"Drug Ineffective" Postmarketing Reports in Drug Safety Surveillance

Pediatric Advisory Committee Meeting

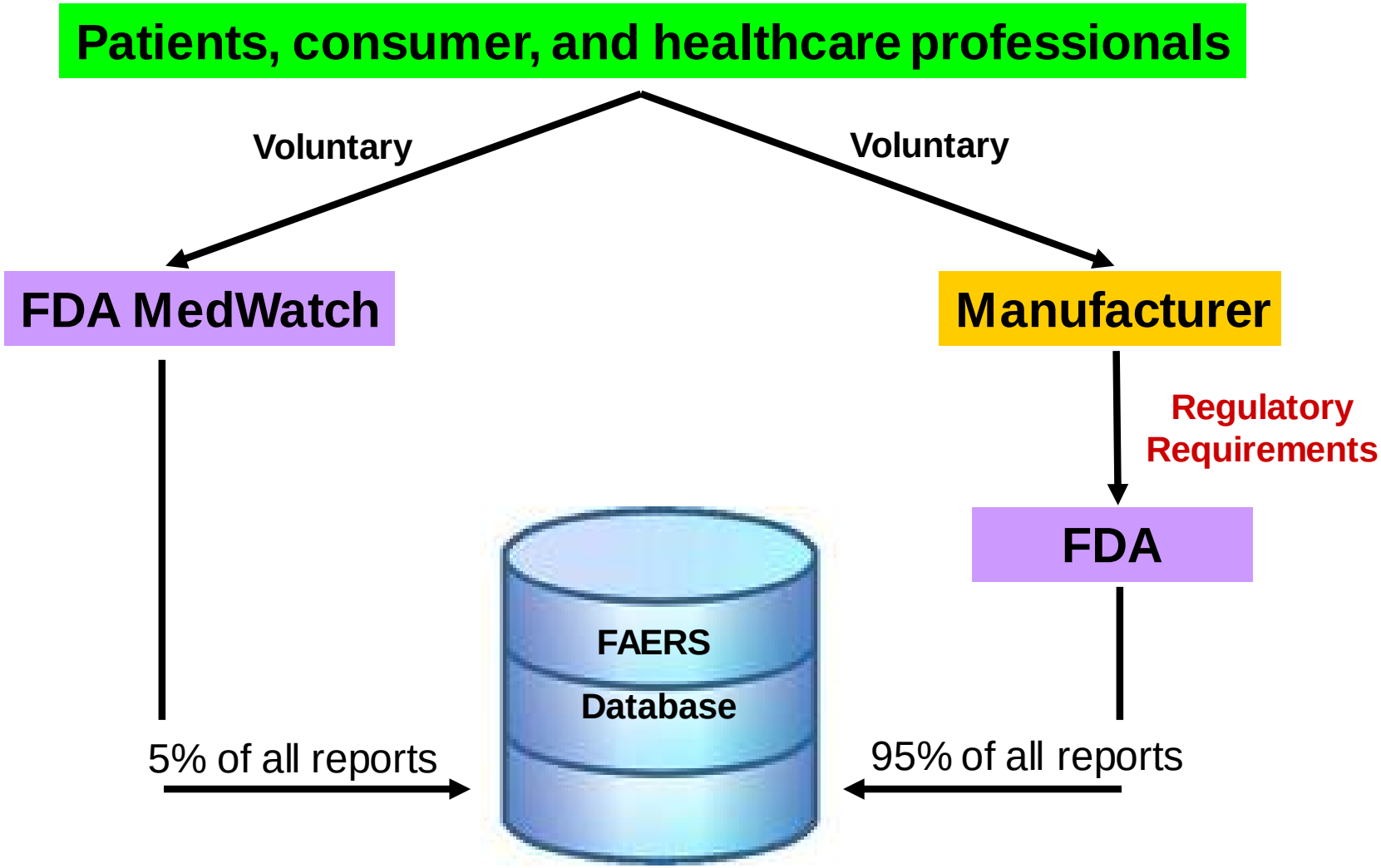
September 20, 2018

Cindy Kortepeter, Pharm.D.
Division of Pharmacovigilance I
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration

