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Analysis of Time to FDA MedWatch Safety Alert for Therapeutic Monoclonal Antibodies

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What is FDA MedWatch alert?



MedWatch is the FDA Safety Information and Adverse Event Reporting Program established for the following purposes:

- To **collect** clinically important safety information after marketing approval. According to the collected information the FDA **issue safety alerts, i.e. important safety warnings to health care professionals, consumers, drug manufactures.**
- The FDA issues an alert
 - for known adverse reaction if this is reported more frequently and/or is more severe,
 - for previously unknown reaction or
 - if new important information related to safety is revealed

How such an alert looks like?

Example: Avastin® (bevacizumab) - used for treatment of several types of cancer which was approved for market on February 26, 2004

Avastin (bevacizumab) Aug 2004

Audience: Oncologists and other healthcare providers

FDA and Genentech, Inc. issued an important drug warning to healthcare providers that there is evidence of an increased risk of serious arterial thromboembolic events, including cerebrovascular accident, myocardial infarctions, transient ischemic attacks, and angina related to Avastin. The risk of fatal arterial thrombotic events is also increased. In randomized, active-controlled studies conducted in patients with metastatic colorectal cancer, the risks of a serious arterial thrombotic event was approximately two-fold higher in patients receiving infusional 5-FU based chemotherapy plus Avastin, with an estimated overall rate of up to 5%. A revised Avastin package insert containing more detailed information on arterial thromboembolic events is in development.

[UPDATE January 6, 2005]

[August 12, 2004 - Letter - Genentech]



<http://www.fda.gov/Safety/MedWatch/default.htm>

Biologics

Product Name	Date Issued/Updated
Avastin (bevacizumab) Aug 2004 [ARCHIVED]	08/13/2004
Humira (adalimumab) Nov 2004 [ARCHIVED]	11/08/2004
Ortho Antibody to HBsAg ELISA Test System 3 [ARCHIVED]	01/09/2004
Procrit (epoetin alfa) Dec 2004 [ARCHIVED]	12/08/2004
Remicade (infliximab) Aug 2004 [ARCHIVED]	08/24/2004
Remicade (infliximab) Dec 2004 [ARCHIVED]	12/22/2004

<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm380008.htm>

Sample of our data

Up to 31-Dec-2013 inclusive, 76 Medwatch alerts for therapeutic monoclonal antibodies were reported
We analyzed time from approval to alert for therapeutic monoclonal antibodies.

Name	Approval Date	Alert Date	Alert Message	Months from approval to alert
Adcetris (brentuximab vedotin)	Aug-2011	Jan-2012	PML **	5
Adcetris (brentuximab vedotin)	Aug-2011	Jan-2012	Pulmonary toxicity (interaction)	5
Arzerra (ofatumumab)	Oct-2009	Sep-2013	Recommendations to Decrease Risk of Hepatitis B Reactivation **	47
Avastin (bevacizumab)	Feb-2004	Aug-2004	Arterial thromboembolic events	6
Avastin (bevacizumab)	Feb-2004	Jan-2005	Arterial thromboembolic events.	11
Avastin (bevacizumab)	Feb-2004	Sep-2006	Reversible posterior leukoencephalopathy syndrome	31
Avastin (bevacizumab)	Feb-2004	Sep-2006	Nasal septum perforation.	31
Avastin (bevacizumab)	Feb-2004	April-2007	Tracheoesophageal fistula	38
Avastin (bevacizumab)	Feb-2004	Jul-2008	Microangiopathic hemolytic anemia in combination with sunitinib malate	53
Avastin (bevacizumab)	Feb-2004	Mar-2013	Serious Eye Infection	109
....				...

