. Higher scores will be allocated to MAHs without a QPPV and those who have had 2 or more QPPV in the two year period.

	None	1	2	More than 2
Number of different QPPVs (%)	1.0	70.0	23.6	5.4
Number of different national contact persons (%)	43.7	41.8	11.6	2.9

4. Marketing

This section refers to the market status of marketing authorization holders. This information will be used for the calculation of scores for other topics.

MAHs that do not actively market ("release into the distribution chain") their medicinal products on the Dutch market and will not market until the year 2020, were not required to complete all sections of the survey. In total, 498 MAHs have marketing authorizations that are actively placed on the Dutch market.

5. License information

This section refers to all medicinal products where a marketing authorization is obtained which enables a MAH to place the medicinal product on the Dutch market (Dutch marketing authorization).

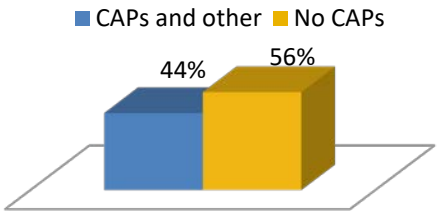


Fig 1. MAHs with marketing authorizations in the Netherlands (n=498)

In figure 1, the number of MAHs with different types of authorization applications are shown. The number of MAHs with CAPs and other marketing authorizations (MRPs and/or NAPs) are shown in blue (n=217). The yellow bar represents the number of MAHs with NAPs (including MRPs and DCPs) and no CAPs (n=281). Priority will be given to MAHs without CAPs.

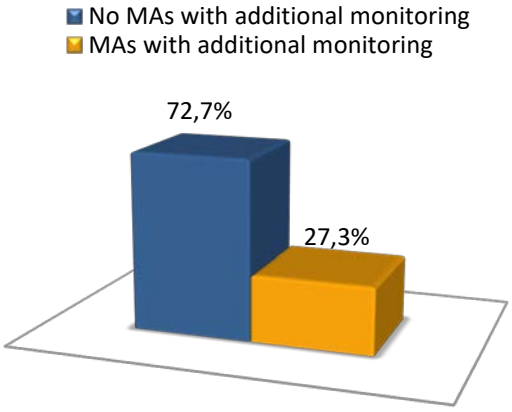


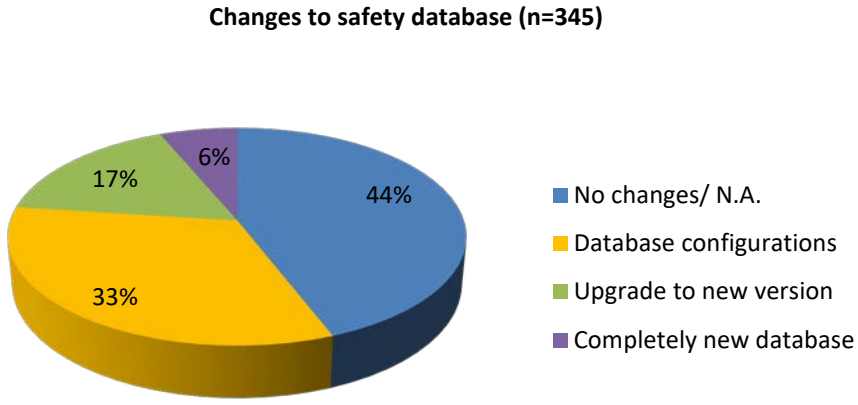
Fig 2. MAHs with or without marketing authorizations (MAs) that are subject to additional monitoring (n=498)

The number (in %) of MAHs with marketing authorizations that are subject to additional monitoring is shown in figure 2. The majority of MAHs do not have marketing authorizations that are subject to additional monitoring (72.7%). Priority will be given to MAHs with marketing authorizations that are subject to additional monitoring.

6. Changes to the pharmacovigilance system

This section refers to the changes in the number of Dutch marketing authorizations (MAs) by change of ownership or withdrawal, mergers with other pharmacovigilance systems and any changes to the safety database. Scores will be calculated based on the number of MAs acquired in relation to the number of existing MAs of the MAHs. Furthermore, higher scores will be allocated to MAHs without safety databases and to those who have changed their safety database to a completely new database.

