Supplementary Materials 1 – Additional information on Methods

A comparison of signals of designated medical events and non-designated medical events: results from a scoping review

Submitted to Drug Safety by:

Daniele Sartori 1,2* (daniele.sartori@who-umc.org), Jeffrey K Aronson 2, Nils Erlanson 1, G Niklas Norén 1, Igho J Onakpoya 2

1: Uppsala Monitoring Centre, Bredgränd 7B, 753 20, Uppsala, Sweden

2: Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, University of Oxford, Woodstock Road, Oxford, OX2 6GG, United Kingdom

Launch year of medicinal products - searches

Searches for trade or substance names of medicinal products were carried out in English or the native language of the competent regulatory agency (see below). All launch dates were compared with VigiBase's dates of first reports: if a launch year followed that of first report, we contacted the regulator that managed the first report at the time of submission, to ascertain whether the launch date was in fact subsequent to that of first report (e.g. in the case of reports from clinical trials). In the case of countries that no longer exist (e.g. Western or Eastern Germany), we contacted the competent regulatory agency that was instated after the formation of the most recent country in the same territory (e.g. Federal Institute for Drugs and Medical Devices in the case of the Federal Republic of Germany). We also contacted regulatory agencies directly if no launch years were available in the lists below. Launch years for drug-drug-interactions referred to the latest of any of the medicinal products involved (including class-related interactions) – since no reports of co-administration could have been considered eligible until all medicinal products were launched.

List of sources to determine the earliest launch date of a medicinal product

- The FDA's Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations [1].
- The FDA's list of Approved Drug Products with Therapeutic Equivalence Evaluations [2].
- The EMA's list of EU reference dates (EURD) [3].
- The Pharmaceutical Manufacturing Encyclopedia 3rd edition [4].
- Stephens' Detection of New Adverse Drug Reactions, 5th edition [5].
- The US National Center for Advancing Translational Sciences's InXight [6].
- The WHO Public Assessment Reports [7].

Lists available on the EMA or FDA websites were merged. We deduplicated the entries from the two agencies and retained the earliest launch year.

We also used the search engines of websites of the following regulatory agencies, and, where available, summaries of products characteristics from:

- The UK Medicines and HealthCare products Regulatory Agency
- Health Canada
- Indian Central Drugs Standard Control Organization
- The Italian Drug Agency
- The Spanish Agency for Medicines and Health Products
- The Japanese Pharmaceuticals and Medical Devices Agency
- The French National Security Agency of Medicines and Health Products
- The German Federal Institute for Drugs and medical Devices
- The Belgian Federal Agency for Medicines and Health Products
- The Czech State Institute for Drug Control
- The New Zealand Medicines and Medical Devices Safety Authority
- The Korean Ministry of Food and Drug Safety
- The Danish Medicines Agency
- The Finnish Medicines Agency
- The Thai Food and Drug Authority
- The Irish Health Products Regulatory Authority
- The Australian Therapeutics Good Administration

- The Argentinian National Administration of Drugs, Foods and Medical Devices
- The Brazilian National Health Surveillance Agency
- The Norwegian Medicines Agency
- The Hungarian National Institute of Pharmacy and Nutrition.
- The South African Health Products Regulatory Authority
- The Ghanian Food and Drug Authority
- The Nigerian National Drug Authority
- The Ugandan National Agency for Food and Drug Administration and Control

For 4 medicinal products we could not find a launch year, namely: ethanol, artemether, the combination of docosahexaenoic acid and eicosapentenoic acid, and the combination of edetic acid, unspecified electrolytes and oxypolygelatin. We defaulted to the year 1900 for ethanol and traced the 'first attested use' for the rest with a search on PubMed on 27/07/2022 searching for substance names 'and' trade names, and sorting by ascending date of publication. For 1 publication involving the detection between chemotherapy agents and traditional herbal medicinal products [8], we used the earliest launch year of the chemotherapy agents involved, under the assumption that traditional medicines had been launched earlier.

For classes of medicinal products, we retrieved the year of launch of the medicinal product involved in the first report found in VigiBase, as described in the manuscript's methods section. Where VigiBase held no reports, we retrieved the launch years of all medicinal products in a class and selected the earliest.

Assignment of Anatomical Therapeutic Chemical (ATC) classifications and MedDRA System Organ Classes (SOC)

For each signal/SDR concerning one medicinal product and one adverse event, we assigned a level 5 ATC and primary MedDRA SOC accordingly. For those concerning classes of medicinal products we used the ATC and SOC belonging to the medicinal product and adverse event terms of the first report of a signal/SDR as entered in VigiBase. If a medicinal product had more than one ATC, we used the most frequent ATC in VigiBase as of September 2022.

When classes of medicinal products were involved in signals/SDRs, we encountered ties of VigiBase entry dates i.e. two medicinal products belonging to the same class featured on two reports, which were entered in VigiBase in the same year and had the same adverse event. In these instances, we selected the report having the medicinal product with the earliest launch year and assigned the ATC and MedDRA SOC accordingly. If two or more medicinal products had the same launch year, we retrieved the total number of reports in VigiBase as of September 2022 at the relevant ATC level 5 and chose the class with the highest count.

If VigiBase held no reports for a given signal/SDR, we assigned the ATC and SOC based on the substance names and Preferred Terms we assigned in the original data set on which this study is based. We assigned no ATC or MedDRA SOC for those signals/SDRs for which we could find no eligible entries in the standardized terminologies.

List of studies excluded from the dataset of signals

See references: [9-38]

References

1. Food and Drug Administration. Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations. 2020. https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/purple-book-lists-licensed-biological-products-reference-product-exclusivity-and-biosimilarity-or. Accessed: 17/01/2023.
2. Food and Drug Administration. Approved Drug Products with Therapeutic Equivalence Evaluations | Orange Book. 2023. https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book. Accessed: 17/01/2023.
3. European Medicines Agency. Periodic safety update reports (PSURs). 2012. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/periodic-safety-update-reports-psurs#submission-requirements-and-eu-reference-dates:-the-eurd-list-section. Accessed: 15/01/2023.
4. Sittig M. Pharmaceutical manufacturing encyclopedia: William Andrew Pub; 2007.
5. Talbot J, Waller P. Stephens' detection of new adverse drug reactions: John Wiley & Sons; 2004.
6. National Center for Advancing Translational Sciences. Inxight Drugs. 2023. https://drugs-dev01.ncats.io/substances. Accessed: 15/01/2023.
7. World Health Organization. WHO Public Assessment Reports (WHOPARs) Medicines. 2023. https://extranet.who.int/pqweb/medicines/prequalification-reports/whopars. Accessed: 12/01/2023.
8. Fahim SM, Mishuk AU, Cheng N, Hansen R, Calderón AI, Qian J. Adverse event reporting patterns of concomitant botanical dietary supplements with CYP3A4 interactive & CYP3A4 non-interactive anticancer drugs in the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS). Expert Opin Drug Saf. 2019;18(2):145-52. http://dx.doi.org/10.1080/14740338.2019.1562546
9. Zhan C, Roughead E, Liu L, Pratt N, Li J. A data-driven method to detect adverse drug events from prescription data. Journal of Biomedical Informatics. 2018;85:10-20. http://dx.doi.org/http://dx.doi.org/10.1016/j.jbi.2018.07.013
10. Li Y, Salmasian H, Vilar S, Chase H, Friedman C, Wei Y. A method for controlling complex confounding effects in the detection of adverse drug reactions using electronic health records. Journal of the American Medical Informatics Association : JAMIA. 2014;21(2):308-14. http://dx.doi.org/10.1136/amiajnl-2013-001718
11. Sauer B, Nebeker J, Shen S, Rupper R, West S, Shinogle JA, et al. Methodological framework to identify possible adverse drug reactions using population-based administrative data. F1000Research. 2014;3:258. http://dx.doi.org/10.12688/f1000research.4816.1
12. Van Puijenbroek EP, Egberts ACG, Meyboom RHB, Leufkens HGM. Signalling possible drug-drug interactions in a spontaneous reporting system: Delay of withdrawal bleeding during concomitant use of oral contraceptives and itraconazole. British Journal of Clinical Pharmacology. 1999;47(6):689-93. http://dx.doi.org/http://dx.doi.org/10.1046/j.1365-2125.1999.00957.x
13. Nikfarjam A, Ransohoff JD, Callahan A, Jones E, Loew B, Kwong BY, et al. Early Detection of Adverse Drug Reactions in Social Health Networks: A Natural Language Processing Pipeline for Signal Detection. JMIR public health and surveillance. 2019;5(2):e11264. http://dx.doi.org/10.2196/11264