Outline

- Spontaneous Adverse Event Reports
- FDA Adverse Event Reporting System (FAERS)
- Drug-Ineffective reports background
- Descriptive study of Drug-Ineffective reports
  - Methods
  - Results
  - Conclusion

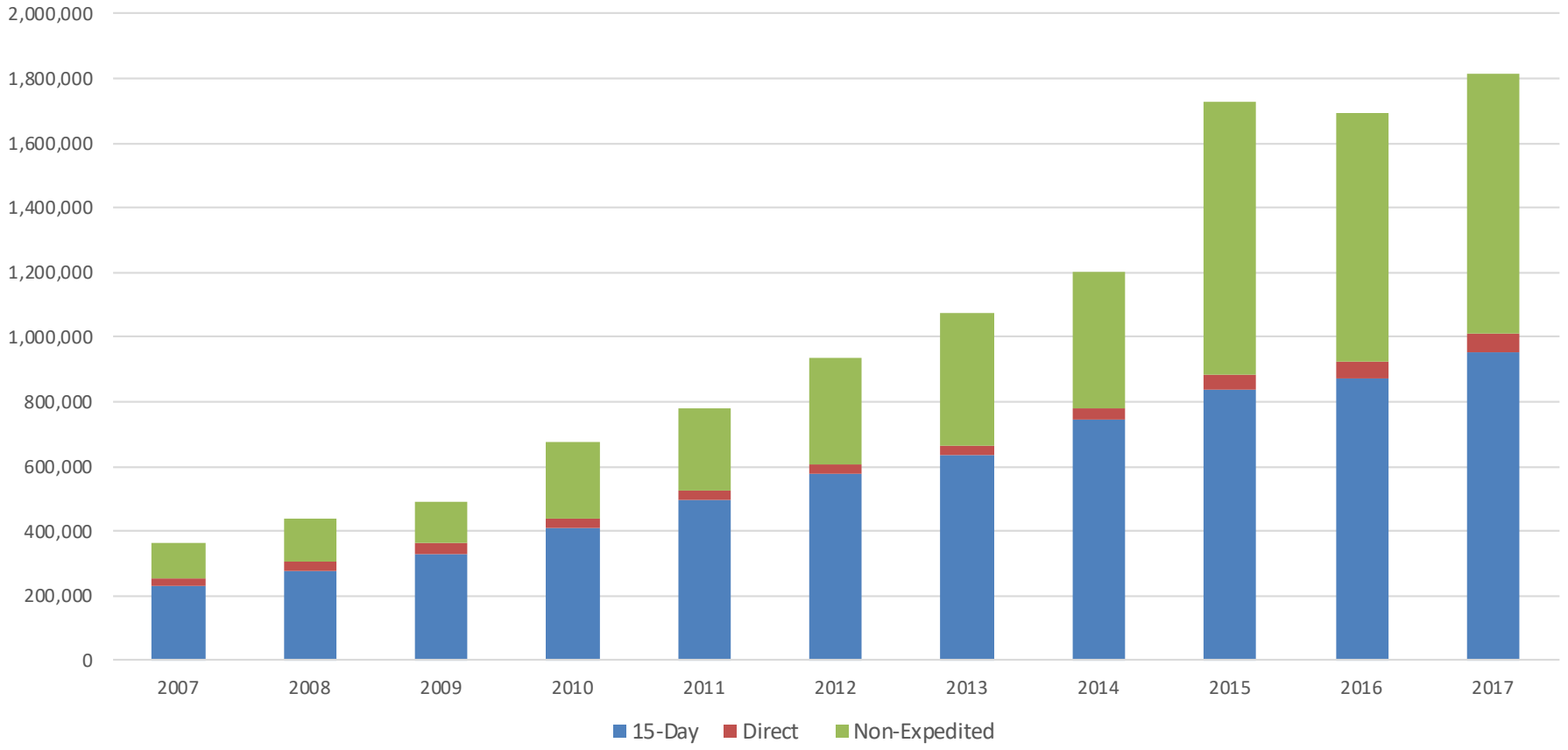
How Safety Reports Get to FDA



FDA Adverse Event Reporting System

- Computerized database
- Spontaneous reports
- Contains human drug and therapeutic biologic reports
- >14 million reports since 1968
- Over 1.8 million new reports in 2017

