Optimising Clinical Trial Strategy by Analysing Marketed Drug Adverse Events
Welcome to the EvaluatePharma®
Adverse Events

Adverse events submitted to FDA through the FDA Adverse Event Reporting System (FAERS) can provide critical insight into the emerging adverse event profile of marketed drugs.

Evaluate have collaborated with AdverseEvents, Inc. (AEI) to provide a truly unique service that combines AEI’s high quality FAERS post-approval safety data and proprietary analyses with the power of EvaluatePharma® commercial intelligence and evaluation tools. This resource can be used to understand emerging adverse event trends, conduct comparative safety assessments of drugs through access to statistical severity rankings and the ability to predict future regulatory action. This insight can finally be leveraged in commercial assessments, licensing/M&A, competitive positioning, clinical trial designs and safety monitoring.

Clients can gain competitive advantage with fast and easy access to FAERS post-approval safety data, all integrated within EvaluatePharma® to help manage risk and optimize R&D and commercial performance.
The clients we collaborated with to shape and review this product particularly valued:

- Access to standardized and easy-to-interpret FAERS data
- Timely access to more recent FAERS reported adverse events
- Evaluation tools that help cut through the “noise” and provide actionable insights
- Ability to easily analyse and integrate FAERS data with their own data sources
- Ability to conduct high quality, turn-key safety assessments of companies and products
- Bespoke analytical services for organizations that are resource short

**Key features of this new intelligence include:** A detailed list can be found at the end of this report.

- Standardized, high quality FAERS data with up-to-date reports via Freedom of Information Act (FOIA) requests
- Proprietary scores of relative safety and signals of potential future drug label risks
- Inclusion of adverse event incidence rates per 100,000 patients treated
- Classification of adverse events as ‘on-label’ or ‘non-label’ depending on whether they appear on the current drug label
- Adverse events defined as serious or non-serious and exclusion of disease-related adverse events
- Screen for class effects across multiple drugs from similar groups
- Screen for patient demographics susceptibility to adverse event
- Comparisons by Indication, Pharmacological Class, EphMRA codes
- Company portfolio and product safety profiles for comparative benchmarking
- Custom analytical services performed by credentialed experts

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In this series of case study reports we demonstrate the value of including adverse event analysis in decision making from the viewpoint of three teams supporting different functions within pharmaceutical companies:

- Commercial Insights and Clinical Trial Project teams optimising clinical strategy;
- Business Development & Licensing Teams assessing drug asset opportunities;
- Product Launch Teams developing product positioning.

**Why Adverse Event Analysis is Commercially Important**

The commercial success of a drug is a complex mix of the product’s profile, based on the efficacy, safety/adverse events, pricing and route of administration/dosing versus competitor products, for the target indication. The relative importance of each component is based on a product’s target indication, for example the efficacy of cancer drugs tends to be more important than the adverse event profile, whilst for mass-market primary care products the side effect profile tends to have a higher weighting.

Understanding the adverse event profile, the undesirable effect of taking a product, is therefore a critical part of a product commercial position and ultimate success via:

- Maximising differentiation vs. competition
- Improving success rate of regulatory approval/delay to approval process
- Direct drug cost vs. adverse event cost

**Limitations of Phase III Clinical Trials to Understand Adverse Event Risk**

The understanding of the efficacy and adverse event profile is initially established via phase III clinical trials. Clinical trials are constrained by the fact they are a sample of the target population and are of limited treatment duration. Certain side effects may only appear after long term exposure or may only appear once the drug is marketed in a much broader homogeneous patient population.

The commercial launch of a product in a market does not mean that the understanding of the adverse event profile stops, nor should investors or business development department ignore the inherent risk associated with marketed drugs. It’s worth remembering historically 1 in 20 new drugs are withdrawn within the first 5 years post launch and recent history is littered with costly product withdrawals and litigation. The high profile product withdrawals of the 1990’s (e.g. Wyeth’s Fen-Phen – linked to heart valve damage and Pulmonary Hypertension (PPH), Merck’s withdrawal of VIOXX – linked to increased heart attack and stroke rates, Bayer’s withdrawal of Baycol linked to a fatal-muscle-wasting syndrome) led to a heightened vigilance by FDA.