14. Tatonetti NP, Fernald GH, Altman RB. A novel signal detection algorithm for identifying hidden drug-drug interactions in adverse event reports. Journal of the American Medical Informatics Association. 2012;19(1):79-85. http://dx.doi.org/http://dx.doi.org/10.1136/amiajnl-2011-000214
15. Iyer SV, Harpaz R, LePendu P, Bauer-Mehren A, Shah NH. Mining clinical text for signals of adverse drug-drug interactions. Journal of the American Medical Informatics Association. 2014;21(2):353-62. http://dx.doi.org/http://dx.doi.org/10.1136/amiajnl-2013-001612
16. Layton D, Heeley E, Shakir SAW. Identification and evaluation of a possible signal of exacerbation of colitis during rofecoxib treatment, using Prescription-Event Monitoring data. Journal of Clinical Pharmacy and Therapeutics. 2004;29(2):171-81. http://dx.doi.org/http://dx.doi.org/10.1111/j.1365-2710.2004.00550.x
17. Tatonetti NP, Denny JC, Murphy SN, Fernald GH, Krishnan G, Castro V, et al. Detecting drug interactions from adverse-event reports: Interaction between paroxetine and pravastatin increases blood glucose levels. Clinical Pharmacology and Therapeutics. 2011;90(1):133-42. http://dx.doi.org/http://dx.doi.org/10.1038/clpt.2011.83
18. Yoon D, Park MY, Choi NK, Park BJ, Kim JH, Park RW. Detection of adverse drug reaction signals using an electronic health records database: Comparison of the Laboratory Extreme Abnormality Ratio (CLEAR) algorithm. Clinical Pharmacology and Therapeutics. 2012;91(3):467-74. http://dx.doi.org/http://dx.doi.org/10.1038/clpt.2011.248
19. Nomura K, Takahashi K, Hinomura Y, Kawaguchi G, Matsushita Y, Marui H, et al. Effect of database profile variation on drug safety assessment: An analysis of spontaneous adverse event reports of Japanese cases. Drug Design, Development and Therapy. 2015;9:3031-41. http://dx.doi.org/http://dx.doi.org/10.2147/DDDT.S81998
20. Lorberbaum T, Sampson KJ, Woosley RL, Kass RS, Tatonetti NP. An Integrative Data Science Pipeline to Identify Novel Drug Interactions that Prolong the QT Interval. Drug Safety. 2016;39(5):433-41. http://dx.doi.org/http://dx.doi.org/10.1007/s40264-016-0393-1
21. Hoffman KB, Dimbil M, Tatonetti NP, Kyle RF. A Pharmacovigilance Signaling System Based on FDA Regulatory Action and Post-Marketing Adverse Event Reports. Drug Safety. 2016;39(6):561-75. http://dx.doi.org/http://dx.doi.org/10.1007/s40264-016-0409-x
22. Arnaud M, Salvo F, Ahmed I, Robinson P, Moore N, Begaud B, et al. A method for the minimization of competition bias in signal detection from spontaneous reporting databases. Drug Safety. 2016;39(3):251-60. http://dx.doi.org/http://dx.doi.org/10.1007/s40264-015-0375-8
23. Chan CL, Rudrappa S, Ang PS, Li SC, Evans SJW. Detecting Signals of Disproportionate Reporting from Singapore's Spontaneous Adverse Event Reporting System: An Application of the Sequential Probability Ratio Test. Drug Safety. 2017;40(8):703-13. http://dx.doi.org/http://dx.doi.org/10.1007/s40264-017-0531-4
24. Lee S, Choi J, Kim HS, Kim GJ, Lee KH, Park CH, et al. Standard-based comprehensive detection of adverse drug reaction signals from nursing statements and laboratory results in electronic health records. Journal of the American Medical Informatics Association. 2017;24(4):697-708. http://dx.doi.org/http://dx.doi.org/10.1093/jamia/ocw168
25. Arnaud M, Begaud B, Thiessard F, Jarrion Q, Bezin J, Pariente A, et al. An Automated System Combining Safety Signal Detection and Prioritization from Healthcare Databases: A Pilot Study. Drug Safety. 2018;41(4):377-87. http://dx.doi.org/http://dx.doi.org/10.1007/s40264-017-0618-y
26. Perez C, Olivier P, Lortal B, Duranton S, Montastruc JL, Colin AL, et al. Detection of drug safety signals from clinical trials data: Role of SUSARs. Pharmacological Research. 2018;131:218-23. http://dx.doi.org/http://dx.doi.org/10.1016/j.phrs.2018.02.010
27. Karapetiantz P, Audeh B, Lillo-Le Louet A, Bousquet C. Signal Detection for Baclofen in Web Forums: A Preliminary Study. Studies in health technology and informatics. 2018;247:421-5.

28. Wei R, Jia LL, Yu YC, Nie XL, Song ZY, Fan DF, et al. Pediatric drug safety signal detection of non-chemotherapy drug-induced neutropenia and agranulocytosis using electronic healthcare records. Expert Opinion on Drug Safety. 2019;18(5):435-41. http://dx.doi.org/http://dx.doi.org/10.1080/14740338.2019.1604682
29. Belamalem S, Benkirane R, Soulaymani A, Talibi I, Ouled Errkhis R, Tebaa A, et al. Implementing the moroccan database by an automated signal detection method. Drug Safety. 2014;37 (10):855. http://dx.doi.org/http://dx.doi.org/10.1007/s40264-014-0208-1
30. Bate A, Lindquist M, Edwards IR, Olsson S, Orre R, Lansner A, et al. A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol. 1998;54(4):315-21.
31. Crooks CJ, Prieto-Merino D, Evans SJW. Identifying Adverse Events of Vaccines Using a Bayesian Method of Medically Guided Information Sharing. Drug Safety. 2012;35(1):61-78. http://dx.doi.org/10.2165/11596630-000000000-00000
32. Feldman SF, Lapidus N, Dorival C, Diallo A, Amri I, Fontaine H, et al. Signal detection on a patient cohort: A disproportionality analysis of the ANRS CO22 HEPATHER cohort to identify associations between direct acting antivirals and adverse events in patients with hepatitis C virus chronic infection. Pharmacoepidemiology and Drug Safety. 2018;27(7):797-805. http://dx.doi.org/10.1002/pds.4552
33. Wang X, Li L, Wang L, Feng W, Zhang P. Propensity score-adjusted three-component mixture model for drug-drug interaction data mining in FDA Adverse Event Reporting System. Stat Med. 2020;39(7):996-1010. http://dx.doi.org/10.1002/sim.8457
34. Berbain T, Pariente A, Miremont-Salamé G, Grandvuillemin A, Micallef J, Chouchana L, et al. Contribution of Causality Assessment for an Automated Detection of Safety Signals: An Example Using the French Pharmacovigilance Database. Drug Saf. 2020;43(3):243-53. http://dx.doi.org/10.1007/s40264-019-00887-2
35. Spachos D, Siafis S, Bamidis P, Kouvelas D, Papazisis G. Combining big data search analytics and the FDA Adverse Event Reporting System database to detect a potential safety signal of mirtazapine abuse. Health informatics journal. 2020;26(3):2265-79. http://dx.doi.org/10.1177/1460458219901232
36. Yu Y, Nie X, Song Z, Xie Y, Zhang X, Du Z, et al. Signal Detection of Potentially Drug-Induced Liver Injury in Children Using Electronic Health Records. Frontiers in pediatrics. 2020;8:171. http://dx.doi.org/10.3389/fped.2020.00171
37. Yu Y, Ruddy K, Mansfield A, Zong N, Wen A, Tsuji S, et al. Detecting and Filtering Immune-Related Adverse Events Signal Based on Text Mining and Observational Health Data Sciences and Informatics Common Data Model: Framework Development Study. JMIR medical informatics. 2020;8(6):e17353. http://dx.doi.org/10.2196/17353
38. King CE, Pratt NL, Craig N, Thai L, Wilson M, Nandapalan N, et al. Detecting Medicine Safety Signals Using Prescription Sequence Symmetry Analysis of a National Prescribing Data Set. Drug Saf. 2020;43(8):787-95. http://dx.doi.org/10.1007/s40264-020-00940-5

