Evaluating adverse events from patient support and market research programs: proposed best practices and regulatory changes

2nd Adverse Event Reporting and Safety Strategies Summit
December 8-9, 2015

Bruce A. Donzanti, PhD.
Sr. Group Director
Regulatory Pharmacovigilance Policy
General Questions

- How should safety data be assessed from solicited programs?
- To what extent does safety data from such sources contribute to the risk profile of a product?

Where do we start?........

Current regulations and guidances
FDA AE reporting regulations do not specify requirements for reporting from solicited sources like patient support programs (PSPs)

Two older guidances:

Clarification Guidance Section III. Individual Case Reports Based on Solicited Information (1997)

“……information concerning potential adverse experiences derived during planned contacts and active solicitation of information from patients (e.g., company sponsored patient support programs, disease management programs) should be handled as safety information obtained from a postmarketing study.”

“……should not report safety information through these types of patient contacts unless the adverse event meets the regulatory definitions of serious and unexpected and there is a reasonable possibility that the drug or biological product caused the adverse experience.”

Draft Guidance Section VI.b. Postmarketing, Clinical Trial, or Surveillance Studies (2001)

“For purposes of safety reporting, reports of suspected adverse experiences obtained from a company sponsored PSP and disease management programs should be handled as if they were study reports and not as spontaneous reports.”
VI.B.1.2. Solicited reports

As defined in ICH-E2D* (see GVP Annex IV), solicited reports of suspected adverse reactions are those derived from organised data collection systems, which include clinical trials, non-interventional studies, registries, post-approval named patient use programmes, other patient support and disease management programmes, surveys of patients or healthcare providers, compassionate use or name patient use, or information gathering on efficacy or patient compliance. Reports of suspected adverse reactions obtained from any of these data collection systems should not be considered spontaneous.

VI.C.2.2.11. Reports from patient support programmes and market research programmes

A patient support programme is an organised system where a marketing authorisation holder receives and collects information relating to the use of its medicinal products. Examples are post-authorisation patient support and disease management programmes, surveys of patients and healthcare providers, information gathering on patient compliance, or compensation/re-imbursement schemes.

A market research programme refers to the systematic collection, recording and analysis by a marketing authorisation holder of data and findings about its medicinal products, relevant for marketing and business development.

Safety reports originating from those programmes should be considered as solicited reports. Marketing authorisation holders should have the same mechanisms in place as for all other solicited reports (see VI.C.2.2.2.) to manage that information and report valid cases of adverse reactions, which are suspected to be related to the concerned medicinal product.

*ICH-E2D: POST-APPROVAL SAFETY DATA MANAGEMENT: DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING (Step 4 Nov 2003)
View on solicited information

“The quality of solicited cases is very low and they should not be put into the same category spontaneous reports regarding information content and potential usefulness. Doing so only floods the system with noise. The chances of learning something important and new from such sources is small, especially given the difficulty of obtaining detailed medical information. These considerations are important in trying to decide on the proper level of attention and regulatory reporting such as reports should receive.”

Concept of Incidental Event

“An incidental event, adverse or otherwise, is one that satisfies the following criteria: although it occurs in reasonable clinical temporal association with the use of a drug product, it is not the intended subject of a spontaneous report (i.e., it did not prompt the contact with the pharmaceutical company or the regulator) and there is no implicit or explicit expression of possible drug causality by the reporter, other parties cited in the medical record or the company’s safety review staff.”

“And reporting such events most likely detracts from the efficiency of a spontaneous reporting system to generate important signals by adding to the already significant background “noise.”

Incidental Events from solicited programs

“……they are usually obtained incidentally to the main purpose of the program.”

“Had the company, its agent, or other party not taken the initiative to contact these people or to solicit their communication for purposes other than safety reporting, the event would mostly likely not have been the subject of independent voluntary to the Healthcare provider or directly to the company.”