Analysis of FAERS (FDA Adverse Event Reporting System) is one way to stay ahead in terms of understanding and acting on emerging adverse events of marketed drugs.
Leveraging the FDA Adverse Event Reporting System (FAERS)

Historically, life science industry professionals have lacked convenient and timely access to the FAERS a key set of adverse event data for marketed drug and biologicals. The Adverse Events module within EvaluatePharma®, is the result of a partnership between Evaluate and AdverseEvents, Inc., enabling detailed FDA post-approval drug safety analysis.

Adverse event data has been standardized and integrated with additional commercial intelligence from the EvaluatePharma® platform, to provide in-depth analyses to supporting strategic and operational decisions affected by product safety, such as: clinical trial strategy, commercial launch safety profiling and business development licensing decisions.

The module’s adverse event intelligence is derived from case reports contained within the FAERS database. Until recently, FAERS data has been difficult to access and interpret so that informed actions can be taken. As the FDA has previously stated: “a simple search of FAERS data cannot be performed with these files by persons who are not familiar with creation of relational databases”.† Healthcare stakeholders have needed a tool that provides accessible, actionable, and predictive drug safety measures product adverse events and related medical costs derived from heterogeneous, real-world, patient populations. The objective of the Adverse Events Module within EvaluatePharma® is to deliver data and insights targeted at meeting these needs.

12 Million Adverse Event Reports Standardized to 2,000 Drugs

The FAERS dataset contains more 12 million individual case reports. These have been standardized to “2,000 products in EvaluatePharma®. The integration allows for quick analysis of Adverse Events by pharmacological class/therapy area (EphMRA code), and also allows you to quickly screen for a class effect and for demographic predisposition to the Adverse Events.

Objectivity in Adverse Event and Label Risk

EvaluatePharma® in its analysis of FAERS data seeks to improve the understanding and create actionable insight of ‘Big data’ which is technically already in the public domain. We have treated all drugs equally and there is no opinion in the analysis. In flagging up an adverse event to a drug, based on reporting-odd-ratio (ROR), the number of times a drug exhibits an adverse event versus all other drugs, we have simply applied statistics to public domain data to create actionable data driven insight. In addition, we have created filters to determine whether an adverse event is on the label or related to the disease. We have also leveraged our proprietary number of patients treated to create an incidence per patient.

Case Studies to Get You Started in Using Adverse Event Analysis

Case Study #1 included in this report demonstrates the insights that can be derived from safety data and their associated analyses in support of strategic and operational decision making. It focuses on Drugs Used in Diabetes (EphMRA code A10) and includes available safety data through March 22, 2015. It illustrates how Commercial Insights Teams can assist Clinical Trial Project Teams by providing data and insights that positively impact the strategy and design of study protocols and the development of associated risk mitigation strategies. These analyses can save time and money throughout the product’s R&D cycle.

Case Study #1: Optimising Clinical Trial Strategy by Analysing Marketed Drug Adverse Events

Overview
Profiling on-label adverse events is essentially monitoring what is already known about how a drug reacts in the patient population. However, understanding the evolving non-label adverse event profile of a post-marketed drug provides valuable insight into new adverse event issues not identified in the original clinical trials. The ability to understand and compare the potential safety risks of marketed products with products of either the same pharmacological class or competing target market can be a powerful tool for clinical development teams.

It can allow developers to proactively incorporate enhanced safety monitoring plans and risk mitigation strategies at a much earlier stage in clinical development, aiding regulatory discussions and chances of approval. Development times can also be shortened due to the avoidance of regulatory delays due to safety concerns. Additionally, product positioning against competitor products becomes easier if your product has an improved safety profile.

EvaluatePharma® already has a range of features that can help with trial design and with the addition of adverse events data significantly enhances this capability.

Common questions related to trial design you can easily answer:
- What marketed products are available for this indication?
- When were they approved by the FDA?
- What are the consensus forecasts for these products?
- What adverse events are listed on a particular product’s label?