Supplementary materials 2- Additional results

A comparison of signals of designated medical events and non-designated medical events: results from a scoping review

Submitted to Drug Safety by:

Daniele Sartori 1,2* (daniele.sartori@who-umc.org), Jeffrey K Aronson 2, Nils Erlanson 1, G Niklas Norén 1, Igho J Onakpoya 2

1: Uppsala Monitoring Centre, Bredgränd 7B, 753 20, Uppsala, Sweden

2: Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, University of Oxford, Woodstock Road, Oxford, OX2 6GG, United Kingdom

Table of Contents

Levels of evidence: descriptive statistics

Table 1 Full break-down by Oxford Centre of Evidence Based Medicine (OCEBM) levels and subtypes of evidence. [a]: Studies that did not prespecify the outcomes of interest (in systematic reviews, meta-analyses, and pooled data from clinical trials this refers to the included studies). [b]: pooled randomized clinical trials without meta-analysis; [c]: pooled clinical trials with different or unclear randomization; [d]: Disproportionality Analyses without clinical reviews; [e]: combinations of level 4 studies, together with unspecified type of evidence (e.g. unspecified literature reviews, epidemiological data, data from clinical trials); R = Studies relying exclusively on reports of adverse drug reactions. N/A = no OCEBM level could be assigned, because the study design was unclear.

	Counts of signals (proportion)	
OCEBM Level of evidence **Subtype of evidence**	**DME signals**	**Non-DME signals**
1	**38 (0.04)**	**195 (0.05)**
1	2 (0.00)	14 (0.00)
1 [b]	0 (0.00)	4 (0.00)
1 [a, b]	23 (0.02)	124 (0.03)
1 [a]	3 (0.00)	21 (0.01)
1 [a, c]	10 (0.01)	32 (0.00)
2	**18 (0.02)**	**113 (0.03)**
2	6 (0.01)	36 (0.01)
2 [b]	0 (0.00)	1 (0.00)
2 [a, b]	0 (0.00)	1 (0.00)
2 [a]	12 (0.01)	75 (0.02)
3	**9 (0.01)**	**77 (0.02)**
3	8 (0.01)	58 (0.02)
3 [a]	1 (0.00)	19 (0.01)
4	**846 (0.92)**	**3137 (0.87)**
4	36 (0.04)	151 (0.04)
4 [d]	307 (0.33)	1136 (0.32)
4 [e]	24 (0.03)	126 (0.03)
4R	479 (0.52)	1724 (0.48)
N/A	**8 (0.01)**	**79 (0.02)**
Total	**919 (1.0)**	**3601 (1.0)**

Box plots by Oxford Centre for Evidence-Based Medicine, broken down by subtypes of evidence

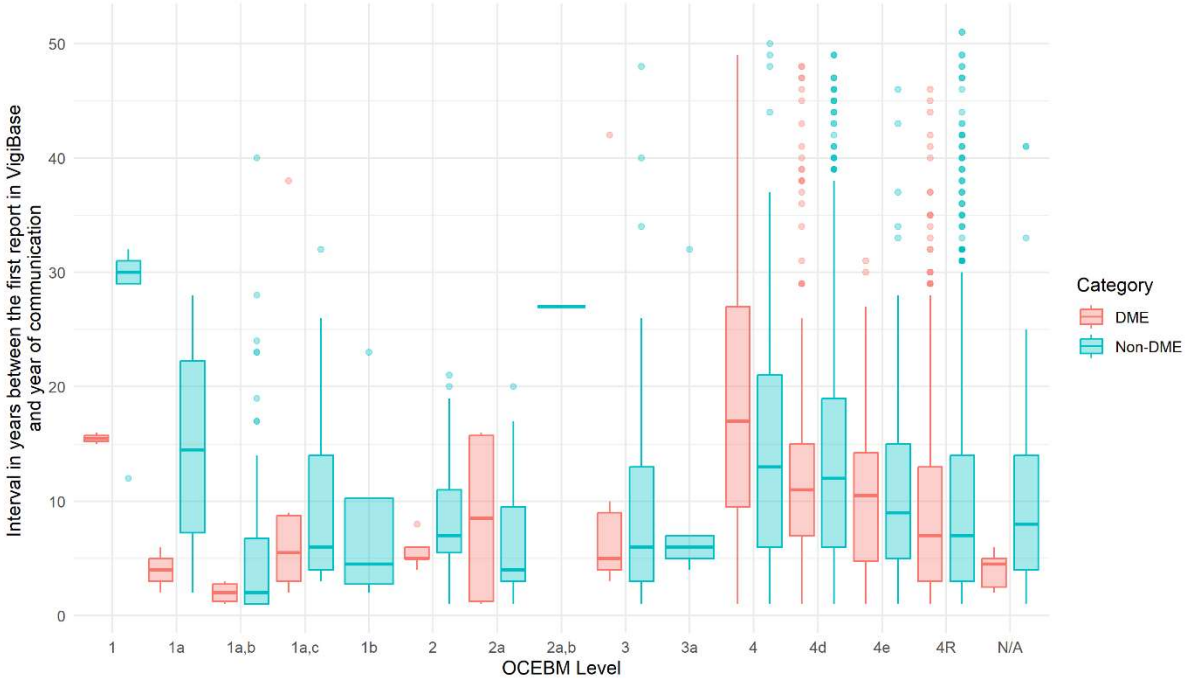

Figure 1 Box plots of the interval in years between the first report in VigiBase and the year of communication vs OCEBM subtype. Refers to 3937 observations, for which there was at least one report in the database. [a]: Studies that did not prespecify the outcomes of interest (in systematic reviews, meta-analyses, and pooled data from clinical trials this refers to the included studies). [b]: pooled randomized clinical trials without meta-analysis; [c]: pooled clinical trials with different or unclear randomization; [d]: Disproportionality Analyses without clinical reviews; [e]: combinations of level 4 studies, together with unspecified type of evidence (e.g. unspecified literature reviews, epidemiological data, data from clinical trials); R = Studies relying exclusively on reports of adverse drug reactions. N/A = no OCEBM level could be assigned, because the study design was unclear.

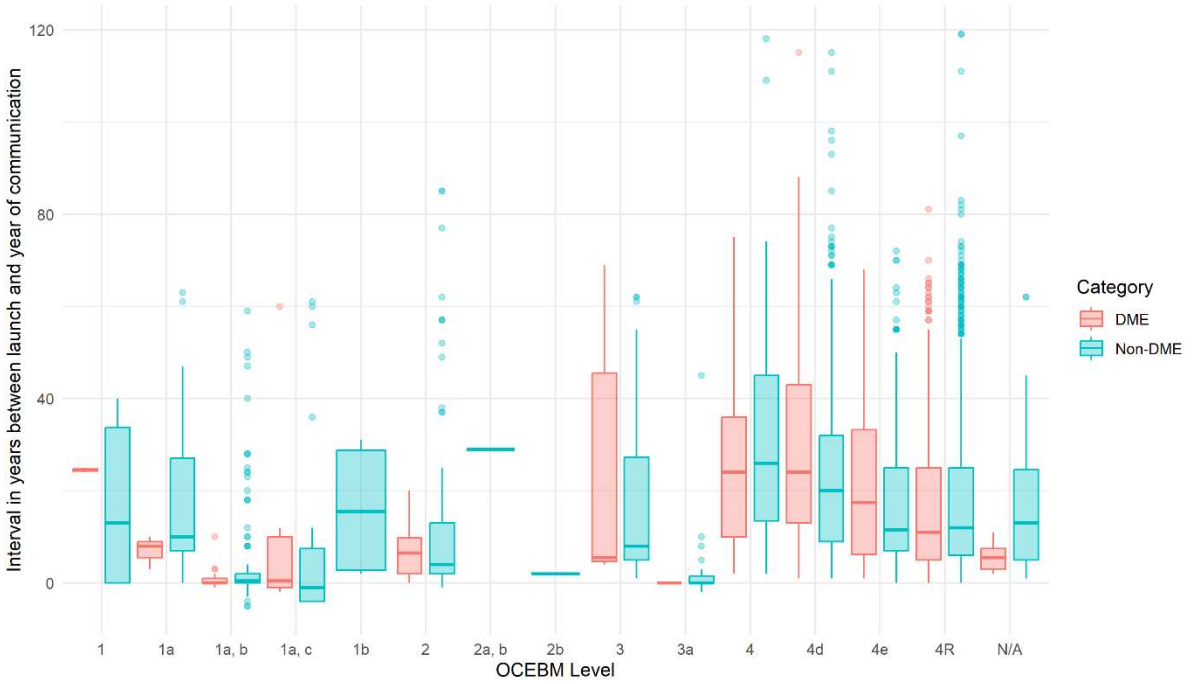

Figure 2 Box plots of the interval in years between the year of launch and that of communication of signals/SDRs involved in the study, broken down by OCEBM subtype. Refers to 4513 observations, the medicinal products of which had an available launch year. [a]: Studies that did not prespecify the outcomes of interest (in systematic reviews, meta-analyses, and pooled data from clinical trials this refers to the included studies). [b]: pooled randomized clinical trials without meta-analysis; [c]: pooled clinical trials with different or unclear randomization; [d]: Disproportionality Analyses without clinical reviews; [e]: combinations of level 4 studies, together with unspecified type of evidence (e.g. unspecified literature reviews, epidemiological data, data from clinical trials); R = Studies relying exclusively on reports of adverse drug reactions. N/A = no OCEBM level could be assigned, because the study design was unclear.

