Measuring Time from Identification of a New Risk to Regulatory Action: Focus on Signaling Tools and Processes

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Disclaimer: The information within this presentation is based on the experience of Biogen Safety and Benefit Risk Management (SABR), and represents the views of the presenter for the purposes of this workshop

Time from Identification of a New Risk to Regulatory Action

Speed (Time) ≠ Quality

- Speed & quality of results need to be balanced
- Faster time may not increase impact of regulatory actions if quality of data or communicatio is poor
- Quantity may not add to the benefit/risk assessment

Communication to Prescribers & Patients

- Quality of data/ communications is critical for giving prescribers ability to make informed decisions
- Collecting & Analysing data take time
- Lessons are learned by all parties as more data is generated and reviewed. Process is iterative

Both time & quality need to be considered when measuring the impact of PV processes

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Example Time & Quality Components: Tysabri & PML

2005:3 PML Cases, off market

2006: Returned to marketed; Educational Programs / Restricted access in some regions

CDS provided rate of risk as **3 cases 1/1,000 treated patients (95% CI: 0.2-2.8)**

2010: PML Database; Data Quality Improvements as more data received

Dec 2010 Three Risk Factors :

- *Time on treatment*
- *Prior Immunosuppression*
- *Presence of Anti-JCV Antibodies*

2016: Algorithm updated in EU and refined to provide further guidance on risk factors

2008: ~5 PML cases

2009: ~20 PML cases

2012: Risk Algorithm available that characterizes risks for prescribers

Biogen Data Collection Ongoing

Tysabri & PML

Balance Between Speed & Quality

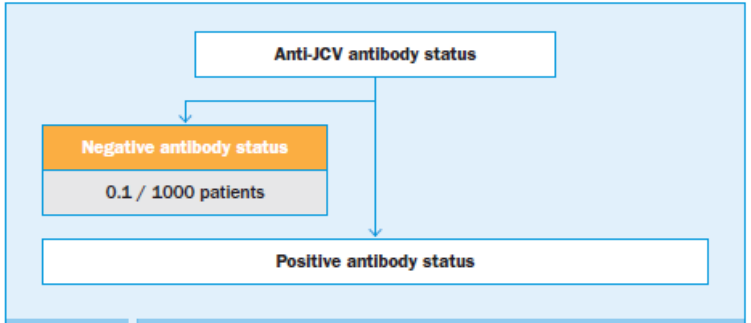
2006 ***Initial Labeling Text***

3 cases 1/1,000 treated patients
(95% CI: 0.2-2.8)

- 10 year process of reviewing data as received
- As data collected, applied learnings to improve data collection and analysis
- Data quality improved with Education of prescribers, patients, etc.
- Different types of data required with multiple experts reviewing
- Multiple reviews and discussions with Regulators globally

2016

Figure 1: PML risk estimates algorithm



Natalizumab exposure	PML risk estimates per 1000 patients				
	Patients without prior IS use				Patients with prior IS use
	No index value	Antibody index ≤ 0.9	Antibody index > 0.9 ≤ 1.5	Antibody index > 1.5	
1-12 months	0.1	0.1	0.1	0.2	0.3
13-24 months	0.6	0.1	0.3	0.9	0.4
25-36 months	2	0.2	0.8	3	4
37-48 months	4	0.4	2	7	8
49-60 months	5	0.5	2	8	8
61-72 months	6	0.6	3	10	6

PML risk estimates in anti-JCV antibody positive patients were derived using life table method based on the pooled cohort of 21,696 patients who participated in the STRATIFY-2, TOP, TYGRIS, and STRATA clinical studies. Further stratification of PML risk by anti-JCV antibody index interval for patients with no prior use of IS were derived from combining the overall yearly risk with the antibody index distribution.

PML risk estimates in anti-JCV antibody positive patients with prior IS exposure are based on TYSABRI clinical data where prior IS use comprised the following IS therapies: mitoxantrone, methotrexate, azathioprine, cyclophosphamide and mycophenolate mofetil. The risk of PML in anti-JCV antibody-negative patients were estimated based on post-marketing data from approximately 125,000 TYSABRI -exposed patients.