New questions you can answer with the integration of Adverse Events:
- What is the distribution of serious adverse events attributed to a particular product since it has been on the market?
- What serious adverse events can be identified for a given product, which are not currently on the label?
- For what adverse events does the number of served cases exceed the number of expected cases?
- How can you identify potential future adverse event risks to a product label?

To demonstrate the power of Adverse Events we have outlined two development scenarios:
1. Developing a GLP-1 agonist competitor to Bydureon to ensure the trial design is structured to confirm/deny the standard risk profile;
2. Developing a diabetes product to compete with Bydureon in order to understand the comparative safety profile to improve market positioning and gain market share.

This use case is based on post-marketing safety information and insights, which were previously very difficult and time intensive to obtain due to a lack of accessibility and difficulty in analyzing the FDA Adverse Event Reporting System (FAERS).
Overview of Bydureon

Bydureon (exenatide synthetic) is a glucagon-like peptide-1 (GLP-1) agonist, approved by the FDA on January 27, 2012 for the treatment of diabetes type II (maturity onset). Bydureon was the first extended-release GLP-1 agonist available for this indication following on from the original version of Byetta (exenatide).

Bydureon was part of the Bristol-Myers Squibb/AstraZeneca acquisition of Amylin in 2013. It became fully owned by AstraZeneca in 2014, when the company bought Bristol-Myers Squibb’s share of their joint global diabetes alliance assets for $4.3bn. In 2020, worldwide sales are expected to reach $742m, behind Victoza (liraglutide [rDNA origin]) and Trulicity (dulaglutide) (Table 1).

Sales of Bydureon are forecast to make up 9.0% of worldwide sales for GLP-1 agonists in 2020 and account for 2.7% of AstraZeneca’s total sales in the same year.

Table 1: GLP-1 Agonists, Ranked by Worldwide Forecast Sales in 2020

<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Generic Name</th>
<th>FDA Approval Date</th>
<th>Annual Sales US ($m) 2014</th>
<th>Forecast Sales US ($m) 2020</th>
<th>Annual Sales WW ($m) 2014</th>
<th>Forecast Sales WW ($m) 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Victoza</td>
<td>Novo Nordisk</td>
<td>Liraglutide (rDNA origin)</td>
<td>01/25/2010</td>
<td>1,612</td>
<td>2,390</td>
<td>2,393</td>
<td>3,333</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trulicity</td>
<td>Eli Lilly</td>
<td>Dulaglutide</td>
<td>09/18/2014</td>
<td>10</td>
<td>641</td>
<td>10</td>
<td>1,091</td>
</tr>
<tr>
<td>Bydureon</td>
<td>AstraZeneca</td>
<td>Exenatide synthetic</td>
<td>01/27/2012</td>
<td>374</td>
<td>565</td>
<td>440</td>
<td>742</td>
</tr>
<tr>
<td></td>
<td>Bristol-Myers Squibb</td>
<td></td>
<td></td>
<td>52</td>
<td>-</td>
<td>62</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>426</td>
<td>565</td>
<td>502</td>
<td>742</td>
</tr>
<tr>
<td>Tanzeum</td>
<td>GlaxoSmithKline</td>
<td>Albiglutide</td>
<td>04/15/2014</td>
<td>18</td>
<td>280</td>
<td>10</td>
<td>446</td>
</tr>
<tr>
<td>Byetta</td>
<td>AstraZeneca</td>
<td>Exenatide synthetic</td>
<td>04/28/2005</td>
<td>199</td>
<td>98</td>
<td>327</td>
<td>193</td>
</tr>
<tr>
<td></td>
<td>Bristol-Myers Squibb</td>
<td></td>
<td></td>
<td>34</td>
<td>-</td>
<td>55</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>233</td>
<td>98</td>
<td>382</td>
<td>193</td>
</tr>
</tbody>
</table>

Source: EvaluatePharma® June 2015
Bydureon’s Adverse Events – Overview

Since Bydureon launched in 2012, it has been used to treat approximately 200,000 patients in the USA with diabetes type II. During this time over 15,000 adverse events have been reported to the FDA from 6,065 unique patients, spanning 1,037 types of adverse events, where Bydureon is listed as the primary suspect drug leading to a particular adverse event (Figure 1).