FAERS Reporting*



* Includes initial and follow-up reports

Most Frequently Reported Events

Preferred Term	Total Reports*	% of FAERS
Drug ineffective	650,946	5.9%
Nausea	449,206	4.1%
Headache	372,569	3.4%
Death	359,185	3.3%
Fatigue	339,940	3.1%
Dyspnoea	335,578	3.0%
Dizziness	317,180	2.9%
Diarrhoea	314,986	2.9%
Pain	304,628	2.8%
Vomiting	293,482	2.7%
Asthenia	239,352	2.2%
Pyrexia	237,988	2.2%
Malaise	233,419	2.1%
Pruritus	209,952	1.9%
Arthralgia	193,476	1.8%
Off label use	175,296	1.6%
Rash	174,046	1.6%
Insomnia	169,827	1.5%
Abdominal pain	167,355	1.5%
Pneumonia	166,681	1.5%

FAERS data through December 31, 2017; Reports may include duplicates.

Code of Federal Regulations*

§314.80 Postmarketing reporting of adverse drug experiences

Adverse drug experience. Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and **any failure of expected pharmacological action**

*e-CFR as of January 19, 2018:
https://www.ecfr.gov/cgi-bin/text-idx?SID=404dca85b24a00aa45ff5f15e8547d51&mc=true&node=pt21.5.314&rgn=div5

FDA U.S. FOOD & DRUG ADMINISTRATION

Evaluation of Postmarket Reports of Drug-Ineffective in the FAERS Database

Study Background

- The most commonly reported AE, based on frequency of MedDRA PTs* in FAERS, is “Drug ineffective”
- “Drug ineffective” (DI) reports in FAERS have not been assessed systematically for quality and inferential value from a pharmacovigilance perspective
- The objective of this study is to describe the DI reports in FAERS and provide data to support recommendations on how to best evaluate these reports

*** Medical Dictionary for Regulatory Activities Preferred Terms**

Methods

- We searched FAERS for all reports received by the FDA between September 1, 2012 and August 31, 2016
- The retrieved reports were stratified by those coded with and without the MedDRA PT* “Drug ineffective”
- We conducted a manual evaluation of a subset of FAERS reports to determine the “usefulness” of the reports from a pharmacovigilance perspective

*** Medical Dictionary for Regulatory Activities Preferred Term**

Criteria Used to Classify Reports as "Useful" for Manual Evaluation

Criterion	Description
1	The suspect product of drug ineffective was clearly identifiable
2	An informative narrative to support the reported drug ineffectiveness
AND one or more of the following four criteria:	
3	MedDRA preferred term(s) in addition to "drug ineffective" was reported
4	Suspect product's batch or lot number was reported
5	A beneficial response prior to the administration of the suspect product was reported
6	Medication switching was reported

MedDRA Medical Dictionary for Regulatory Activities

Results

- 3,872,843 reports* were entered into FAERS in the study period
- 247,513 reports* were coded with DI
- 552 reports* of DI were reviewed manually
- 43 reports* of DI were deemed “useful”

* Best representative report (i.e., initial or follow-up report, not both)

