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Assessment of the Impact of Scheduled Postmarketing Safety Summary Analyses on Regulatory Actions

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Abstract

In addition to standard postmarketing drug safety monitoring, Section 915 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) requires the US Food and Drug Administration (FDA) to conduct a summary analysis of adverse event reports to identify risks of a drug or biologic product 18 months after product approval, or after 10,000 patients have used the product, whichever is later. We assessed the extent to which these analyses identified new safety signals and resultant safety-related label changes. Among 458 newly approved products, 300 were the subjects of a scheduled analysis; a new safety signal that resulted in a safety-related label change was found for 11 of these products. Less than 2% of 713 safety-related label changes were based on the scheduled analyses. Our study suggests that the safety summary analyses provide only marginal value over other pharmacovigilance activities.

Pharmacovigilance is a continuous effort to identify drug risks and take necessary actions to inform the public about these risks and to avoid or reduce these risks. The FDA reviews a wide variety of postmarketing safety-related information, including adverse event reports, clinical trial reports, observational study reports, scientific literature, input from international regulatory agencies, and other sources. As a result of these efforts, safety-related regulatory actions, usually safety-related label changes, are made when necessary.¹

In addition to the FDA's postmarketing drug safety monitoring processes, Section 915 of the FDAAA² requires the FDA to conduct a scheduled safety summary analysis 18 months after a drug or biologic product is approved, or after 10,000 patients have used the product, whichever is later. In preparing these analyses, the Center for Drug Evaluation and Research (CDER) staff review adverse event reports, periodic safety reports, and findings from clinical trials and studies. For drug products that are new molecular entities and for all

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Additional Supporting Information may be found in the online version of this article.

CONFLICT OF INTEREST/DISCLOSURE

The authors report no conflicts of interest. The views expressed in this paper are those of the authors and do not necessarily reflect the official views of the US Food and Drug Administration or the Japanese Pharmaceuticals and Medical Devices Agency.

AUTHOR CONTRIBUTIONS

S.S. and G.D.P. wrote the article; S.S., E.P., R.K., M.H., and G.D.P. designed the research; S.S., E.P., E.W., and R.K. contributed to data collection and manual review of data sources; S.S. and E.P. analyzed the data; all authors contributed edits to the article.

therapeutic biologic products, CDER staff also review data from clinical pharmacology studies, product usage data, scientific literature, reports of medication errors, and assessments of risk evaluation and mitigation strategies.

The scheduled safety summary analyses aim at identification of risks, including any new risks not previously identified, potential new risks, or known risks reported in unusual number. The impact of these analyses on subsequent regulatory actions is unknown. We assessed the extent to which the scheduled safety summary analyses resulted in new safety signals, and the extent to which these new safety signals resulted in safety-related label changes.

RESULTS

The CDER approved 469 original New Drug Applications (NDAs) and therapeutic Biologic License Applications (BLAs) between September 27, 2007, the date FDAAA was enacted, and March 31, 2013. We excluded nine products that were discontinued, withdrawn, or under a withdrawal process before a scheduled safety summary analysis was completed, and two products that were approved under the President's Emergency Plan for AIDS Relief (PEPFAR). The remaining 458 products comprised the study products. Thirty (6.6%) were therapeutic biologic products (Table 1). Of the remaining 428 drug products, 128 (29.9%) were new molecular entities. As of April 30, 2015, there were 300 (65.5%) products for which a scheduled safety summary analysis was completed, seven (1.5%) that were undergoing the analysis, and 151 (33.0%) that had not undergone an analysis because the 10,000-patient threshold had not been met. Scheduled safety summary analyses were completed for a higher percentage of drug products (68.7%) than for biologic products (20.0%). They were completed for a slightly higher percentage of drug products that were not new molecular entities (72.0%) than for new molecular entities (60.9%).

Table 2 describes the study products according to three regulatory characteristics. Priority review and accelerated approval are expedited programs for products to treat serious or life-threatening conditions.³ Orphan product designation refers to a product intended for use in a disease that affects fewer than 200,000 persons in the United States.⁴ Supplemental Tables S1 and S2-1,2,3 online show the interrelationship of these characteristics. The majority of products with these regulatory characteristics did not meet the 10,000-patient threshold and thus did not have a completed scheduled safety summary analysis. By contrast, an analysis was completed for the majority of products without these characteristics.