Bydureon’s Adverse Events – Overview

Since Bydureon launched in 2012, it has been used to treat approximately 200,000 patients in the USA with diabetes type II. During this time over 15,000 adverse events have been reported to the FDA from 6,065 unique patients, spanning 1,037 types of adverse events, where Bydureon is listed as the primary suspect drug leading to a particular adverse event (Figure 1).

Adverse events within EvaluatePharma® have been classified in a number of ways to provide previously unavailable insights into Bydureon’s safety profile since it was launched. Importantly for clinicians, these include serious and non-serious related adverse events not originally included on the approval label (Table 2).

### Case Study #1: Optimising Clinical Trial Strategy by Analysing Marketed Drug Adverse Events

![Figure 1: FAERS Report Timeline of Total Adverse Event Counts with Key Regulatory Events](source: EvaluatePharma® June 2015)

Figure 1: FAERS Report Timeline of Total Adverse Event Counts with Key Regulatory Events

Source: EvaluatePharma® June 2015

**Non-disease related versus disease related**
- A total of 15,393 adverse events cases have been reported through FAERS since the Bydureon launch, spanning 1,037 types of adverse events.
- Of the reported adverse events, 5% (750 adverse event cases) have been identified as disease related, spanning eight types of adverse events (including increased blood glucose, increased glycosylated haemoglobin, and hyperglycaemia).
- The remaining 95% (14,643 adverse event cases) have been identified as non-disease related, spanning 1,029 types of adverse events.

**Labeled versus non-labeled adverse events (non-disease related)**
- A total of 38% (5,537 adverse event cases) of non-disease related adverse event cases have been reported through FAERS for a total of 865 types of adverse events which are not on the current label of the drug.
- Of the 5,537 non-labeled adverse events 10% were defined as serious.

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**Table 2: Summary of Adverse Events Reported to FAERS for Bydureon**

<table>
<thead>
<tr>
<th>Adverse Event Status</th>
<th>Types of Adverse Events</th>
<th>Proportion of Adverse Events (%)</th>
<th>Total Primary Suspect Cases</th>
<th>Proportion of Primary Suspect Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Disease Related</td>
<td>1,029</td>
<td>99</td>
<td>14,643</td>
<td>95</td>
</tr>
<tr>
<td>Non-Labeled</td>
<td>865</td>
<td>84</td>
<td>5,537</td>
<td>38</td>
</tr>
<tr>
<td>Non-serious</td>
<td>636</td>
<td>74</td>
<td>5,002</td>
<td>90</td>
</tr>
<tr>
<td>Serious</td>
<td>229</td>
<td>26</td>
<td>535</td>
<td>10</td>
</tr>
<tr>
<td>On-Label</td>
<td>164</td>
<td>16</td>
<td>9,106</td>
<td>62</td>
</tr>
<tr>
<td>Non-serious</td>
<td>122</td>
<td>74</td>
<td>8,697</td>
<td>96</td>
</tr>
<tr>
<td>Serious</td>
<td>42</td>
<td>26</td>
<td>409</td>
<td>4</td>
</tr>
<tr>
<td>Disease Related</td>
<td>8</td>
<td>1</td>
<td>750</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>1,037</td>
<td>15,393</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: EvaluatePharma® June 2015

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1 Number of patients from EvaluatePharma®’s proprietary sales volume price model for 2012-14.
2 Includes adverse events with less than 5 primary suspect cases; excludes counts in Full Report listed as n/a.
**Analysing Bydureon's Adverse Events**

As can be seen from the data above, understanding the evolving adverse event profile of a marketed product as it transitions from clinical trial to being used in the general population can provide valuable insights for an R&D team with a comparator product. Additionally, an assessment can be made of the factors which influence prescribing behaviors, patient adherence and continuation of treatment, which can also be used to gain competitive advantage for drugs in development. Below we describe how this data can be applied by R&D teams.