DI Report Characteristics

	Drug Ineffective Reports (N=247,513)		All Non-DI FAERS Reports [a] (N=3,625,330)	
	N	%	N	%
Report Type				
Manufacturer	241291	97.5	3482423	96.1
Direct	6222	2.5	142907	3.9
Reporter Type				
Consumer	172834	69.8	1744954	48.1
Healthcare Provider	69770	28.2	1692858	46.7
Other	444	0.2	115558	3.2
Missing	4465	1.8	71960	2
Reporter Country				
USA	217966	88	2673274	73.7
Non-USA	29547	12	952056	26.3
Patient Age (years)				
0 - 17	6007	2.4	110215	3
18 - 64	80313	32.4	1341823	37
> 65	38612	15.6	771500	21.3
Missing	122581	49.5	1401792	38.7
Patient Gender				
Female	139671	56.4	2037500	56.2
Male	82326	33.3	1261002	34.8
Unknown/Null	25516	10.3	326828	9

DI Report Characteristics (Cont'd.)

	Drug Ineffective Reports (N=247,513)		All Non-DI FAERS Reports [a] (N=3,625,330)	
	N	%	N	%
All Outcomes				
Hospitalization	20380	8.2	829646	22.9
Death	4842	2	365601	10.1
Disability	2832	1.1	67991	1.9
Life Threatening	2150	0.9	85168	2.3
Required Intervention	179	<0.1	10919	0.3
Congenital Anomaly	13	<0.1	14408	0.4
Other	49853	20.1	1184076	32.7
No serious outcome was reported	182628	73.8	1583848	43.7
Primary Suspect Product's Application Type				
NDA	144168	58.3	1973700	54.4
BLA	48946	19.8	822300	22.7
ANDA	19704	8	271748	7.5
Missing	34695	14	557582	15.4
Additional PTs other than Drug Ineffective				
Reported	153555	62		
Not reported	93958	38		

DI Report Characteristics

Results of manual evaluation of 552 reports

Recorded information	Observation	N	%
The suspect product of drug-ineffective was specified from narrative field	Yes	526	95.3
	No	26	4.7
Suspect product's type from narrative field	Brand	415	75.2
	Generic	42	7.6
	Both	13	2.4
	Unknown	56	10.2
	N/A	26	4.7
Most frequently identified products (Top 3)	TNF blocker	47	8.5
	TNF blocker	30	5.4
	NSAID	19	3.4
Medication switch reported	Yes	34	6.2
	No	518	93.8
A prior beneficial response to the suspect product	Yes	75	13.6
	No/Unknown	477	86.4
Suspect product was continued	Yes	78	14.1
	No	164	29.7
	Not reported/Unknown	310	56.2

DI Report Characteristics

Characteristics of the 43 reports determined to be "Useful"

Recorded information	Observation	N	%
The suspect product of drug-ineffective was specified from narrative field	Yes	43	100.0
	No	0	0.0
Suspect product's type from narrative field	Brand	19	44.2
	Generic	22	51.2
	Unknown	2	4.7
Most frequently identified products (Top 3)	Opioid	4	9.3
	Benzodiazepine	3	7.0
	TNF blocker	2	4.7
Medication switching was reported	Yes	19	44.2
	No	24	55.8
A prior beneficial response to the suspect product	Yes	20	46.5
	No/Unknown	23	53.5
Suspect product was continued	Yes	9	20.9
	No	16	37.2
	Not reported/Unknown	18	41.9

DI Report Characteristics (Cont'd.)

Characteristics of the 43 reports determined to be "Useful"

Recorded information	Observation	N	%
Suspect product's batch or lot number was reported	Yes	17	39.5
	No	26	60.5
Product application type	NDA	13	30.2
	BLA	3	7.0
	ANDA	16	37.2
	Missing	11	25.6
PT(s) other than "*Drug ineffective*" was reported	Yes	36	83.7
	No	7	16.3
Additional PTs other than *Drug ineffective* (Top 3)	Product quality issue	10	23.3
	Product substitution issue	8	18.6
	Feeling abnormal	5	11.6

Findings

- The majority of DI reports
  - did not report a serious outcome
  - were more likely to be reported by consumers
  - the suspect products were primarily used for the management of symptomatic conditions, suggesting that consumers have self-awareness of worsening or no improvement of their own subjective experiences