Legend: * Immunological reaction; ** Cancers and opportunistic infections;

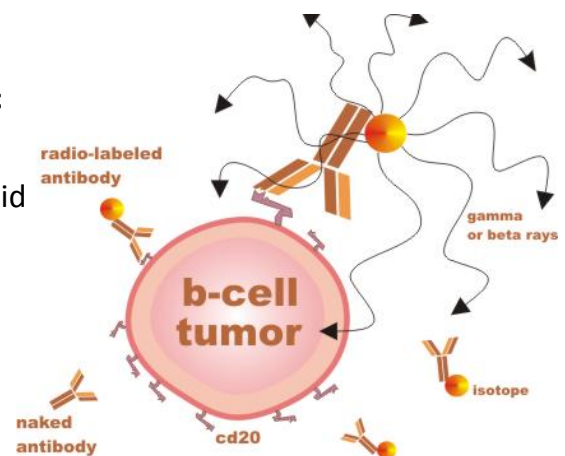
Why we analyze time to alert for Therapeutic Monoclonal Antibodies?

Therapeutic Monoclonal Antibodies

- Monoclonal antibody (mAb) are **innovative therapeutic agents** with excellent potential.
- Can be used in a **variety of indications**: from rheumatoid arthritis and other immune-mediated inflammatory diseases to cancer.

Why we analyze time to alert for Therapeutic Monoclonal Antibodies?

- In general, premarketing clinical trials are carried out in controlled settings on sample of patients and in limited time; therefore, it might happen that not all adverse drug reactions are detected.
- **mAb were hoped to be free from a wide range of adverse effects** because they are binding very specifically their target.
- **Now it is clear that they are causing important adverse drug reactions**, many of them have been identified only after their approval for market. Adverse reactions of mAb are under priority review by the FDA.



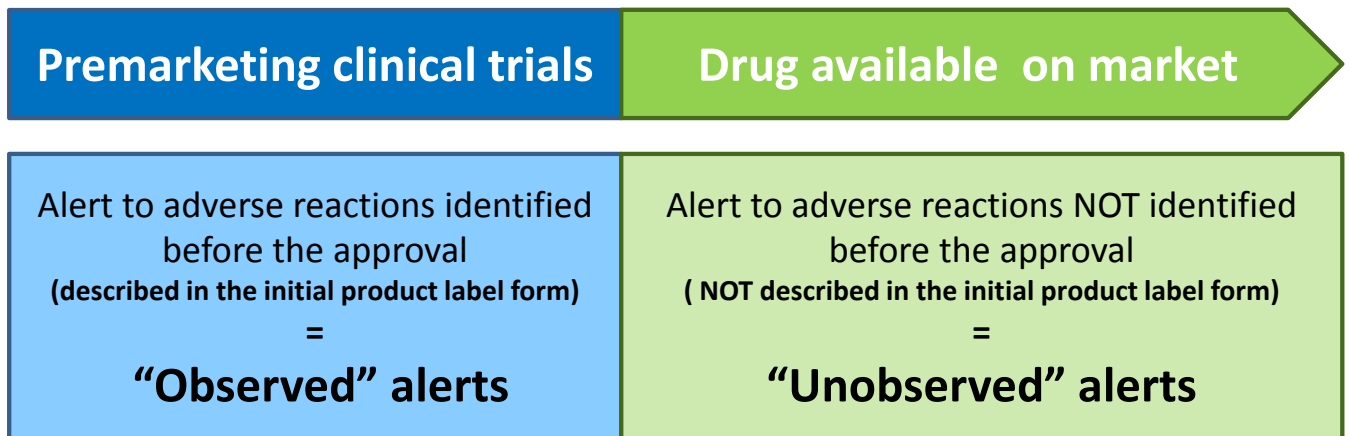
Example:

Avastin® (bevacizumab) approved for market on February 26, 2004

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We compared time to “Observed” and “Unobserved” alerts

Knowing that premarketing clinical trials do not detect all adverse drug reactions we classified the MedWatch alerts to “Observed” and “Unobserved”.