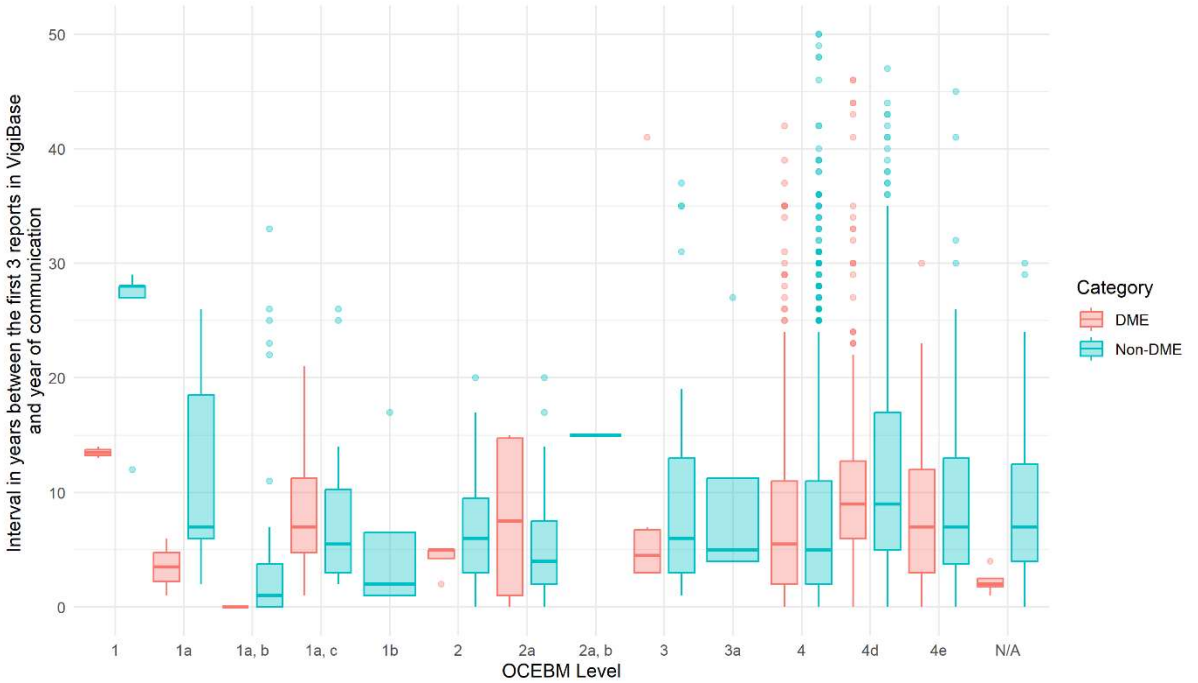

Figure 3 Box plots of the interval in years between the year in which VigiBase included at least 3 reports for a given signal/SDR and that of communication involved in the study, broken down by OCEBM subtype. Refers to 3639 observations. [a]: Studies that did not prespecify the outcomes of interest (in systematic reviews, meta-analyses, and pooled data from

clinical trials this refers to the included studies). [b]: pooled randomized clinical trials without meta-analysis; [c]: pooled clinical trials with different or unclear randomization; [d]: Disproportionality Analyses without clinical reviews; [e]: combinations of level 4 studies, together with unspecified type of evidence (e.g. unspecified literature reviews, epidemiological data, data from clinical trials); R = Studies relying exclusively on reports of adverse drug reactions. N/A = no OCEBM level could be assigned, because the study design was unclear.

Table 2 Median years, with interquartile (IQR) ranges and quantiles, for the interval in years between first report in VigiBase and communication, and for launch year to communication.

		From year of first report in VigiBase	**From launch year**
OCEBM level	**Category**	Median years to communication (IQR, quantiles)	Median years to communication (IQR, quantiles)
1-3	DME	4 (6.5, 2.25 – 8.75)	2 (8, 0 – 8)
1-3	Non-DME	6 (9, 3 – 12)	4 (12, 0 – 12)
4	DME	9 (10, 4 – 14)	17 (27, 6 – 33)
4	Non-DME	9 (12, 4 – 16)	15 (22, 7 – 29)
N/A	DME	4.5 (2.5, 2.5 – 5)	5.5 (4.5, 3 – 7.5)
N/A	Non-DME	8 (10, 4 – 14)	13 (19.5, 5 -24.5)

Completeness of reports: descriptive statistics and box plots of different time measurements and completeness categories

Table 3 Counts and proportions (over column totals) of DME and non-DME signals supported by well-documented reports in VigiBase in the years leading up to communication, broken down by Oxford Centre of Evidence Based Medicine (OCEBM) levels and subtypes of evidence. [a]: Studies that did not prespecify the outcomes of interest (in systematic reviews, meta-analyses, and pooled data from clinical trials this refers to the included studies). [b]: pooled randomized clinical trials without meta-analysis; [c]: pooled clinical trials with different or unclear randomization; [d]: Disproportionality Analyses without clinical reviews; [e]: combinations of level 4 studies, together with unspecified type of evidence (e.g. unspecified literature reviews, epidemiological data, data from clinical trials); R = Studies relying exclusively on reports of adverse drug reactions. N/A = no OCEBM level could be assigned, because the study design was unclear.

OCEBM subtype	**DME (proportion)**	**Non-DME (proportion)**	**Total**
4R	49 (0.70)	77 (0.68)	126
4[d]	14 (0.20	17 (0.15	31
1[a, b]	2 (0.03)	6 (0.05)	8
N/A	2 (0.03)	3 (0.03)	5
4[e]	0 (0.00)	4 (0.04)	4
2[a]	1 (0.01)	3 (0.03)	4
2	1 (0.01)	1 (0.01)	2
3	0 (0.00)	1 (0.01)	1
1[a, c]	0 (0.00)	1 (0.01)	1
1[a]	1 (0.01)	0 (0.00)	1
Total	**70**	**113**	**183**

Table 4 Median count of reports for DME and non-DME signals, by category of completeness score; data refers to any of the 4519 signals/SDRs with at least 1 report in VigiBase in the year before communication.