Of the 458 products, 227 reached the 10,000-patient threshold at the 18-month timepoint (Figure 1). For the remaining 231 products, product usage monitoring was repeated every 12–18 months, until usage reached the 10,000-patient threshold. The number of products that met the 10,000-patient threshold and underwent the summary safety analysis declined at each subsequent usage monitoring cycle.

New safety signals were identified for 49 (16.3%) of the 300 drug and therapeutic biologic products for which a scheduled safety summary analysis was completed (Figure 2). New safety signals were identified for 46 (15.6%) of 294 drug products, 28 (35.9%) of 78 new-

molecular-entity drugs, 18 (8.3%) of 216 non-new-molecular-entity drugs, 3 (50.0%) of 6 therapeutic biologic products, 11 (26.8%) of 41 products that underwent a priority review, 2 of 5 (40.0%) products approved via the accelerated approval pathway, and 4 (25.0%) of 16 orphan products. These new safety signals resulted in safety-related label changes for 11 drug and therapeutic biologic products: six new-molecular-entity drugs, three non-new-molecular-entity drugs, and two therapeutic biologic products. A total of 13 risks were noted in these label changes (Table 3). The new safety signals for the other 38 products have not led to a safety-related label change.

During the study period, 713 label changes were made for the 458 products in our study (Table 4). The safety signals identified from the scheduled safety summary analyses thus contributed 11/713 (1.5%) of the safety-related label changes. Approximately one-fifth (19.9%) of the 713 safety-related label changes were made prior to the 18-month postapproval timepoint. This pattern was true both for products that met the 10,000-patient threshold and those that did not. Of the 300 products for which a scheduled safety summary analysis was completed, 215 (39.6%) of 543 safety-related label changes were made before the scheduled safety summary analyses were completed.

In a sensitivity analysis we included signals of increased frequency, signals of increased severity of known risks, and signals based on known pharmacological effects or class effects in addition to the new signals that were included in the primary analysis. A safety signal was identified for 65 (21.7%) of 300 products for which a scheduled safety summary analysis was completed (see Supplemental Figure S3 online). These safety signals led to 20 label changes accounting for 20/713 (2.8%) safety-related label changes.

New safety signals from the scheduled safety summary analyses contributed to 0.5%, 0%, 1.0%, and 3.8% of the safety-related label changes for priority review products, accelerated approvals products, orphan products, and therapeutic biologic products respectively (Table 4).

DISCUSSION

Scheduled safety summary analyses conducted 18 months after a product's approval or after 10,000 patients had taken the product, whichever is later, identified new safety signals for 11 of 458 products and contributed to less than 2.0% of the 713 safety-related label changes for these products during the study period. These scheduled safety summary analyses are conducted in addition to the FDA's ongoing pharmacovigilance activities. Our results suggest that the scheduled safety summary analyses provide only a small, incremental benefit over ongoing, FDA pharmacovigilance activities.

A total of 13 new signals identified for 11 drug and biologic products across the 300 completed scheduled safety summary analyses led to safety-related label changes. Changes were made most frequently to the *Adverse Reactions* and *Warnings and Precautions* sections. We observed no patterns among the type of product application, regulatory characteristics, or adverse events across these safety-related label changes.

The threshold criteria for the scheduled safety summary analyses resulted in completed analyses for 65.5% of products. As all products had been approved for at least 18 months, failure to meet the 10,000-patient threshold was the reason analyses were not conducted for approximately one-third of products, including the majority of products approved via priority review and accelerated approval pathways and the majority of orphan products and therapeutic biologic products. In contrast, scheduled safety summary analyses were completed for the majority of products without these regulatory characteristics.

It is not surprising that orphan products rarely met the 10,000-patient threshold, as they are developed to treat diseases or conditions affecting fewer than 200,000 people in the US. However, historically half of the orphan designations were for a prevalence of fewer than 40,000 patients; the most common population size for the approval was fewer than 10,000 patients.⁵ In our study, 22.9% of safety-related label changes for orphan products had been made by the 18-month postapproval timepoint, despite relatively low numbers of patients who were using the products. Therefore, for orphan products, use of the 10,000-patient use threshold may not be an appropriate threshold for performing safety analyses.