“A rational approach to handling solicited reports without compromising patient safety is outlined below:……

➢ suspected serious, unexpected ADRs should be regarded in the same way as they would be for a clinical trial; thus, for purposes of regulatory postmarketing drug safety reporting on an expedited basis, a causality assessment should be conducted by the manufacturer (currently adopted by US FDA)

Council for International Organizations of Medical Sciences (CIOMS)
Other than MAH PV-specific inspections ……………

- EMA Patients’ and Consumers’ Working Party Meeting (June 2013)

European Federation of Pharmaceutical Industries and Associations (EFPIA)
Should the same reporting rules apply to all solicited program types (e.g., reimbursement PSP vs. compliance & persistency PSP vs. qualitative or quantitative MRPs)?

Should all solicited programs by default be considered organized data collection systems?

Should all solicited programs be considered equal with regard to the risk level for potentially being a source of valuable safety information?

Does the CIOMS concept of incidental events play a role in data obtained via solicited programs?

What value does assessing all information from such programs bring to the safety profile of a product?
How Solicited Safety Information Stacks Up By……

**AE Source**
- **PSP**: 45%
- **Market Research**: 9%
- **Spontaneous**: 40%
- **NIS**: 6%
- **Qual MR**: 1%
- **Quant MR**: 8%

**Program Volume**
- **Total # Programs**: >1,400
  (1997 to Aug 2015)
- **PSP**: 4%
- **Market Research**: 96%

**Interactions**
- **Total # Interactions**: >1.1M
  (Source Data Quality Check Program Q1Y13 to Q1Y15)
- **PSP**: 85%
- **Quant MR**: 15%
- **Qual MR**: 0.27%

**Total Cases** = 168,587
(Q3Y13 to Q2Y15)
Risk Analysis: AEs vs. Interactions by Program Type

Number of AE's vs. Number of Interactions

- Patient Support Programs
- Quantitative Market Research
- Qualitative Market Research

Number of AE's
- 0
- 5000
- 10000
- 15000
- 20000
- 25000
- 30000

Number of Interactions
- 0
- 100,000
- 200,000
- 300,000
- 400,000
- 500,000
- 600,000
- 700,000
- 800,000
- 900,000
- 1,000,000
Serious vs. Non-serious Adverse Events by Source

Chi-Square Test: Proportions are significantly different (p-value<0.0001)
Follow-Up Response Rate by Source

Chi-Square Test: Proportions are significantly different (p-value<0.0001)
Completeness of Patient Demographic Information: MedWatch Forms

Completeness of Patient Demographic Information: PSPs

Data Source:
Global Safety Database 1 July 2013 to 30 June 2015
Completeness of Patient Demographic Information: MRP Quantitative

Data Source:
Global Safety Database 1 July 2013 to 30 June 2015
Completeness of Patient Demographic Information: MRP Qualitative

Data Source:
Global Safety Database 1 July 2013 to 30 June 2015
Completeness of Patient Demographic Information:

- FDA MedWatch system > PSP > MRP (qual) > MRP (quan)

Data Sources:
Completeness of Patient History Information: PSPs

Data Source:
Global Safety Database 1 July 2013 to 30 June 2015
Completeness of Patient History Information: MRP Quantitative

Data Source:
Global Safety Database 1 July 2013 to 30 June 2015
Completeness of Patient History Information: MRP Qualitative

Data Source:
Global Safety database 1 July 2013 to 30 June 2015
Completeness of Patient History Information

- Completeness of patient history information: PSP > MRP(qual) > MRP (quan)

Data Source:
Global Safety Database 1 July 2013 to 30 June 2015
Impact of AEs from a Solicited Program on Benefit-Risk Profiles

Retrospective Review
(from 24-May-2011 to 23-May-2013)

- 34 products
- Reviewed over 1.2M source documents with over 4M pages
- Confirmed 19,570 AE cases
  - 3,265 Serious AE Cases (17%)
  - 16,305 Non-Serious AE Cases (83%)

Prospective Review
(from 24-May-2013 to 28-Nov-2014)

- 37 products
- Reviewed over 970K source documents
  (On average, 4 pages per document reviewed. Pages per document range from 1-100 pages)
- Confirmed 19,405 AE cases
  - 6,092 Serious AE Cases (31%)
  - 13,313 Non-Serious AE Cases (69%)

No change in benefit-risk profiles to date
Distribution and Serious Cases by Product Age