Category of completeness score	Type of signal/SDR	Median number of reports
Above average	DME	17
Above average	Non-DME	21
Below average or average	DME	15
Below average or average	Non-DME	23
Well-documented	DME	2
Well-documented	Non-DME	3

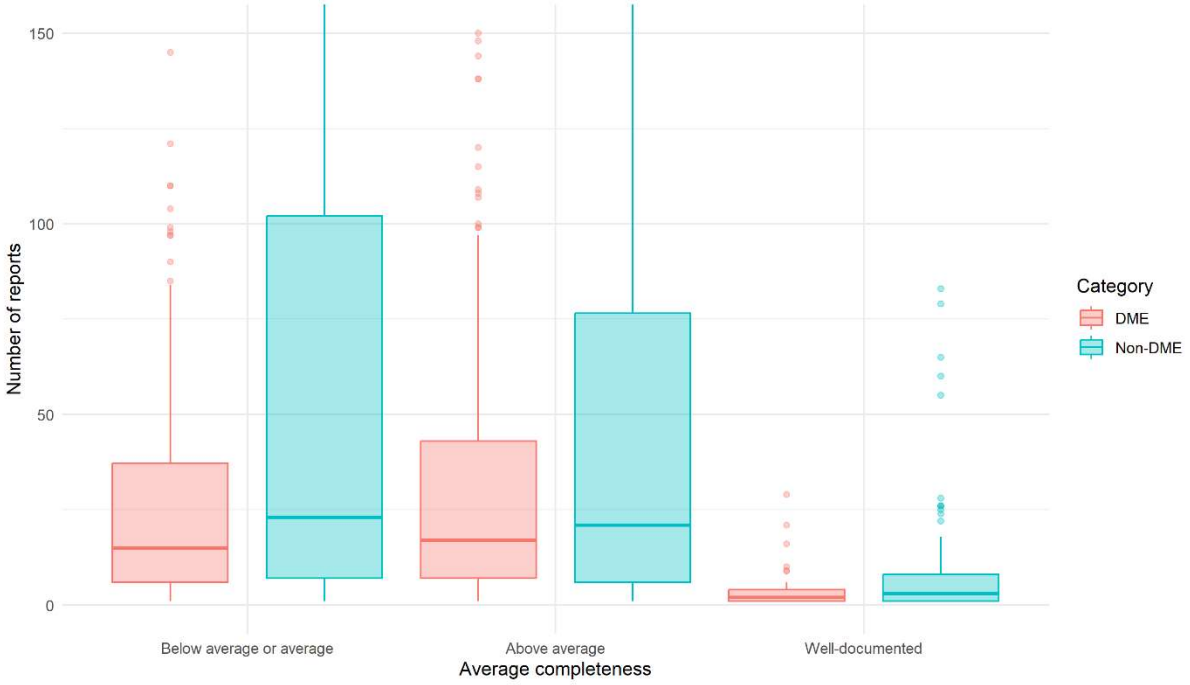

Figure 4 Box plots of the number of reports in VigiBase supporting any DME and non-DME signals/SDRs, grouped by categories of vigiGrade completeness score. "Well-documented" was defined as an average completeness of strictly above 0.80; "below average or average" refers to an average completeness score between 0.00 and 0.46, based on the average completeness in VigiBase as of August 2020; median values are indicated by horizontal lines within the boxes. y-axis truncated at 150 reports to improve clarity, (with a maximum of 63277 for the category "below average or average", non-DME category).

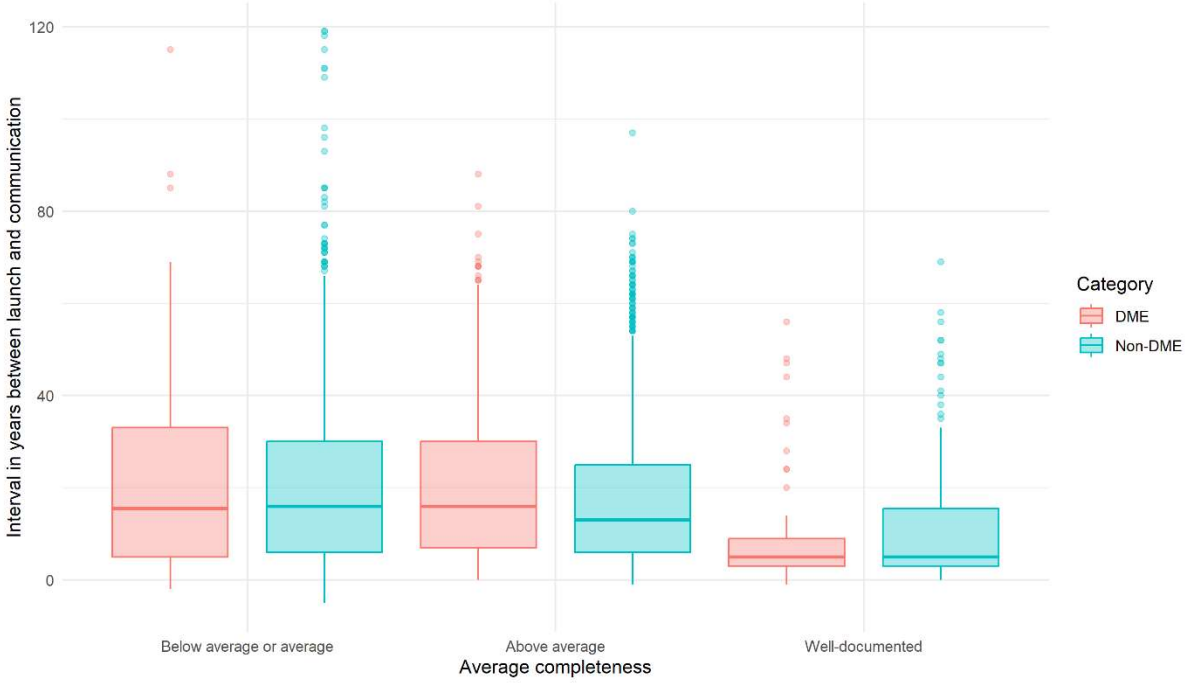

Figure 5 Box plots of the interval in years from launch and communication of 3937 signal/SDR vs categories of vigiGrade completeness score, with at least 1 report in VigiBase before communication. "Well-documented" was defined as an average completeness of strictly above 0.80; "below average or average" refers to an average completeness score between 0.00 and 0.46, based on the average completeness in VigiBase as of August 2020. In red signals of DMEs, in blue signals concerning non-DME events. Median values are indicated by horizontal lines within the boxes.

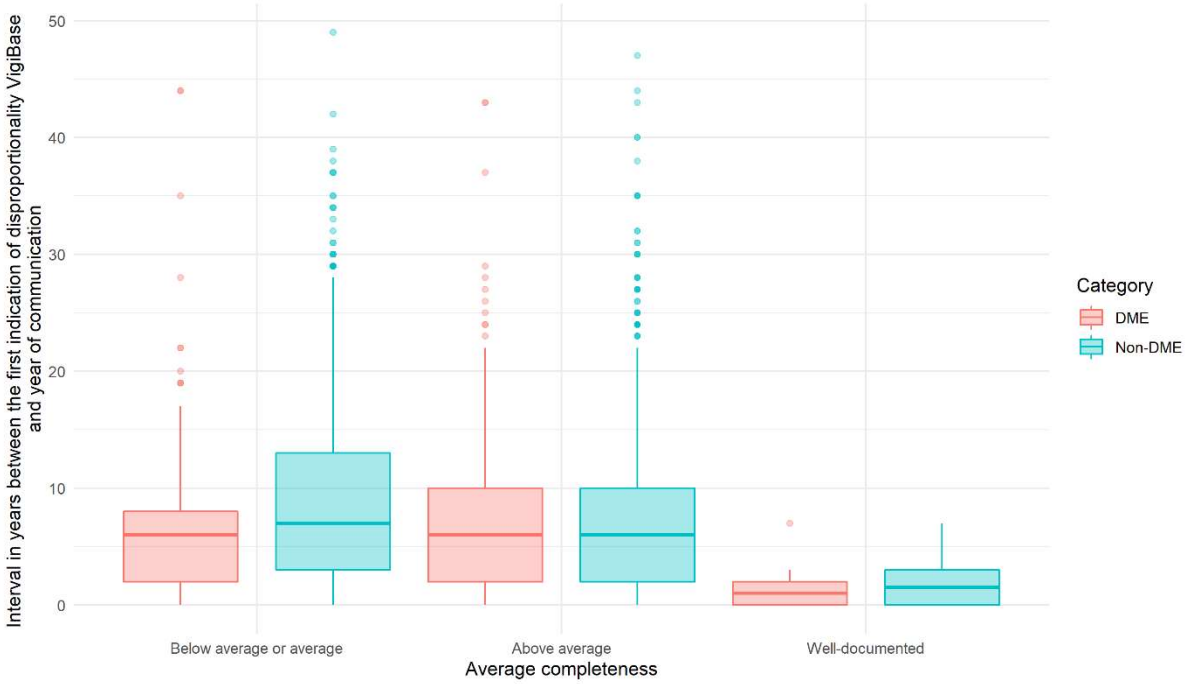

Figure 6 Box plots of the intervals from the year in which a signal/SDR became disproportionate in VigiBase and communication of each 2448 signal/SDR vs categories of vigiGrade completeness score. "Well-documented" was defined as an average completeness of strictly above 0.80; "below average or average" refers to an average completeness score between 0.00 and 0.46, based on the average completeness in VigiBase as of August 2020. In red signals of DMEs, in blue signals concerning non-DME events. Median values are indicated by horizontal lines within the boxes.