- Previous analysis published in 2011 showed that large proportion of “Unobserved” alerts can be predicted based on mechanism of action or based on extrapolation from “Observed” adverse drug reactions.
- In this study we expanded the previous analysis to assess **whether “Observed” alerts are detected sooner than “Unobserved” alerts.**
- As we believe that large proportion of unobserved alerts can be predicted the comparison of time to “Observed” and “Unobserved” alerts show us delay of safety warning which can be potentially avoided.

We compared time to “Observed” and “Unobserved” alerts

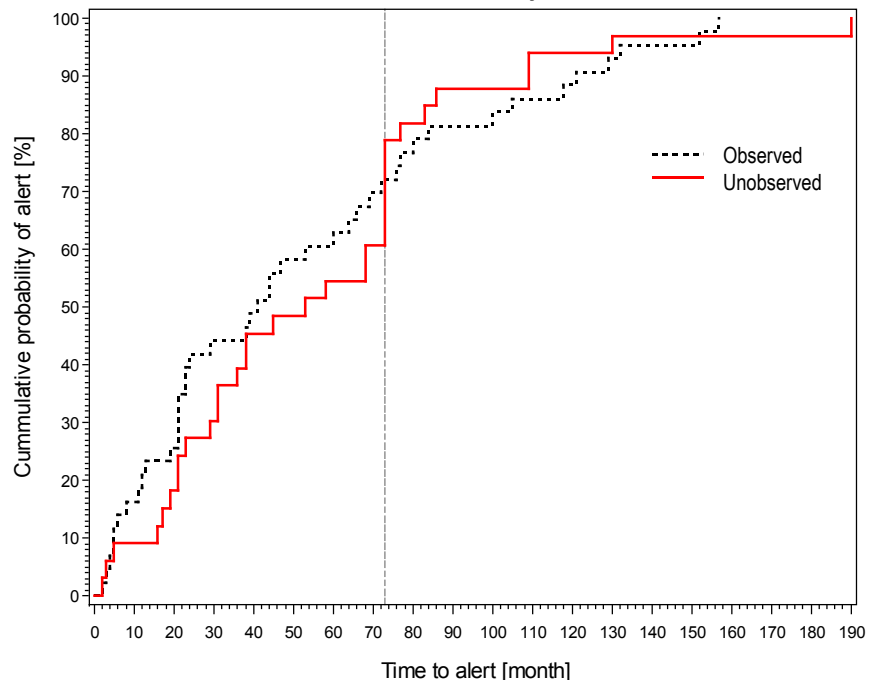
Up to 31-Dec-2013 inclusive, 76 Medwatch alerts for therapeutic monoclonal antibodies were reported; 43 “Observed” vs. 33 “Unobserved”.

Name	Approval Date	Alert Date	Alert Message	Observed (Yes/No)	Months from approval to alert
Adcetris (brentuximab vedotin)	Aug-2011	Jan-2012	PML **	N	5
Adcetris (brentuximab vedotin)	Aug-2011	Jan-2012	Pulmonary toxicity (interaction)	Y	5
Arzerra (ofatumumab)	Oct-2009	Sep-2013	Recommendations to Decrease Risk of Hepatitis B Reactivation **	Y	47
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Avastin (bevacizumab)	Feb-2004	Sep-2006	Reversible posterior leukoencephalopathy syndrome	N	31
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Legend: * Immunological reaction; ** Cancers and opportunistic infections;

Are “Observed” alerts detected sooner than the “Unobserved” alerts?

Cumulative frequencies for „Observed“ and „Unobserved“ Medwatch safety alert



- We used curves displaying cumulative frequencies of alerts over time.
- The curves of cumulative frequencies provide more informative view into the data than standard descriptive statistics or tests.