Scheduled safety summary analyses were completed much less frequently for therapeutic biologic products than for drug products. This is not unexpected, as half of the therapeutic biologic products were approved for orphan indications. While approximately the same proportion of biologic and drug products had safety-related label changes, a smaller percentage of the label changes for biologic products were made by 18 months postapproval or prior to the completion of the scheduled safety summary analyses. Ebberts *et al.* found no differences in the time to first safety-related regulatory action between biologic and drug products.⁶ Their data, however, spanned only a 24-month period and are not directly comparable to ours.

Scheduled safety summary analyses were not completed for the majority of products approved via priority review and accelerated approval pathways. One reason is that these approval pathways are also correlated with an orphan designation, with more than half of orphan products receiving priority review or accelerated approval. There are arguments whether the FDA's reduced review time after introducing a goal date program to the FDA's review process, under the Prescription Drug User Fee Act, increased the risk of a drug.⁷⁻¹² We observed that the scheduled safety summary analyses detected a similar proportion of new signals that led to safety-related label changes for products approved via an expedited pathway and products not approved via these pathways. Scheduled safety summary analyses do not identify increased number of risks among products approved via expedited pathways, although we cannot conclude the argument only by these data.

To explore whether the 18-month criterion is too short a time for the generation of safety signals, we examined the extent of safety-related label changes that occurred before the 18-month postapproval timepoint. A total of 142 safety-related label changes in 458 study products were made before the 18-month timepoint. This result demonstrates that safety signaling occurs during the first 18-months postapproval for these products. Importantly, numerous safety signals were identified during this time period regardless of whether the product ever met the 10,000-patient threshold. This pattern was also observed for orphan

products and products approved via the priority review and accelerated approval pathways. Because the scheduled safety summary analysis begins as early as 18-months postapproval (but often later, depending on when the 10,000-patient threshold was met), we examined the extent of safety-related label changes prior to completion of the analysis for the 300 products for which the analysis was completed. Our finding that 215 safety-related label changes were made before the completion of the scheduled safety summary analysis further suggests that pharmacovigilance is continuously active in the postapproval period. Taken together, these findings suggest that neither the 18-month timepoint nor the 10,000-patient threshold is necessary for meaningful pharmacovigilance activities.

We further observed that for the 300 products for which the analysis was completed, 60.4% of the safety-related label changes occurred after the completion of the analysis. Since most of these label changes were not triggered by the scheduled safety summary analysis, this finding suggests that new safety signals continue to be identified in the postapproval period. Because safety-related label changes for these study products were made, both before and after the completion of the scheduled safety summary analysis, and because the proportion of safety-related label changes based on safety signals identified by these analyses was low, it is possible that the safety signals identified by the scheduled safety summary analysis were those that would have been detected as part of ongoing pharmacovigilance activities around the time the scheduled safety summary analysis was performed. Our data, however, cannot confirm this hypothesis.

Eleven of the 13 new safety signals that led to safety-related label changes were identified in spontaneous adverse event reports. This finding is consistent with an analysis that found spontaneous adverse event reports were responsible for over half of the safety-related label changes made by the FDA.¹ By contrast, we found that a review of the literature, and a review of the periodic safety reports, each led to the detection of one new safety signal that resulted in a safety-related label change. The relatively low yield of the periodic safety report review is consistent with the findings of a study of the cost-effectiveness of the Periodic Safety Update Report (PSUR) for biologics in Europe over a 15-year period, which found that the PSUR detected only two of 24 urgent safety issues for these products.¹³ However, our finding contrasts with that of a European study¹⁴ of 70 PSURs for centrally approved biopharmaceutical products, which showed that potential safety concerns were identified in 58 (83%) of PSURs and changes to the Summary of Product Characteristics were required for 26 (37%) of those products. The reason for these different findings is not clear, but it may relate to differences in the role of the PSUR in safety signal detection.