	0	1	2	More than 2
MAs acquired (%)	83.7	6.6	3.4	6.3
MAs withdrawn (%)	87.7	2.9	3.2	6.3
Number of safety databases (%)	1.1	93.4	4.6	0.9



7. PhV activities

This section refers to the availability of employees for a specific task or multiple tasks for the period 1 January 2016 until 31 December 2016. MAHs that have not received and processed any cases, have not produced any PSURs or did not submit any safety variations in 2016 were excluded. Higher scores will be allocated to MAHs with the highest number of cases, PSURs and safety variations per FTE in 2016.

	Mean	Min	Max
Number of cases processed per FTE in 2016	274.3	1.0	7410.0
Number of PSURs produced per FTE in 2016	4.4	1.0	44.0
Number of safety variations submitted per FTE in 2016	6.1	1.0	95.0

8. Compliance

This section refers to the compliance for spontaneous and solicited post-marketing reporting and clinical trial reporting from post-authorization interventional studies. Higher scores will be allocated to MAHs with the lowest compliance rates. MAHs that have not received and submitted any cases were excluded.

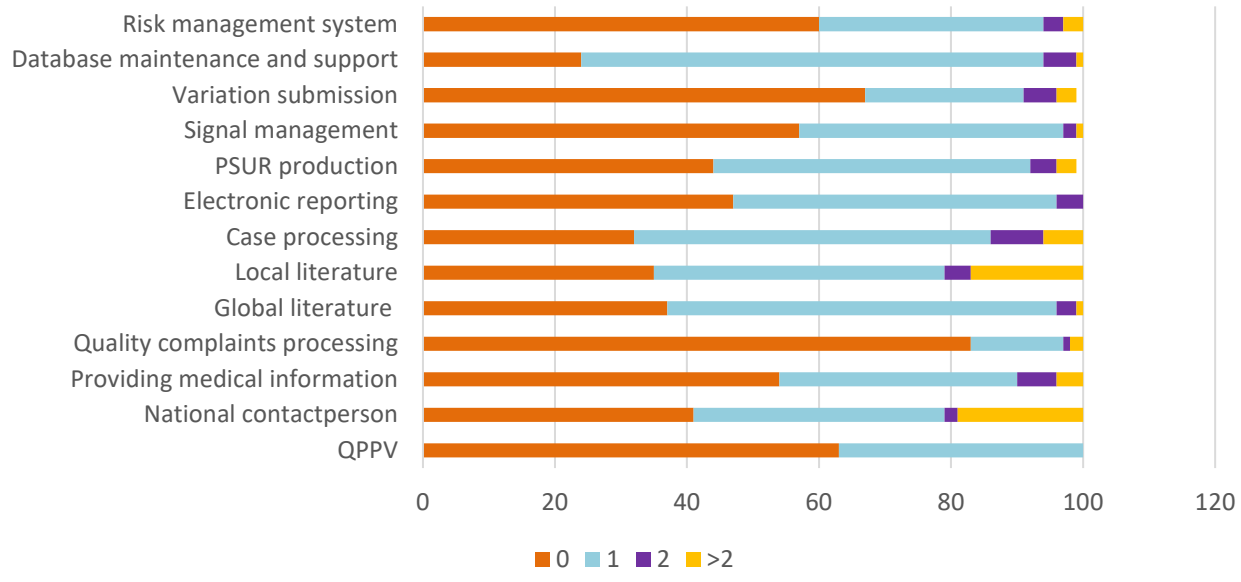
	Mean (%)	Min (%)	Max (%)
Compliance ICSR submission NL	94.5	39.2	100.0
Compliance ICSR submission outside EU	94.9	64.5	100.0
Compliance submission interventional CT cases	88.5	33.3	100.0
Compliance submission PSURs	98.0	50.0	100.0
Compliance submission safety variations	91.5	33.3	100.0

9. Contracts and agreements

This section refers to all licensing agreements worldwide for every active ingredient which is authorized in the Netherlands (not just licensing agreements in the Netherlands only). No scores will be calculated for this section, but this information will be considered for the interpretation of scores of other topics.