**On-Label Adverse Events**

<table>
<thead>
<tr>
<th>Rank</th>
<th>Label Status</th>
<th>Seriousness</th>
<th>Adverse Event</th>
<th>Total Primary Suspect Cases</th>
<th>Proportion of Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>On-label</td>
<td>Non-serious</td>
<td>Injection site nodule</td>
<td>1,044</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>On-label</td>
<td>Non-serious</td>
<td>Injection site haemorrhage</td>
<td>786</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>On-label</td>
<td>Non-serious</td>
<td>Injection site pain</td>
<td>713</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>On-label</td>
<td>Non-serious</td>
<td>Nausea</td>
<td>631</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>Non-label</td>
<td>Non-serious</td>
<td>Weight decreased</td>
<td>596</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>On-label</td>
<td>Non-serious</td>
<td>Injection site pruritus</td>
<td>518</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>On-label</td>
<td>Non-serious</td>
<td>Injection site swelling</td>
<td>430</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>On-label</td>
<td>Non-serious</td>
<td>Injection site mass</td>
<td>397</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>Non-label</td>
<td>Non-serious</td>
<td>Product quality issue</td>
<td>326</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>On-label</td>
<td>Non-serious</td>
<td>Injection site erythema</td>
<td>307</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>On-label</td>
<td>Non-serious</td>
<td>Injection site extravasation</td>
<td>296</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>On-label</td>
<td>Non-serious</td>
<td>Diarrhoea</td>
<td>277</td>
<td>2</td>
</tr>
<tr>
<td>13</td>
<td>On-label</td>
<td>Non-serious</td>
<td>Vomiting</td>
<td>276</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>On-label</td>
<td>Non-serious</td>
<td>Decreased appetite</td>
<td>273</td>
<td>2</td>
</tr>
<tr>
<td>15</td>
<td>Non-label</td>
<td>Non-serious</td>
<td>Underdose</td>
<td>258</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>15,393</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Summary of Key Findings**

- Comparison with post-marketed FAERS data shows that the most common adverse events (nausea, diarrhea, headache, vomiting, constipation, injection site pruritus, injection-site nodule and dyspepsia) identified in clinical trials all appeared within the twenty-five most commonly reported adverse events for Bydureon.
- The most common post-marketing adverse events, based on the number of primary suspect cases, are multiple injection site issues, nausea, diarrhea and vomiting (Table 3).
- Injection site nodule was the most common adverse event for Bydureon, accounting for 7% of all primary suspect cases reported to the FDA. It was also the most prevalent non-serious, on-label adverse event totaling 52% of the all non-serious, on-label adverse events reported through FAERS for Bydureon (Figure 2b).
- Despite a Boxed Warning for the Risk of Thyroid C-Cell Tumors for Bydureon, no reported cases of medullary thyroid carcinoma have been reported through FAERS. However, there have been eight reports of thyroid cancer post launch.
- Of all the Warnings and Precautions on the label, the most prevalent serious post-marketing adverse events have been: pancreatitis, injection-site reactions and renal impairment, which account for 39%, 15% and 2% of Bydureon’s serious adverse events respectively (Figure 2a).

**Conclusions**

The issues with injection site reaction for Bydureon are consistent with the known properties of poly (D,L-lactide co-glycolide) polymer microsphere formulations used to encapsulate Bydureon. As such, R&D teams developing rival products have an opportunity to remove the need for reconstitution before administration and/or alternative formulations to reduce antibody formation at the injection site and/or revise delivery method.

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1 Calculations based on pancreatitis primary suspect cases as a percentage of all adverse event primary suspect cases for serious adverse events currently on the label.
2 Calculations based on injection site reactions suspect cases as a percentage of all adverse event primary suspect cases for non-serious adverse events currently on the label.
Case Study #1: Optimising Clinical Trial Strategy by Analysing Marketed Drug Adverse Events

(a) Serious On-Label Adverse Events
- Pancreatitis (157, 39%)
- Injection site abscess (29.7%)
- Pancreatitis acute (27, 7%)
- Renal failure acute (26, 6%)
- Angioedema (25, 6%)
- Injection site cellulitis (20, 5%)
- Anaphylactic reaction (16, 4%)
- Renal failure (13, 3%)
- Injection site infection (12, 3%)
- Renal impairment (9, 2%)
- Other (75, 18%)