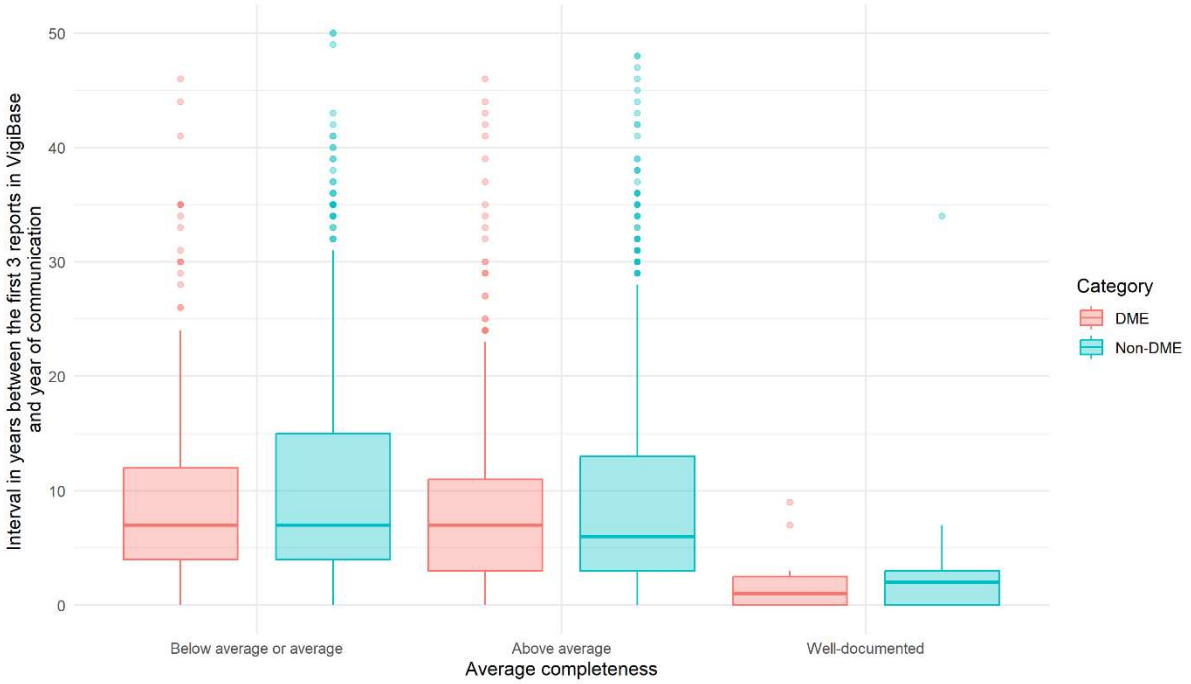

Figure 7 Times to communication vs average completeness for 3639 signals/SDRs with at least 3 reports in VigiBase in the years leading up to that of communication. In red DME signals, in blue non-DME signals; "Well-documented" was defined as an average completeness of strictly above 0.80; "below average or average" refers to an average completeness score between 0.00 and 0.46, based on the average completeness in VigiBase as of August 2020; median values are indicated by horizontal lines within the boxes.

Full statistical analysis

Table 5 Full results of the Brunner-Munzel test across all groups of signals/SDRs analysed, together with P values and degrees of freedom. df = degrees of freedom, irrespective of significant digits. C.I = confidence interval. TTC = time to communication. Well documented, refers to a vigiGrade completeness score > 0.8. [a]: Studies that did not prespecify the outcomes of interest (in systematic reviews, meta-analyses, and pooled data from clinical trials this refers to the included studies). [b]: pooled randomized clinical trials without meta-analysis; [c]: pooled clinical trials with different or unclear randomization; [d]: Disproportionality Analyses without clinical reviews; [e]: combinations of level 4 studies, together with unspecified type of evidence (e.g. unspecified literature reviews, epidemiological data, data from clinical trials); R = Studies relying exclusively on reports of adverse drug reactions. N/A = no OCEBM level could be assigned, because the study design was unclear.

Unit of analysis	Groups for comparison		Stratum	df	95% C.I.	Sample effect size estimate	*P* value	Statistical significance
	Group 1	Group 2						
Number of reports	DME Signals	Non-DME Signals	-	1494.4	0.5415949, 0.5831778	0.5623863	4.883E-09	*
Number of reporting countries	DME Signals	Non-DME Signals	-	1354	0.5035767, 0.5466264	0.5251015	0.02231	*
Number of dechallenge	DME Signals	Non-DME Signals	-	1348.6	0.5118246, 0.5547623	0.5332934	0.002394	*
Number of spontaneous reports	DME Signals	Non-DME Signals	-	1495.8	0.5416445, 0.5832036	0.562424	4.686E-09	*
Number of rechallenges	DME Signals	Non-DME Signals	-	1505.6	0.5408959, 0.5706378	0.5557668	3.103E-13	*
Number of study reports	DME Signals	Non-DME Signals	-	1341.2	0.5084954, 0.5485923	0.5285438	0.005296	*

Number of reports marked as 'other' type	DME Signals	Non-DME Signals	-	1136.9	0.4610072, 0.4929358	0.4769715	0.004733	*
Number of postmarketing surveillance reports	DME Signals	Non-DME Signals	-	1315.8	0.5045460, 0.5295426	0.5170443	0.007558	*
Interval of time between the launch year and that of communication	DME Signals	Non-DME Signals	-	691.92	0.5108697, 0.5685829	0.5397263	0.007041	*
TTC	DME Signals	Non-DME Signals	OCEBM 1, type 1*	14.393	0.7671602, 1.0661732	0.9166667	0.00003095	
TTC	DME Signals	Non-DME Signals	OCEBM 4, type 4	46.704	0.2724122, 0.4979713	0.3851918	0.04618	*
TTC	DME Signals	Non-DME Signals	OCEBM N/A	18.511	0.6333039, 0.8826778	0.7579909	0.0003735	*
Interval of time between the launch year and that of communication	DME Signals	Non-DME Signals	OCEBM 4, type 4-	468.24	0.3981963, 0.4714847	0.4348405	0.0005207	*
Interval of time between the launch year and that of communication	DME Signals	Non-DME Signals	OCEBM N/A	15.629	0.6135249, 0.8848929	0.7492089	0.001322	*
Interval of time between the launch year and that of communication	OCEBM 4	OCEBM 1-3	DME Signals	68.077	0.1269234, 0.2571633	0.1920434	5.473E-14	*
TTC	OCEBM 4	OCEBM 1-3	DME Signals	35.427	0.2414583, 0.4492856	0.345372	0.004672	*
TTC	OCEBM 4	OCEBM 1-3	Non-DME Signals	238.11	0.3584931, 0.4410742	0.3997836	0.00003052	*
Interval of time between the launch year and that of communication	Communicated between 1986 - 2005	2006-2020	DME Signals	180.77	0.5229252, 0.6252768	0.574101	0.004777	*
TTC	Communicated between 1986 - 2005	2006-2020	DME Signals	119.58	0.5439844, 0.6737884	0.6088864	0.001187	*
TTC	OCEBM 4R	OCEBM 1-3	Non-DME Signals	261.45	0.4138706, 0.4994526	0.4566616	0.04716	*
Average Completeness	DME Signals	Non-DME Signals	-	1243.9	0.3643298, 0.4076570	0.3859934	< 0.00000000000000022	*
TTC	Well documented	Other categories of completeness	DME Signals	52.254	0.7893718, 0.8887691	0.8390704	< 0.00000000000000022	*
Interval of time between the launch year and that of communication	OCEBM 4	OCEBM 1-3	Non-DME Signals	407.85	0.2129701, 0.2761300	0.24455	< 0.00000000000000022	*
Interval of time between the launch year and that of communication	Communicated between 1986 - 2005	2006-2020	Non-DME Signals	916.53	0.5985152, 0.6456372	0.6220762	< 0.00000000000000022	*
TTC	Communicated between 1986 - 2005	2006-2020	Non-DME Signals	696.76	0.6838478, 0.7332884	0.7085681	< 0.00000000000000022	*
Number of reports	Well documented	Other categories of completeness	DME Signals	53.499	0.8370621, 0.9131945	0.8751283	< 0.00000000000000022	*
Number of reports	Well documented	Other categories of completeness	Non-DME Signals	145.48	0.7708461, 0.8436281	0.8072371	< 0.00000000000000022	*
TTC	DME Signals	Non-DME Signals	-	1274.5	0.4911643, 0.5353774	0.5132709	0.2391	
Number of reports marked as 'unknown' type	DME Signals	Non-DME Signals	-	1393.8	0.4999628, 0.5156445	0.5078037	0.05109	
Interval of time between the year in which VigiBase included 3 reports and that of communication	DME Signals	Non-DME Signals	-	1234.3	0.4890301, 0.5342494	0.5116397	0.3127	
TTC	DME Signals	Non-DME Signals	OCEBM 1, type 1	4	0.244711, 1.355289	0.8	0.208	
TTC	DME Signals	Non-DME Signals	OCEBM 1, type 1~*	6.1228	0.1447650, 0.9962606	0.5705128	0.7004	
TTC	DME Signals	Non-DME Signals	OCEBM 1, type 1#*	12.834	0.4156558, 0.7910109	0.6033333	0.2552	
TTC	DME Signals	Non-DME Signals	OCEBM 2, type 2	16.51	0.4952979, 0.9047021	0.7	0.05489	