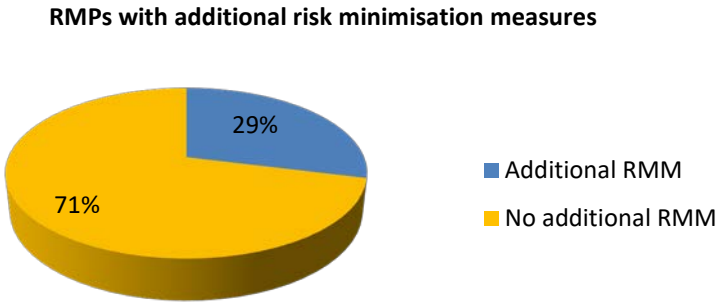
10.Outsourcing of pharmacovigilance activities

This section refers to the outsourcing of global pharmacovigilance activities and those outsourced by the marketing authorization holder. Higher scores will be allocated to MAHs that have outsourced their activities to two or more service providers/ companies.



11.Risk Management Plan (RMP)

This section refers to the risk management plans (RMPs) that are in place for medicinal products in the Netherlands. Priority will be given to RMPs with additional risk minimization measures.



12.Quality management system

This section refers to the procedures in place at the MAH, the availability of trainings records and the performance of audits which are part of the quality management system. Higher scores will be allocated to MAHs that do not have the standard operating procedures (SOPs) in place as described below, and MAHs who have not conducted any internal (within a period of 3 years) or external audits.

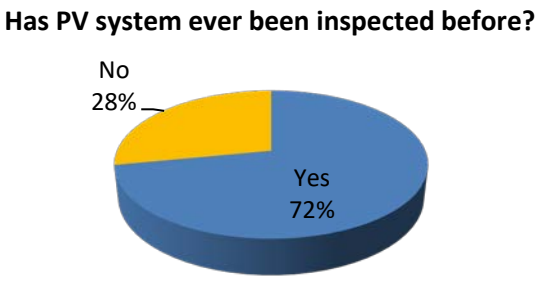
	Yes	No
SOP available describing tasks and responsibilities QPPV and back-up (%)	98.3	1.7
SOP available for case processing (%)	99.7	0.3
Training records available for PV employees (%)	100.0	0.0
Audit of PV system in past 3 years (%)	88.5	11.5
External audits conducted by MAH (%)	81.9	18.1

13.Product safety issues

This section refers to the variations that are initiated by the MAH where the initial safety issue was also identified by the MAH. No scores will be calculated for this section, but the information will be used for the interpretation of scores of other topics.

14.Previous inspections

This section refers to the pharmacovigilance inspections that are conducted by regulatory authorities (no audits). Higher scores will be allocated to MAHs that have never been inspected before by a regulatory authority.



Evaluation

The information in the survey that was collected were used to make a risk profile for each MAH. These risk profiles were used as a tool to set up a risk-based national inspection program where also other information sources were used. In order to use this tool for our inspection program in the future, the survey needs to be evaluated. In the inspection program of 2018, we have been focusing on the MAHs with a high risk profile, based on the results of the survey. The inspection outcomes will be used to verify the answers and to test the risk-based tool that has been developed. Some of the answers provided in the survey were already verified using other information sources, such as the XEVMPD database.

In the inspection planning of 2018, MAHs with a high risk profile were selected, but priority were given to the following MAHs:

- MAHs which did not complete the survey
- MAHs where no PSMF information was available
- MAHs where no QPPV information was available

MAHs with a mid- or low risk profile were also selected as part of the evaluation process to assess if the MAHs were categorized correctly.

XEVMPD database

We observed that the product information in the XEVMPD database was not up to date for a large number of marketing authorization holders. Marketing authorization holders are obliged to submit and maintain the information as described in the EMA (European Medicines Agency) Guidance documents, in the XEVMPD database (article 57(2) of Regulation (EC) No 726/2004).

MAHs are required to submit notifications on any changes that impact the data such as transfers, renewals or withdrawal of the marketing authorisation as soon as possible and no later than within 30 calendar days. This also includes change of QPPV or PSMF location. Furthermore, they should notify the EMA of any new marketing authorisations within 15 calendar days from the date of notification of the granting of the marketing authorisation by the competent authority. These changes also include updates of general information such as the QPPV contact details or address of the MAH. This information should be updated for each product.

The supervisory authority inspections are not within the scope of the risk-based national inspection program and will therefore be conducted as planned according to the inspection program of the EMA.

Reference:

GVP module III, III.B.2. Inspection planning
Regulation (EC) No 726/2004
MEB 14: Parallel import: marketing authorization and maintenance