(b) Non-Serious Adverse Events
- Injection site nodule (1044, 12%)
- Injection site haemorrhage (786, 9%)
- Injection site pain (713, 8%)
- Nausea (631, 7%)
- Injection site pruritus (518, 6%)
- Injection site swelling (430, 5%)
- Injection site mass (397, 5%)
- Injection site extravasation (296, 3%)
- Diarrhoea (277, 3%)
- Other (3298, 38%)

Figure 2: Percentage Distribution of Adverse Events for Bydureon

Non-Label Adverse Events

Actionable Information from non-label adverse events to support Clinical Trials
- The most commonly reported adverse event is a decrease in weight.
- The most commonly reported serious adverse events are impaired gastric emptying and pancreatic carcinoma.
- To date, three cardiac events appear in the most common serious adverse events reported for Bydureon – although they do not exceed the number of expected cases.

Summary of Key Findings
- The most commonly reported serious, non-label, adverse events are impaired gastric emptying and pancreatic carcinoma the most commonly reported serious, non-label adverse events (Figure 3a).
- The top ten most common reported serious adverse events includes three types of cardiac events (atrial fibrillation, myocardial infarction and cardiac failure congestive) although they do not exceed the number of expected cases.
- The main non-serious, non-label adverse event reported is decreased weight. The non-serious, non-label adverse events that are also worth noting are method of administration, including underdose, drug administration errors and incorrect dose administered (Figure 3b).

Conclusions
The observed weight loss (linked to reduced gastric emptying and appetite suppression) is consistent with clinical trials findings. This is important as diabetes type II is invariably associated with obesity and prior to GLP-1 agonists, a majority of existing anti-diabetic agents including insulin, sulfonylureas and thiazolidinedione’s are associated with weight gain.
Case Study #1: Optimising Clinical Trial Strategy by Analysing Marketed Drug Adverse Events

Figure 3: Top 10 Non-Label Adverse Events for Bydureon by the Number of Primary Suspect Cases

Source: EvaluatePharma® June 2015
Analyzing an Adverse Events Reporting Odds Ratio (ROR) to Establish Bydureon’s Relative Risk vs. Other Drugs

In the previous section we identified the most common non-label adverse events reported for Bydureon, while this is valuable insight for an R&D team this information alone doesn’t provide the answer to the question: “Does the number of observed cases exceed the number of expected cases?”.

The need to put reported non-label adverse event into context can be answered in EvaluatePharma® by using the Reporting Odds Ratio (ROR).

ROR is a disproportionality measure identifying drug-associated adverse events which are reported more frequently than would be expected.

The ROR is the ratio of the odds of reporting one specific event versus all other events for a given drug – this is then compared to the reporting odds for all other drugs present in the adverse event dataset (where this is used as a proxy for the background occurrence of adverse events).

An ROR score of >1.0 indicates there is a higher than normal reporting rate for a given adverse event. While there is no widely accepted benchmark regarding the numerical level at which disproportionality analysis yields a “safety signal,” many in the drug industry assume that results above 2.0 warrant attention.

Summary of Key Findings

- An elevated disproportionality results for pancreatic carcinoma and impaired gastric emptying, where the number of observed cases exceeded the number of expected cases (Table 4a).
- A total of seven of the top 10 previously identified commonly occurring non-serious, non-label adverse events exceed the number of expected cases (Table 4b).
- The issues with dosing were particularly disproportionate to other non-serious adverse events (Figure 4).
- Of the serious non-label adverse events Bydureon showed elevated disproportionality results for pancreatic mass, impaired gastric emptying, pancreatic carcinoma and cardiac flutter (Figure 4).