TTC	DME Signals	Non-DME Signals	OCEBM 2, type 2*	5.145	-0.01563062, 0.98074690	0.4825581	0.9323	
TTC	DME Signals	Non-DME Signals	OCEBM 3, type 3	6.5846	0.2216569, 0.8273627	0.5245098	0.8521	
TTC	DME Signals	Non-DME Signals	OCEBM 4, type 4-	553.86	0.4888339, 0.5600386	0.5244363	0.1781	
TTC	DME Signals	Non-DME Signals	OCEBM 4, type 4^	30.083	0.3445183, 0.6350414	0.4897799	0.8867	
TTC	DME Signals	Non-DME Signals	OCEBM 4, type 4R	653.2	0.4884743, 0.5508056	0.5196399	0.2164	
Interval of time between the launch year and that of communication	DME Signals	Non-DME Signals	OCEBM 1, type 1	13	0.1320550, 0.7250879	0.4285714	0.6115	
Interval of time between the launch year and that of communication	DME Signals	Non-DME Signals	OCEBM 1, type 1~*	24.374	0.2041341, 0.5864909	0.3953125	0.2698	
Interval of time between the launch year and that of communication	DME Signals	Non-DME Signals	OCEBM 1, type 1#*	46.644	0.4601753, 0.6748177	0.5674965	0.212	
Interval of time between the launch year and that of communication	DME Signals	Non-DME Signals	OCEBM 1, type 1*	4.3295	0.3330349, 1.0637905	0.6984127	0.2119	
Interval of time between the launch year and that of communication	DME Signals	Non-DME Signals	OCEBM 2, type 2	35.119	0.4289151, 0.7701589	0.599537	0.2443	
Interval of time between the launch year and that of communication	DME Signals	Non-DME Signals	OCEBM 2, type 2*	14.847	0.2745408, 0.6676814	0.4711111	0.7582	
Interval of time between the launch year and that of communication	DME Signals	Non-DME Signals	OCEBM 3, type 3	8.0792	0.1932221, 0.7873814	0.4903017	0.9419	
Interval of time between the launch year and that of communication	DME Signals	Non-DME Signals	OCEBM 4, type 4	48.682	0.3750890, 0.6022841	0.4886865	0.8422	
Interval of time between the launch year and that of communication	DME Signals	Non-DME Signals	OCEBM 4, type 4^	30.429	0.3170525, 0.5992835	0.458168	0.5496	
Interval of time between the launch year and that of communication	DME Signals	Non-DME Signals	OCEBM 4, type 4R	713.7	0.4944353, 0.5544746	0.524455	0.1102	
Interval of time between the launch year and that of communication	DME Signals	Non-DME Signals	-	1346.2	0.4669592, 0.5097912	0.4883752	0.2871	
Interval of time between the launch year and that of communication	DME Signals	Non-DME Signals	Year of communication: 1985-2005	171.09	0.3938165, 0.5081895	0.451003	0.09261	
Interval of time between the launch year and that of communication	DME Signals	Non-DME Signals	Year of communication: 2006-2020	1170.4	0.4740203, 0.5203777	0.497199	0.8126	
TTC	DME Signals	Non-DME Signals	OCEBM 1 (all subtypes)	30.014	0.4146230, 0.6975521	0.5560876	0.4245	
TTC	DME Signals	Non-DME Signals	OCEBM 2 (all subtypes)	12.336	0.3041309, 0.7496463	0.5268886	0.7975	
TTC	DME Signals	Non-DME Signals	OCEBM 3 (all subtypes)	6.2482	0.2170441, 0.8424797	0.5297619	0.825	
TTC	OCEBM 4R	OCEBM 1-3	DME Signals	38.311	0.3100425, 0.5185627	0.4143026	0.1044	
TTC	Well-documented	Other categories of completeness	Non-DME Signals	145.07	0.7406839, 0.8186411	0.7796625	< 2.2e-16	

Full counts of signals/SDRs by Anatomical Therapeutic Chemical and Medical Dictionary for Regulatory Activities classifications

We present ATC at level 3 for brevity in Table 5, but the results at 5th level of the hierarchy can be made available upon request.

Table 6 Proportions over row of Anatomical Therapeutic Chemical (ATC) level 3 for the signals/SDRs in the dataset, ranked by descending frequency of the designated medical events (DME) column. ATC codes separated by "-" indicate signals/SDRs of drug-drug interactions. Refers to 4507 observations, for 13 we could not assign an ATC code. DME = designated medical events.

ATC	DME signals/SDRs (proportion)	Non-DME signals/SDRs (proportion)	Grand Total
L01	147 (0.30)	339 (0.70)	486
L04	79 (0.25)	235 (0.75)	314
J05	75 (0.35)	139 (0.65)	214
N05	68 (0.19)	287 (0.81)	355
A10	34 (0.14)	201 (0.86)	235
J01	31 (0.29)	77 (0.71)	108
D04	28 (0.38)	45 (0.62)	73
B01	26 (0.13)	168 (0.87)	194
N06	24 (0.11)	194 (0.89)	218
S01	23 (0.14)	143 (0.86)	166
C10	21 (0.16)	109 (0.84)	130
A02	21 (0.14)	127 (0.86)	148
C09	21 (0.36)	38 (0.64)	59
C01	15 (0.22)	53 (0.78)	68
N03	14 (0.27)	38 (0.73)	52
D06	14 (0.20)	56 (0.80)	70
J07	13 (0.08)	151 (0.92)	164
L02	11 (0.31)	24 (0.69)	35
L03	11 (0.19)	46 (0.81)	57
N02	10 (0.09)	103 (0.91)	113
C03	9 (0.32)	19 (0.68)	28
R06	9 (0.43)	12 (0.57)	21
H02	8 (0.42)	11 (0.58)	19
A04	8 (0.27)	22 (0.73)	30
V03	8 (0.22)	28 (0.78)	36
M04	8 (0.36)	14 (0.64)	22

J05 - M02	7 (1)	0 (0)	7
N07	7 (0.15)	39 (0.85)	46
M05	7 (0.10)	60 (0.90)	67
C07	6 (0.38)	10 (0.63)	16
M02	6 (0.14)	37 (0.86)	43
J02	6 (0.46)	7 (0.54)	13
C08	6 (0.32)	13 (0.68)	19
A07	6 (0.19)	25 (0.81)	31
N04	6 (0.12)	43 (0.88)	49
P01	5 (0.22)	18 (0.78)	23
H03	5 (0.42)	7 (0.58)	12
R03	5 (0.07)	69 (0.93)	74
A01	5 (0.33)	10 (0.67)	15
J04	4 (0.36)	7 (0.64)	11
C02	4 (0.15)	23 (0.85)	27
H01	4 (0.31)	9 (0.69)	13
D07	4 (0.33)	8 (0.67)	12
B02	4 (0.33)	8 (0.67)	12
M01	4 (0.15)	22 (0.85)	26
H05	3 (0.18)	14 (0.82)	17
R01	3 (0.12)	22 (0.88)	25
D01	3 (0.19)	13 (0.81)	16
B03	3 (0.43)	4 (0.57)	7
N01	3 (0.30)	7 (0.70)	10
G01	3 (0.21)	11 (0.79)	14
V90 - L04	3 (0.75)	1 (0.25)	4
D10	3 (0.10)	26 (0.90)	29
D11	3 (0.07)	40 (0.93)	43
V91	3 (0.19)	13 (0.81)	16
L03 - J05 - R01	2 (1)	0 (0)	2
V10	2 (0.33)	4 (0.67)	6
L04 - G02	2 (0.67)	1 (0.33)	3
G02	2 (0.17)	10 (0.83)	12
C05	2 (0.20)	8 (0.80)	10
A03	2 (0.29)	5 (0.71)	7
L04 - C01	2 (1)	0 (0)	2
C03 - C09	2 (1)	0 (0)	2
R05	2 (0.29)	5 (0.71)	7
J05 - M01	2 (1)	0 (0)	2
V90	2 (0.11)	16 (0.89)	18
C04	2 (0.40)	3 (0.60)	5
C09 - C09	2 (0.33)	4 (0.67)	6
M04 - L04	1 (1)	0 (0)	1
V08	1 (0.14)	6 (0.86)	7