- A higher proportion of suspect products were identified as generic (51.2%) in the reports deemed "useful" compared to the proportion of DI reports sampled during the study period (generic 8.0%)

Limitations

- We did not capture all the potential reports describing drug ineffectiveness
  - we limited our search to the PT "Drug ineffective." Other reports describing the concept of ineffectiveness would not have been captured by relevant terms included in the HLT* because they may be coded with event-specific PTs
- We determined the sample size needed to accurately estimate the proportion of DI reports considered "useful," our resulting sample of "useful" cases limits the generalizability of the specific characteristics within the subset
- Our definition of "useful" was based on the expertise of reviewers with pharmacovigilance experience, which may limit reproducibility

*** High Level Term**

Conclusion

In the “useful” reports

- generic products tend to be reported as a suspect product more frequently
- often accompanied with the PTs “Product quality issue” or “Product substitution issue”
- information about medication switching or information on batch/lot numbers can be useful

Drugs - Real World Outcomes
https://doi.org/10.1007/s40801-018-0131-3

ORIGINAL RESEARCH ARTICLE

An Evaluation of "Drug Ineffective" Postmarketing Reports in Drug Safety Surveillance

Takashi Misu[1,2] · Cindy M. Kortepeter[1] · Monica A. Muñoz[1] · Eileen Wu[1] · Gerald J. Dal Pan[1]

Abstract

Introduction The most commonly reported adverse event, based on frequency of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs), in the US FDA Adverse Event Reporting System (FAERS) database is "drug ineffective" (DI). This study aimed to describe the DI reports and provide data to support recommendations on how to best evaluate these reports.

Methods We characterized all FAERS reports coded with the MedDRA PT "drug ineffective" received between 1 September 2012 and 31 August 2016 using all other FAERS reports as a comparator. Additionally, we conducted a manual evaluation to identify informative data elements in the report narratives.

Results During the study period, 247,513 (6.4% of all FAERS reports) DI reports were entered in FAERS. Compared with non-DI reports, DI reports were more likely to be reported by consumers (69.8 vs. 48.1%) and less likely to report a serious outcome (26.2 vs. 56.3%). Most DI reports (88%) were from the USA. Manual evaluation of 552 sample US reports identified 43 reports (7.8%) deemed "useful"; a higher proportion of "useful" reports provided a batch or lot number (39.5 vs. 17.2%) and were coded with additional PTs beyond "drug ineffective" (83.7 vs. 59.2%), the most frequent of which were "product quality issue" (23.3%) and "product substitution issue" (18.6%).

Conclusions DI was the most frequently reported adverse event in the FAERS database; however, the yield from these reports in terms of usefulness from a pharmacovigilance perspective was low. Efficient strategies are needed to identify which DI reports are more likely to contain useful information.

Key Points

The most frequently reported adverse event in the US FDA Adverse Event Reporting System (FAERS) database was "drug ineffective" (DI).

Most DI reports in FAERS were reported by consumers and were non-serious.

A minority of DI reports were deemed "useful". Many of these provided a batch or lot number, and the majority were coded with additional preferred terms beyond DI.

Disclaimer The views expressed are those of the authors and do not necessarily represent the position of, nor imply endorsement from, the US FDA, the US Government, or the Japanese Pharmaceuticals and Medical Devices Agency.

✉ Cindy M. Kortepeter
Cindy.Kortepeter@fda.hhs.gov

[1] Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, USA

[2] Office of Safety II, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan

Published online: 23 February 2018

1 Introduction

Adverse event (AE) reporting has been a central part of the US FDA's postmarketing drug safety surveillance for nearly 50 years [1]. While population-based databases

Acknowledgements

Pharmaceuticals and Medical Devices Agency, (PMDA), Japan
Takashi Misu

Office of Surveillance and Epidemiology, FDA
Gerald Dal Pan
Monica Muñoz
Eileen Wu


FDA
U.S. FOOD & DRUG
ADMINISTRATION