We used safety-related label changes as the primary measure of the scheduled safety summary analyses' public health value. We chose this measure because it is readily quantifiable and reflects the FDA's determination that the adverse events noted in the safety signal are reasonably likely to be causally related to the product. We also examined the number of new safety signals generated by the scheduled safety summary analyses, but we do not believe that this is the best primary measure of the effectiveness of a pharmacovigilance process for several reasons. First, the quality, detail, and strength of signals vary because there is an inherent element of subjectivity in the designation of a safety signal and the thresholds to identify one. Second, many new safety signals, after

careful review, are refuted, and thus do not represent new risks of the drug.¹⁵ We note, however, that several studies have shown the many safety-related label changes do not necessarily lead to desired changes in prescribing patterns.^{16–18}

The strengths of this study are that the data were systematically collected, and have been confirmed by FDA staff to ensure completeness. A standard approach to identifying safety findings was used, and a linkage was created between each new signal and its associated safety-related label change. There are also limitations to our study. The duration of follow-up time after the completion of the scheduled safety summary analyses may be insufficient to capture all safety-related label changes that could be made based on those analyses, especially if such safety-related label changes are time-dependent. This study did not consider the clinical importance of the identified safety signals or quantify the impact of the resulting safety-related label changes.

Our analysis suggests that these scheduled safety summary analyses provide only marginal value over existing pharmacovigilance and other drug safety monitoring activities. Routine postmarketing surveillance activities account for the majority of safety-related label changes,¹ while the scheduled safety analyses contributed less than 2% of safety-related label changes in our study. Additional research is needed to identify ways to optimize use of available signal sources and timing of enhanced assessments, and if different monitoring strategies based on product characteristics could result in more efficient safety signal detection. Using a standardized approach and schedule to review the safety of newly approved drugs and therapeutic biologic products might not be the most effective and efficient approach for safety signal detection. Rather, an improved approach that considers each product's pharmacological characteristics and clinical use to inform the time, nature, and extent of safety review strategies could result in more efficient safety signal detection.

METHODS

We used data from the FDA's website and from internal agency records to identify newly approved drug products and therapeutic biologic products, reviews of those drug and biologic products conducted pursuant to Section 915 of FDAAA, and postmarketing safety records and actions.

Study products included original NDAs and original BLAs approved by CDER between September 27, 2007, the date of enactment FDAAA, and March 31, 2013. We chose this study period to ensure that all study products had at least 18 months of postapproval follow-up time and would meet the 18-month criterion of Section 915 of FDAAA. We excluded products approved under the PEPFAR and products withdrawn, discontinued, or under a withdrawal process before the scheduled safety summary analysis was completed. For each product, we recorded the date of approval, whether it was a new molecular entity (NDAs only), whether it was an orphan product, whether it was granted priority review status, and whether it was approved under the accelerated approval provisions of 21 CFR Part 314, Subpart H.¹⁹

For each study product, we determined whether a scheduled safety summary analysis was conducted, the date the scheduled safety summary analysis was completed, and whether the scheduled safety summary analysis identified any new safety signals. We recorded these data on study products through April 2015. As of that date, for each product, we classified the scheduled safety summary analysis as completed, ongoing, or not yet started. Because FDA staff classified some safety signals as identified, but not yet fully evaluated, prior to the conduct of the scheduled safety summary analysis as a new safety signal, we developed an algorithm (Figure 3) to identify only those safety signals that resulted from the scheduled safety summary analyses. To focus on new safety signals, we excluded previously identified safety signals as well as known risks that appeared with greater frequency, greater severity, and those that were class effects or known pharmacological effects. In the sensitivity analysis we expanded the definition of a signal identified as a result of a scheduled summary safety analysis to include signals of increased frequency, signals of increased severity of known risks, or signals based on known pharmacological effects or class effects in addition to new signals from the scheduled safety summary analyses in the primary analysis.

For each newly identified safety signal, we determined the source of the data that gave rise to the safety signal (e.g., adverse event reports, clinical trials, literature review, and review of periodic safety report). We also determined if the safety signal resulted in safety-related label change. Safety-related label changes made between October 2007 and April 2015 were identified from the FDA MedWatch Website.²⁰ For each product we determined the number of times its label was updated with new safety information. Each instance was counted as a single safety-related label change regardless of the number of safety issues that were updated as part of that safety-related label changes. Data were collected by S.S., E.P., and R.K. Safety signals identified in the safety summary analysis, source of the safety signals, and subsequent safety-related labeling changes identified by each of the reviewers were confirmed by an independent review by E.W.

