Balancing access and patient safety

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- Dr. Weiss Smith is an employee of the University of Maryland Baltimore and the National Cancer Institute
- All statements made here are personal opinion and do not represent official policy
- Ongoing funded research on the effectiveness, comparative effectiveness, and safety of biologics used in cancer care (funding by grants/contracts from NCI and Novartis)

Disclosures
• Access impacts safety
• Balancing benefits with risks
• Biologics – identifying risks
  • Safety surveillance and discovery
  • Issues novel to biologics & generics
• Balancing Safety (Potential Risks) with Access

Outline

"Biological products touch people's lives on a daily basis with over 200 million vaccinations, 29 million transfusions of blood and blood components, and 1.6 million musculoskeletal tissue transplants each year. Many of the products we regulate are vital for the public health, such as pandemic influenza vaccines and life-saving blood products."

- Karen Midthun, MD
  Director, CBER, FDA

Biologic products
ACCESS IMPACTS SAFETY

FEDERAL DRUG ADMINISTRATION

Import Alert #66-71
Published Date: 03/18/2011
Type: DWPE
Import Alert Name:
"Detention Without Physical Examination of Human Growth Hormone (HGH), Also Known As Somatropin"

Reason for Alert:
Human Growth Hormone (HGH) is the active ingredient in a number of human prescription drugs approved for marketing in the U.S. under new drug applications (NDAs). FDA-approved HGH can be legally prescribed for a limited number of conditions including:

The high cost of HGH products has led to counterfeits and unapproved products being sold in the U.S. HGH has important benefits, but also has the potential for serious, known risks:

Increased risk of cancer, nerve pain, and elevated cholesterol and glucose levels

Cost spur illegal imports

Source: FDA Import Alert http://www.accessdata.fda.gov/cms_ia/importalert_204.html
Avastin Injections Are Reported to Cause Blindness

By ANDREW POLLACK
Published August 30, 2011

At least 16 people in two states have gotten severe eye infections, and some have been blinded, from injections of the drug Avastin, according to health authorities and to lawyers representing the patients.

The incidents, in Florida and Tennessee.

Avastin (bevacizumab) is approved for cancer.
Used off-label for age related macular degeneration (AMD) it costs ~ $50/injection
Lucentis (ranibizumab) is approved for AMD.
It costs approximately $2000/injection

Access impacts Safety

Source: New York Times, 8/30/11
Benefits are considered in terms of impact of therapy on the labeled indication:
- Seriousness of disease*
- Chronicity of disease
- Impact of agent

Risks are the adverse effects of therapy and are weighed in terms of:
- Severity
- Incidence
- Preventability
- Predictability

**APPROVAL decisions are based on the balance between the benefits of treatment for the labeled indication and the known risks**

* The therapy may be undertaken to prevent, mitigate, or cure a disease/condition

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**Benefit-Risk Balance**

- **RISK**
  - minor
  - major

- **BENEFIT**
  - minor
  - major

Unacceptable balance

Acceptable balance

Potential for REMS

Adapted from CIGMS IV 1998
- Preclinical studies
- Premarketing clinical studies
- Postmarketing surveillance and monitoring
  - Passive (AERS and VAERS)
  - Active (Sentinel, Vaccine Safety Datalink)
  - Lot testing
- Postmarketing research
  - Registries
  - Observational studies and meta-analyses
  - Clinical trials
- Evolving issues from similar agents and therapeutic class

Sources of safety information

Number of reports received by FDA and entered into AERS

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<thead>
<tr>
<th>Brand name</th>
<th>Case Reports, 2000-2009</th>
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**Biologic predominate among 10 top brand name drugs reported agents in AERS**


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**BIOLOGICS – IDENTIFYING RISKS**

SAFETY SURVEILLANCE & DISCOVERY
University of Maryland
- BK Shamloo, MD
- Pankdeep Chhabra, MD
- Sheila Weiss Smith, PhD
Georgetown University
- Arnold Potosky, PhD

National Cancer Institute
- Andrew Freedman, PhD
- Leah Sansbury, PhD
- Joan Warren, PhD
Veterans Administration
- Jennifer Malin, MD

Safety of biologics in cancer care: Collaborators

Applied Data Mining
3-step process
### Bevacizumab - Effectiveness

Source: [Website]

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<thead>
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<th>Medical Disorder Group</th>
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Source: Shamloo et al. Drug Safety 2012
### AERS Analysis

Comparison of Avastin & Lucentis

Route: Intraocular Injection

Avastin use signaled for with intraocular infections

Lucentis signaled for systemic effects typically seen with infused Avastin


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### BIOLOGICS – IDENTIFYING RISKS

ISSUES NOVEL TO BIOLOGICS & GENERICS
Utilization impacts ability to identify risks:
- Used in life threatening conditions (cancer)
- May be last line of therapy for chronic debilitating conditions (IBS, arthritis)
- Used together or sequentially with other agents
- Off-label uses may be common
- Mode of administration may also be “off-label”

BIOLGICS POSE UNIQUE CHALLENGES

Manufacturing process is critical:
- Lot-to-lot variation
- Opportunities for contamination
- Storage and transportation
- Counterfeiting

Safety issues require different tools and perspective
Factors likely to impact identification and evaluation of risks from follow-on biologics:

- Adverse event reports may use generic and brand name interchangeably (or not due to bias)
- This may become critically important as there will be real differences between brand and any generics
- Differences in the distribution of indications among users will impact what gets reported, concomitant drugs, and background event rates
- Costs and reimbursement policies may channel agents to very different patient populations impacting risks (e.g. Avastin/Lucentis)
- Reporting volume continues to increase and is sensitive to publicity

**GENERICs AND SAFETY**

**BALANCING ACCESS & SAFETY**
INDICATIONS
Because medical products are approved based on indication:
- labeling is restricted
- marketing is restricted
- reimbursement is often restricted

Incentives for the innovator to pursue new indications are lacking

ACCESS AND SAFETY

Differences between biologics and drugs require different perspectives and approaches to identifying risks:
- Spatial and temporal mapping of events
- Tracking of individual products & lots
- Monitoring and evaluating evolving uses
- Dissemination of critical safety information regarding off-label / extra-label uses

NEW APPROACHES ARE NEEDED
RISKS
- Real time hospital-based risk monitoring/surveillance
- Integration of safety monitoring with other public health initiatives (e.g. biohazard/bioterrorism)
- Prediction-based risk assessment

ACCESS
- Better understanding of the impact of risks (and publicity about potential risks) and risk management activities on access to biologics
- New ways to disseminate evolving knowledge beyond the labeling
- Ways to add new indications when the innovator will not

FUTURE DIRECTIONS