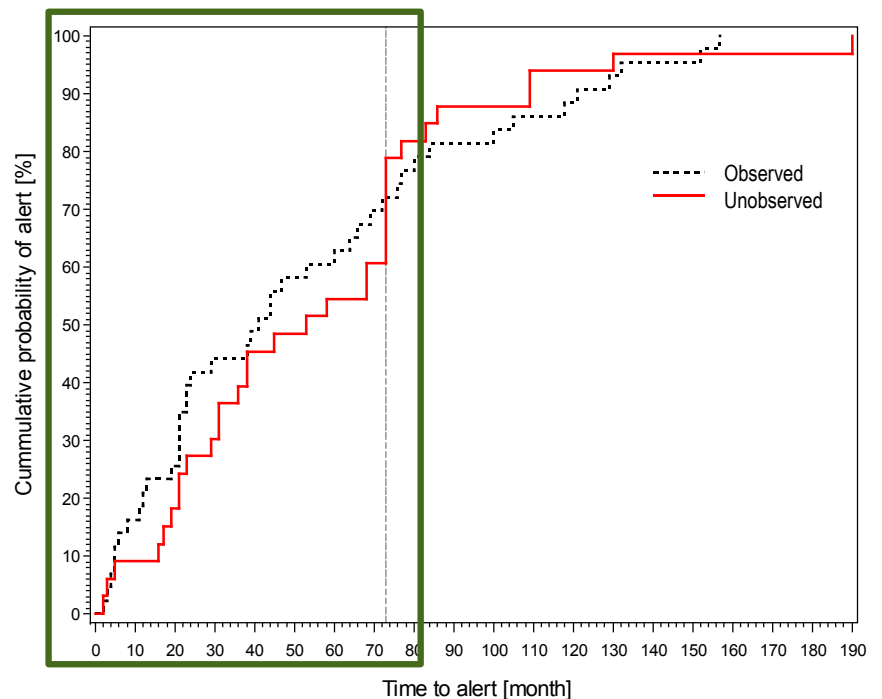
Kolmogorov-Smirnov test: $p=0.822$

Mann-Whitney test: $p=0.524$.

Time to alert [months]	“Observed” 43 (57%)	“Unobserved” 33 (43%)
median (IQR)	41 (19-77)	53 (23-73)
mean (SE)	52.07 (6.69)	55.91 (7.06)

Are “Observed” alerts detected sooner than the “Unobserved” alerts?

Cumulative frequencies for „Observed“ and „Unobserved“ Medwatch safety alert



- The curves show that OBSERVED alerts were detected **sooner** than UNOBSERVED alerts **until month 73 after approval**.
- Such finding suggested to analyze the alerts issued up to 73 months after approval (n=47) separately

Kolmogorov-Smirnov test: $p=0.373$
Mann-Whitney test: $p=0.086$.

Time to alert [months]	“Observed” 31 (57%)	“Unobserved” 26 (43%)
median (IQR)	23 (11-44)	37 (21-68)
mean (SE)	29.29 (3.90)	40.77 (4.88)

Even though this analysis has limitations it brings important view into safety profile of the drug

Even though this analysis has limitations such analysis brings important view into safety profile of the drug which should be considered as supportive tool for Pharmacovigilance and risk management planning.

- The analysis demonstrated a trend towards earlier reporting of OBSERVED alerts, but without clear statistical significance.
- However, this finding should be interpreted taking into account the type of data analyzed. Our study provides an innovative option for analysis of safety concerns.
- Such a type of analysis should be considered as supportive tool of Pharmacovigilance and risk management planning which must aim for more proactive approach to predict adverse effects and avoid them, and only detect and assess them.
- The methods may be applied to other datasets in Pharmacovigilance identifying, in real time, adverse drug reaction reporting frequencies leading to earlier detection of drug safety concerns.
- Our study has several limitations.
 - The analysis is based only on reported alerts excluding reactions which can be assumed (according initial product label) however have not occurred yet.
 - No adjustment for frequency of application of the corresponding drugs.
 - The sample size can be an issue.
 - Way how to improve our results could be to analyze time from the first application instead of time from approval for market.



<http://www.ubc.com/categories/risk-management-pharmacovigilance>



Thank you for your attention.

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