We analyzed our findings using descriptive statistics. SAS 9.3 (SAS Institute, Cary, NC)²¹ was used to perform the analyses. This study was granted an exemption for review by the FDA Institutional Review Board.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

- ✓ Section 915 of the Food and Drug Administration Amendments Act of 2007 requires the FDA to conduct a summary analysis of adverse event reports to identify risks of a drug or biologic product 18 months after product approval, or after 10,000 patients have used the product, whichever is later. The added value of these scheduled analyses over the FDA's standard pharmacovigilance activities is unknown.

WHAT QUESTION DID THIS STUDY ADDRESS?

- ✓ To what extent do the scheduled analyses contribute to the identification of new safety signals that result in safety-related label changes?

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

- ✓ Safety signals that resulted in safety-related label changes were found for 11 of 300 products that underwent the summary analysis. Less than 2% of safety-related label changes were based on these analyses. This finding suggests that safety summary analyses provide only marginal value over other pharmacovigilance activities.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

- ✓ Quantifying the impact of a pharmacovigilance activity might help to optimize pharmacovigilance systems.

Figure 1.
Number of products meeting the 10,000-patient threshold as a function of usage monitoring cycle.

NDA=New Drug Application; NME=New Molecular Entity; BLA=Biologic License Application

Figure 2.

Number of the new safety signals identified and safety-related label changes as a result of the scheduled safety summary analyses: Overall, stratified by product application type, and by regulatory characteristic.

Figure 3.
Algorithm for new safety signal identification.

Table 1

Status of scheduled safety summary analyses stratified by product application type

	Product application type					
	NDA					
	All products	All	NME	Non-NME	BLA	
Status of scheduled safety summary analyses	N = 458 n (%)	N = 428 n (%)	N = 128 n (%)	N = 300 n (%)	N = 30 n (%)	
Not eligible for review ^a	151 (33.0)	127 (29.7)	48 (37.5)	79 (26.3)	24 (80.0)	
Undergoing review ^b	7 (1.5)	7 (1.6)	2 (1.6)	5 (1.7)	0	
Completed	300 (65.5)	294 (68.7)	78 (60.9)	216 (72.0)	6 (20.0)	

BLA, Biologic License Applications; NDA, New Drug Applications; NME, New Molecular Entities.

^aProducts not eligible for review are those products which had not been used by 10,000 patients.

^bProducts undergoing review are those that met the 18-month and 10,000-patient threshold for which the scheduled safety analysis was underway and not completed as of the April 30, 2015 cutoff date.

Table 2

Status of scheduled safety summary analyses stratified by regulatory characteristic

	Regulatory characteristic							
	Priority review		Accelerated approval		Orphan product			
	Yes	No	Yes	No	Yes	No		
Status of the scheduled safety summary analyses	N = 99	N = 359	N = 18	N = 440	N = 76	N = 382		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
Not eligible for review ^a	57 (57.6)	94 (26.2)	13 (72.2)	138 (31.4)	60 (78.9)	91 (23.8)		
Undergoing review ^b	1 (1.0)	6 (1.7)	0	7 (1.6)	0	7 (1.8)		
Completed	41 (41.4)	259 (72.1)	5 (27.8)	295 (67.0)	16 (21.1)	284 (74.3)		

^aProducts not eligible for review are those products which had not been used by 10,000 patients.

^bProducts undergoing review are those that met the 18-month and 10,000-patient threshold for which the scheduled safety analysis was underway and not completed as of the April 30, 2015 cutoff date.

Table 3
Safety-related labeling changes for new safety signals identified in the scheduled safety summary analyses