D05	1 (0.33)	2 (0.67)	3
B05	1 (0.14)	6 (0.86)	7
M03	1 (0.13)	7 (0.88)	8
C - L04	1 (0.50)	1 (0.50)	2
N05 - L01	1 (1)	0 (0)	1
J01 - C10	1 (1)	0 (0)	1
D06 - V90	1 (1)	0 (0)	1
J01 - D06	1 (1)	0 (0)	1
A16	1 (0.17)	5 (0.83)	6
A08	1 (0.13)	7 (0.88)	8
C10 - B01	1 (1)	0 (0)	1
C03 - C03	1 (1)	0 (0)	1
N02 - M02	1 (1)	0 (0)	1
J05 - J05	1 (0.50)	1 (0.50)	2
N05 - M01	1 (1)	0 (0)	1
J05 - J05 - R01	1 (0.50)	1 (0.50)	2
D06 - C09	1 (1)	0 (0)	1
J05 - M02 - C09	1 (1)	0 (0)	1
S01 - C10	1 (1)	0 (0)	1
J06	1 (0.17)	5 (0.83)	6
V09	1 (0.25)	3 (0.75)	4
G03	1 (0.02)	53 (0.98)	54
G04	1 (0.04)	24 (0.96)	25
S01 - J02	0 (0)	1 (1)	1
B01 - C10	0 (0)	2 (1)	2
N05 - J01	0 (0)	1 (1)	1
G01 - G02	0 (0)	1 (1)	1
D06 - C08	0 (0)	1 (1)	1
H03 - J05	0 (0)	4 (1)	4
N03 - N02	0 (0)	1 (1)	1
J05 - R01	0 (0)	1 (1)	1
N06 - B01	0 (0)	1 (1)	1
J05 - V91	0 (0)	2 (1)	2
P01 - P01	0 (0)	1 (1)	1
J01 - N02	0 (0)	2 (1)	2
J05 - G03	0 (0)	2 (1)	2
G01 - G03	0 (0)	1 (1)	1
V04	0 (0)	1 (1)	1
A10 - A10	0 (0)	1 (1)	1
D01 - N02	0 (0)	6 (1)	6
L01 - A04	0 (0)	2 (1)	2
J05 - B01	0 (0)	3 (1)	3
L01 - B01	0 (0)	2 (1)	2
N06 - G03	0 (0)	1 (1)	1

L01 - L01	0 (0)	6 (1)	6
J05 - C01	0 (0)	3 (1)	3
A11	0 (0)	1 (1)	1
B01 - D06	0 (0)	1 (1)	1
L02 - A10	0 (0)	1 (1)	1
J05 - D07	0 (0)	3 (1)	3
A14	0 (0)	1 (1)	1
S01 - C01	0 (0)	1 (1)	1
G01 - N02	0 (0)	3 (1)	3
B01 - J05	0 (0)	1 (1)	1
L03 - L01	0 (0)	1 (1)	1
B06	0 (0)	1 (1)	1
B01 - N05	0 (0)	1 (1)	1
D01 - G02	0 (0)	1 (1)	1
B01 - N06	0 (0)	1 (1)	1
N05 - A10	0 (0)	2 (1)	2
C01 - B01	0 (0)	1 (1)	1
G01 - B01	0 (0)	1 (1)	1
L04 - L01	0 (0)	1 (1)	1
D01 - N05	0 (0)	3 (1)	3
L04 - L04	0 (0)	24 (1)	24
N06 - C09	0 (0)	1 (1)	1
J02 - C07	0 (0)	1 (1)	1
N06 - N05	0 (0)	3 (1)	3
G03 - G02	0 (0)	1 (1)	1
N07 - N05	0 (0)	2 (1)	2
G04 - N02	0 (0)	1 (1)	1
P01 - C07	0 (0)	1 (1)	1
C10 - A10	0 (0)	1 (1)	1
P02	0 (0)	1 (1)	1
J02 - C08	0 (0)	6 (1)	6
R01 - L03	0 (0)	8 (1)	8
A06	0 (0)	11 (1)	11
G03 - B01	0 (0)	1 (1)	1
A05	0 (0)	1 (1)	1
R07	0 (0)	2 (1)	2
A01 - N05	0 (0)	1 (1)	1
S01 - B01	0 (0)	1 (1)	1
M09	0 (0)	1 (1)	1
J05 - G04	0 (0)	1 (1)	1
D01 - C05	0 (0)	4 (1)	4
S02	0 (0)	1 (1)	1
D01 - C07	0 (0)	6 (1)	6
V03 - D07	0 (0)	1 (1)	1

N02 - L04	0 (0)	1 (1)	1
J01 - B01	0 (0)	1 (1)	1
A02 - A01	0 (0)	2 (1)	2
G01 - C07	0 (0)	4 (1)	4
D01 - C08	0 (0)	1 (1)	1
M01 - B01	0 (0)	1 (1)	1
M01 - C09	0 (0)	1 (1)	1
J02 - G02	0 (0)	3 (1)	3
J02 - L01	0 (0)	1 (1)	1
Grand Total	918 (0.20)	3589 (0.80)	**4507**

Table 7 Table 6. Proportions over row of signals/SDRs by MedDRA System Organ Class. Refers to 4438 observations, excluding 82 for which coding to a MedDRA Preferred Term was not possible based on the information available in the original publications.

	Type of signal (proportion)		
MedDRA System Organ Class	**DME**	**Non-DME**	**Total**
Skin and subcutaneous tissue disorders	164 (0.41)	236 (0.59)	400
Infections and infestations	105 (0.42)	144 (0.58)	249
Blood and lymphatic system disorders	81 (0.45)	101 (0.55)	182
Renal and urinary disorders	78 (0.48)	85 (0.52)	163
Hepatobiliary disorders	69 (0.49)	73 (0.51)	142
Cardiac disorders	62 (0.18)	281 (0.82)	343
Musculoskeletal and connective tissue disorders	59 (0.23)	199 (0.77)	258
Gastrointestinal disorders	54 (0.21)	200 (0.79)	254
Immune system disorders	50 (0.59)	35 (0.41)	85
Investigations	50 (0.25)	151 (0.75)	201
Ear and labyrinth disorders	43 (0.65)	23 (0.35)	66
Respiratory, thoracic and mediastinal disorders	36 (0.15)	201 (0.85)	237
Nervous system disorders	34 (0.06)	521 (0.94)	555
General disorders and administration site conditions	13 (0.1)	121 (0.9)	134
Eye disorders	12 (0.1)	113 (0.9)	125
Vascular disorders	5 (0.03)	149 (0.97)	154
Metabolism and nutrition disorders	4 (0.03)	155 (0.97)	159
Surgical and medical procedures	0 (0)	4 (1)	4
Endocrine disorders	0 (0)	45 (1)	45
Injury, poisoning and procedural complications	0 (0)	67 (1)	67
Psychiatric disorders	0 (0)	258 (1)	258
Social circumstances	0 (0)	3 (1)	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0)	154 (1)	154
Congenital, familial and genetic disorders	0 (0)	50 (1)	50
Reproductive system and breast disorders	0 (0)	121 (1)	121
Pregnancy, puerperium and perinatal conditions	0 (0)	29 (1)	29

Grand Total	**919 (0.21)**	**3519 (0.79)**	**4438**