Table 4: Top 10 Non-Label Adverse Events for Bydureon by the Number of Primary Suspect Cases with ROR values

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>ROR</th>
<th>Total Primary Suspect Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic carcinoma</td>
<td>5.01</td>
<td>28</td>
</tr>
<tr>
<td>Impaired gastric emptying</td>
<td>11.77</td>
<td>28</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>1.14</td>
<td>21</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.46</td>
<td>17</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0.16</td>
<td>16</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.12</td>
<td>15</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>0.25</td>
<td>15</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>0.11</td>
<td>10</td>
</tr>
<tr>
<td>Cardiac failure congestive</td>
<td>0.19</td>
<td>9</td>
</tr>
<tr>
<td>Aphagia</td>
<td>1.45</td>
<td>8</td>
</tr>
</tbody>
</table>

(a) Serious Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>ROR</th>
<th>Total Primary Suspect Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight decreased</td>
<td>7.52</td>
<td>596</td>
</tr>
<tr>
<td>Product quality issue</td>
<td>4.22</td>
<td>326</td>
</tr>
<tr>
<td>Underdose</td>
<td>39.99</td>
<td>258</td>
</tr>
<tr>
<td>Drug dose omission</td>
<td>4.85</td>
<td>225</td>
</tr>
<tr>
<td>Off label use</td>
<td>3.95</td>
<td>207</td>
</tr>
<tr>
<td>Drug ineffective</td>
<td>0.64</td>
<td>193</td>
</tr>
<tr>
<td>Weight increased</td>
<td>1.04</td>
<td>80</td>
</tr>
<tr>
<td>Malaise</td>
<td>0.6</td>
<td>79</td>
</tr>
<tr>
<td>Drug administration error</td>
<td>2.91</td>
<td>77</td>
</tr>
<tr>
<td>Incorrect dose administered</td>
<td>2.24</td>
<td>73</td>
</tr>
</tbody>
</table>

(b) Non-Serious Adverse Events

Source: EvaluatePharma® June 2015
Conclusions

Compared to all other drugs in the database, injection site cellulitis was reported 27.50 times more frequently for Bydureon. This data supports the FDA actions in May 2014 to approve new warnings to be added to the label for Bydureon about the risk of abscesses, cellulitis and necrosis reported at injection sites.

Figure 4: Top 10 Serious Adverse Events for Bydureon, by ROR

Source: EvaluatePharma® June 2015
Using the RxSignal® to Warn of Risk to Label

So far we have identified a number of serious and non-serious, non-label adverse events and placed their occurrence in context. However, it would be more useful for development teams to identify post-marketing adverse events that could lead to an FDA safety alert well in advance of any regulatory action.

In this section we demonstrate how proprietary RxSignal® analytics integrated into EvaluatePharma® can be used to predict a potential label risk from an adverse event, currently not on the label, showing increased reporting rates. The RxSignal® uses the value of the ROR to predict future FDA action. The RxSignal® status can be ‘Active’ or ‘Watchlist’ depending on the value of ROR.

Summary of Key Findings

- Pancreatic carcinoma identified as the only RxSignal® with an elevated ROR value of 5.01.
- Watchlist RxSignal®’s for Cholelithiasis and generalized rash.

Active RxSignal® inclusion criteria:
- Must not appear on the product’s most recent label.
- Is not related to the disease being treated.
- Has at least five primary suspect case reports for the product being reviewed.
- Has a ROR value of 2.0 or greater.
- Is on the list of adverse events previously subject to regulatory action (RxSignal® eligible event).

Watchlist RxSignal® inclusion criteria:
- Has the same requirements listed above, but with a ROR value of between 1.0 and 2.0.

Table 5: Bydureon: RxSignals®

<table>
<thead>
<tr>
<th>Signal</th>
<th>Adverse Event</th>
<th>ROR</th>
<th>Primary Suspect Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td>Pancreatic carcinoma</td>
<td>5.01</td>
<td>28</td>
</tr>
<tr>
<td>Watchlist</td>
<td>Cholelithiasis</td>
<td>1.06</td>
<td>20</td>
</tr>
<tr>
<td>Watchlist</td>
<td>Rash generalised</td>
<td>1.01</td>
<td>18</td>
</tr>
</tbody>
</table>

Summary and Official Position on Incretin Adverse Events

While our analysis has identified a number of interesting points for R&D teams, in February 2014, the FDA and EMA jointly published an article in the New England Journal of Medicine which concluded that the current data do not support the potential risk of pancreatic cancer with incretin therapy and that, as reiterated in liraglutide’s weight management briefing document published in September 2014, “the current labeling is appropriate for what is currently known about risks of pancreatic disease, including pancreatic cancer for which no signal has been identified.”