Physician Information & Management Guidelines

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Safety Data Evaluation & Signal Identification

Challenges for Signal Detection

- Assessment of initial cases limited
- Quality of post-marketing data is often poor
- Significant efforts collecting data that may not be meaningful
- Decision making based on medical judgment

Possible Solutions

- Focus on most meaningful data and rely on experience to improve data quality
- Use Statistical and Visualization tools to improve efficiency and exclude noise
- Use technology to support data collection and analysis
- Clarify roles / responsibilities regarding decision making

Desired Impact:

- Faster signal detection leads to faster risk assessment
- Improved quality of safety data increases speed and accuracy
- Processes support clear decisions making & medical judgment

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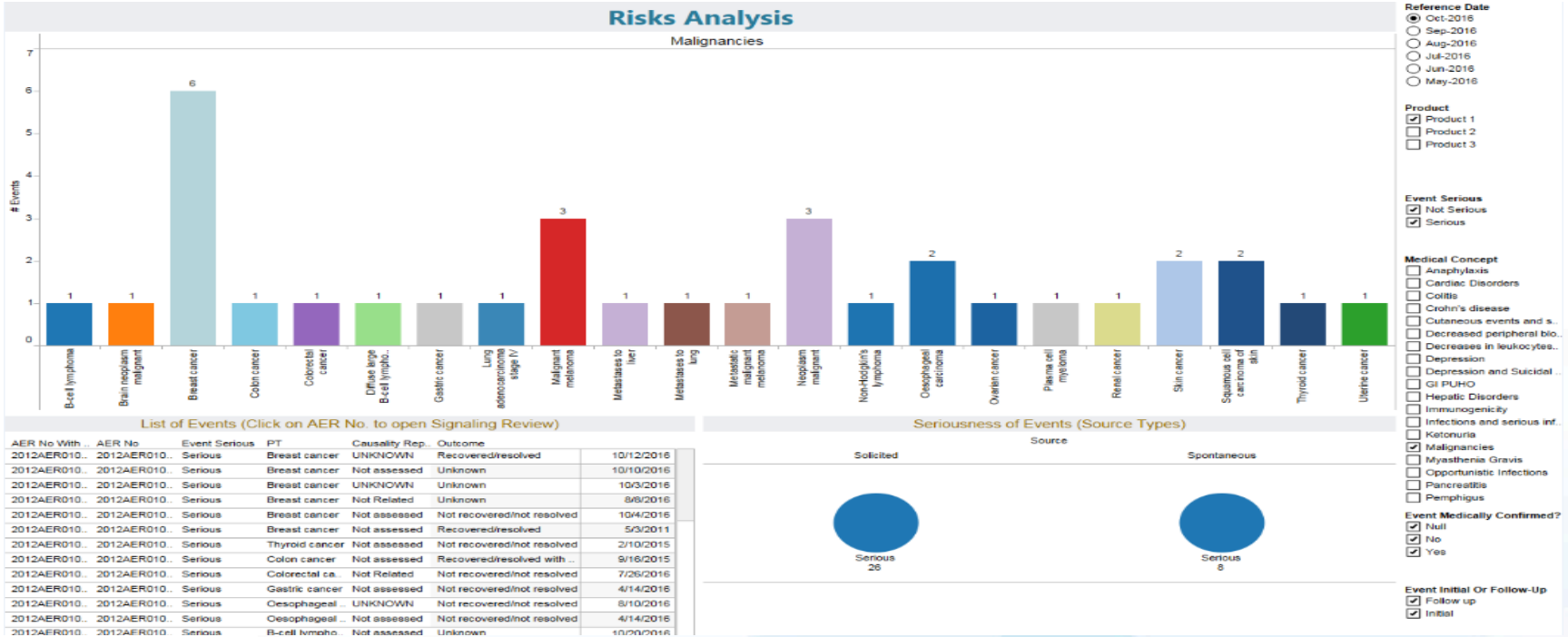
Stage 1: Examples of Tools

Visualizations: Providing easier ways to quickly identify trends and rule out noise



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Example: Risk assessment with Tableau

Risk Assessment & Recommendations for Action

- Risk assessment to determine actions as quickly as possible
- High quality of data essential for accurate medical judgment
- Often risk assessment is performed on minimal data, therefore initial assessments may be limited
- Alternate data sources and analyses provide further understanding of risk – including epidemiology, study data, statistical approaches
- Processes need to be simple and clear on decision making
- Ideal to complete one assessment for all regions, differences in requirements can delay or impede assessments

Lessons Learned

Data collection quality improved over time, as MAH, HCPs and Regulators learn from experience and educational outreach. More HCP training may be beneficial

Explore many sources of data, such as laboratory data, epidemiology, clinical studies, large data collection systems (i.e., claims data) may improve quality and reduce time

Technology supporting data collection & analysis, such as visualizations, statistics, etc. may reduce detection and analysis time

Medical judgment is always required. Clear processes for decision making, including roles / responsibilities, and appropriate expertise, not just clinical, but also public health are critical

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