**Distribution of Cases**

- **0 - 2** (3 Retro, 1 Prosp): 1% (0%), 0%
- **>2 - 5** (1 Retro, 4 Prosp): 1% (5%)
- **>5 - 10** (4 Retro, 1 Prosp): 42% (31%)
- **>10** (26 Retro, 31 Prosp): 56% (64%)

**Product Age**

- **% of Cases**
  - 0% - 20%
  - 20% - 40%
  - 40% - 60%
  - 60% - 80%

**Serious Cases**

- **0 - 2** (3 Retro, 1 Prosp): 0% (0%)
- **>2 - 5** (1 Retro, 4 Prosp): 1% (5%)
- **>5 - 10** (4 Retro, 1 Prosp): 59% (28%)
- **>10** (26 Retro, 31 Prosp): 39% (39%)

**Product Age**

- **% Seriousness**
  - 0% - 20%
  - 20% - 40%
  - 40% - 60%
  - 60% - 80%
A Risk-Based Approach to Solicited Program Management

Risks are categorized in two primary ways

**Vendor Level Risks**
- Vendor level risks are focused on the adequacy of internal controls to identify, capture, and report adverse events.
- Assessment of the design and effectiveness of a vendor’s:
  - Quality System
  - Standard operating procedures (SOPs)
  - Governance and communications

**Program Level Risks**
- Program level risks are focused on the “type” of program.
- Program-level risk factors:
  - Patient Support Programs (PSPs)
  - Quantitative Market Research (Qualitative Market Research Programs Lower Risk)
- Other risk factors:
  - Volume of Interactions
  - Duration of Programs
### Value of Safety Information received from diverse programs

**Derived from efpi ‘Patient Support Programmes’ presentation at EMA Industry Forum - 12 June 2015**

<table>
<thead>
<tr>
<th>Characteristics of a LOW Value Programme</th>
<th>Characteristics of a HIGH Value Programme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examples of interactions</td>
<td>Quality of safety information received</td>
</tr>
<tr>
<td>- Large patient population</td>
<td>- Orphan drug</td>
</tr>
<tr>
<td>- Unintentional Interaction</td>
<td>- Intentional Interaction</td>
</tr>
<tr>
<td>- Single interaction</td>
<td>- Multiple interactions</td>
</tr>
<tr>
<td>- No HCP Involved</td>
<td>- HCP Involved</td>
</tr>
<tr>
<td>- Safety naïve reporter</td>
<td>- Informed / knowledgeable reporter</td>
</tr>
<tr>
<td>- No follow up likely</td>
<td>- Follow Up Possible</td>
</tr>
<tr>
<td>- Established product</td>
<td>- Product launched &lt; 3 years</td>
</tr>
<tr>
<td>- Single safety data point</td>
<td>- Safety data over time</td>
</tr>
<tr>
<td>- Limited safety info</td>
<td>- Data possible across safety spectrum</td>
</tr>
<tr>
<td>- No medical/clinical or safety purpose</td>
<td>- Programme associated with RMP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality of safety information received</th>
<th>Usefulness of safety information received</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of safety information received</td>
<td>Usefulness of safety information received</td>
</tr>
</tbody>
</table>

**Value of Safety Information**

- Large patient population
- Unintentional interaction
- Single interaction
- No HCP involved
- Safety naïve reporter
- No follow up likely
- Established product
- Single safety data point
- Limited safety info
- No medical/clinical or safety purpose

**Outgoing reminders/mailers**

- Delivery services
- Interactive websites
- Call centres
- Education & training
- Patient support interviews
- Face-to-face HCP visit

**Characteristics of a LOW Value Programme**

- Orphan drug
- Intentional interaction
- Multiple interactions
- HCP involved
- Informed / knowledgeable reporter
- Follow Up Possible
- Product launched < 3 years
- Safety data over time
- Data possible across safety spectrum
- Programme associated with RMP
Conclusions

• Not all solicited programs contain the same risk level for identification of valid adverse events

• The CIOMS concept of incidental events appears to play a very valid role in certain types of solicited programs

• To date, no changes in the benefit-risk profiles of any Genentech/Roche products have been attributed to information assessed from solicited programs, including those products approved within the past few years.

**Question still remains:** Do all solicited programs require the same level of scrutiny with regard to AE assessment as clinical study and spontaneous reports?
Genentech
A Member of the Roche Group