No.	Nonproprietary name (brand name)	Type	Signal	Data source	Section of labeling
1	Everolimus (AFINITOR)	NME	Pneumocystis jirovecii pneumonia (PJP)	FAERS	• Warning and precaution
2	Azelastine HCl (ASTEPRO)	Non-NME	Nausea	Periodic Report	• Adverse reaction
3	Certolizumab pegol (CIMZIA)	BLA	Preparation and administration on viral form	FAERS	• Dosage and administration
4	azilsartan kamedoxomil (EDARBI)	NME	Angioedema	FAERS	• Adverse reaction
5	degarelix for injection (FIRMAGON)	NME	Effect on QT/QTc Interval	Literature	• Warning and precaution
6	Regadenoson (LEXISCAN)	NME	Hypersensitivity including anaphylaxis	FAERS	• Warning and precaution • Adverse reaction
7	Regadenoson (LEXISCAN)	NME	Bronchoconstriction	FAERS	• Warning and precaution • Adverse reaction
8	Omeprazole delayed release tablets	Non-NME	Hypomagnesemia	FAERS, Literature	• Warning and precaution • Adverse reaction • Patient counseling information • FDA approved patient labeling
9	Clobazam (ONFI)	NME	Hypersensitivity	FAERS, Periodic Report	• Contraindication • Adverse reaction
10	Clobazam (ONFI)	NME	Urinary retention	FAERS, Periodic Report	• Adverse reaction
11	Denosumab (PROLIA)	BLA	Marked elevations of serum parathyroid hormone (PTH)	FAERS	• Warning and precaution • Adverse reaction
12	Pazopanib hydrochloride (VOTRIENT)	NME	Retinal detachment	FAERS	• Adverse reaction
13	Welchol powder for oral suspension	Non-NME	Dysphagia	FAERS	• Adverse reaction

NME, New Molecular Entity; BLA, Biologic License Application; QT, QT interval; QTc, Corrected QT interval; FAERS, FDA Adverse Event Reporting System.

Number and timing of safety-related label changes made between October 2007 and April 2015 for all products, stratified by regulatory characteristic and product application type

Table 4

Status of scheduled safety summary analyses	Number of products <i>n</i>	Number of label changes <i>n</i>	Number of label changes before 18 months <i>n</i> (%)	Number of label changes before the scheduled safety analyses was completed <i>n</i> (%)	Number of label changes triggered by the scheduled safety summary analyses <i>n</i> (%)
All study products					
Not eligible for review ^a	151	162	48/162 (29.6%)	N/A	N/A
Undergoing review ^b	7	8	2/8 (25.0%)	N/A	N/A
Completed	300	543	92/543 (16.9%)	215/543 (39.6%)	11/543 (2.0%)
Total	458	713	142/713 (19.9%)	N/A	11/713 (1.5%)
Priority review					
Not eligible for review ^a	57	84	24/84 (28.6%)	N/A	N/A
Undergoing review ^b	1	0	0	N/A	N/A
Completed	41	119	21/119(17.6%)	54/119 (45.4%)	1/119 (0.8%)
Total	99	203	45/203 (22.2%)	N/A	1/203 (0.5%)
Accelerated approval					
Not eligible for review ^a	13	20	7/20 (35.0%)	N/A	N/A
Undergoing review ^b	0	0	0	N/A	N/A
Completed	5	31	2/31 (6.5%)	13/31 (41.9%)	0
Total	18	51	9/51(17.6%)	N/A	0
Orphan products					
Not eligible for review ^a	60	74	21/74 (28.4%)	N/A	N/A
Undergoing review ^b	0	0	0	N/A	N/A
Completed	16	31	3/31 (9.7%)	15/31 (48.8%)	1/31 (3.2%)
Total	76	105	24/105 (22.9%)	N/A	1/105 (1.0%)
All drug products					
Not eligible for review ^a	127	133	43/133 (32.3%)	N/A	N/A

Status of scheduled safety summary analyses	Number of products <i>n</i>	Number of label changes <i>n</i>	Number of label changes before 18 months <i>n</i> (%)	Number of label changes before the scheduled safety summary analyses was completed <i>n</i> (%)	Number of label changes triggered by the scheduled safety summary analyses <i>n</i> (%)
Undergoing review ^b	7	8	2/8 (25.0%)	N/A	N/A
Completed	294	519	90/519 (17.3%)	208/519 (40.1%)	9/519 (1.7%)
Total	428	660	135/660 (20.5%)	N/A	9/660 (1.4%)
All therapeutic biologic products					
Not eligible for review ^a	24	29	5/29 (17.2%)	N/A	N/A
Undergoing review ^b	0	0	0	N/A	N/A
Completed	6	24	2/24 (8.3%)	7/24 (29.2%)	2/24 (8.3%)
Total	30	53	7/53 (13.2%)	N/A	2/53 (3.8%)

N/A = not applicable.

^aProducts not eligible for review are those products which had not been used by 10,000 patients.

^bProducts undergoing review are those that met the 18-month and 10,000-patient threshold for which the scheduled safety analysis was underway and not completed as of the April 30,2015 cutoff date.