Since the FDA and EMA have not reached a final conclusion regarding a causal relationship - systematic capture of data on pancreatitis and pancreatic cancer from ongoing clinical trials will contribute to further knowledge about these risks in future investigations.

In Summary

Pre-marketing clinical trials are the established means for determining a drug’s safety and efficacy during the approval process, but they are by no means perfect. When a new drug comes to market a more heterogeneous population uses it and, accordingly, real-world side effects begin to appear.

Accordingly, R&D teams need accessible and actionable adverse event data that reflect a given medications effects in the population at large that require these types of medications.

By definition, none of the above RxSignals® are currently listed on the product label and are not associated with Bydureon from a safety perspective as defined by the FDA. However, the RxSignal® can be used to determine where future regulatory safety alerts or label changes for a product may be anticipated.

As such, we believe clinical development protocols and the operational process can be enhanced by integrating this type of analysis into safety monitoring plans and risk mitigation strategies, supporting a competitive advantage leading to clinical trial cost reduction and time savings.

Disclaimers

Data, disproportionality measures, and RxSignal®’s change over time as a result of new case report procurement. As a result, the data you see in this report might not reflect the latest update.

In general, post-marketing data may be subject to biases such as underreporting, stimulated reporting, and confounding by comorbidities. An adverse event report does not definitively ascertain causality.

The incretins (i.e., GLP-1 and glucose-dependent insulinotropic polypeptide) are intestinal hormones that regulate the postprandial production of insulin and glucagon by the pancreas.
Key Features

EvaluatePharma® Adverse Events Module

**FDA Adverse Event Reporting System (FAERS) Data:** High quality, standardized post-marketed adverse event data from FAERS for ~2,000 drugs updated on a monthly basis with access to exclusive proprietary data via Freedom of Information Act (FOIA) requests.

**RxSignal**: Proprietary signal used to predict if the FDA are likely to issue a post-marketed safety alert on a drug in the future.

**RxScore**: Relative 1 to 100 drug safety ranking system based entirely on the amount of post-marketing downstream costs of the serious adverse events and outcomes associated with a drug, to understand the relative position of a product vs. its competitors.

**Incidence per 100,000**: Estimate of incidence of adverse events occurring for 100,000 patients using the drug in the USA.

**Reporting Odds Ratio (ROR)**: Estimate the relative reporting frequency of an adverse event associated with the use of specific drug to identify drug-associated adverse events that are reported more frequently than expected.

**Label Reviewed**: For each post-marketed drug, labels are reviewed to state whether the adverse event is currently on the label.

**Patient Demographics**: Average age, treatment duration in days, % male, % female for patients experiencing an adverse event reported to the FDA.

**Label Risk**: Identification of adverse events which are not currently on the drug label but are predicted to be the cause for FDA action in the future.

**Screen for Class Effects**: Analyse the adverse event data at the level of EphMRA code to determine if an adverse event is occurring across all drugs in a class.

**Population Screen**: Analyse the adverse event profile for all drugs for a particular indication to understand how susceptible these patients are to individual adverse events.

**On-Label Analyses**: In-depth analysis of the emerging adverse event profile of a drug (serious and non-serious) limited to adverse events which are currently on the drug label.

**Non-Label AE Analyses**: In-depth analysis of the emerging adverse event profile of a drug (serious and non-serious) limited to adverse events which are not currently on the drug label.

**Drug Profile**: In-depth analysis of the adverse event profile for a post-marketed drug including on-label versus non-label and serious versus non-serious adverse events and potential risks to the drug label.

**Company Profile**: Comparison of a company’s US post-marketed products.

**Safety Alerts**: E-mail alerts that can be customized by the user.
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**AdverseEvents, Inc.** is a California-based healthcare informatics company that improves patient safety and reduces systemic healthcare costs through the comprehensive analysis of post-marketing drug side effect data. Utilizing data-mining and analysis technology, through its proprietary RxSuite™ of analytics, AEI makes post-marketing drug safety data accessible, actionable, and predictable. For more information please visit:

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