Update on Federal and State Biosimilars Activity

Mary Jo Carden, RPh, JD
Vice Prewsident, Government and Pharmacy Affairs

AMCP Academy of Managed Care Pharmacy

Biosimilars Federal Update

- FDA approved Sandoz' version of filgrastim-sndz (Neupogen®) in March 2015
  - Marketed in September 2015
- CMS issues guidance and proposals on reimbursement for biosimilars under Medicare and Medicaid
- FDA issues guidance and proposed rule on naming for biosimilars and biologics
- Issues on labeling and interchangeability remain unclear
- Exclusivity period for reference biologics remains at 12 years with some efforts to reduce the number of years

AMCP Academy of Managed Care Pharmacy

Current State Activity on Biosimilars

December 31, 2015

Blue – Pending Legislation	
Purple – Failed in 2015	
Blue Lines – Current Law but 2015 Activity	
Beige – No Activity	
Gray – States with Laws	

Pending: MA, MI, PA

Failed: HI, ID, MD, MS, OK, OR, VA, VT

States with Laws: CA, CO, DE, FL, GA, IL, IN, LA, MA, NC, ND, NJ, OR, TN, TX, UT, WA & PR

3

AMCP/HOPA Biosimilars Survey

- Conducted in June 2015 as a follow-up to an AMCP survey conducted in December 2014
- 781 respondents
  - All segments of pharmacists represented but most were managed care and hospital pharmacists
- Survey respondents slightly preferred nonproprietary name (INN) over other naming conventions *but* level of confidence in substituting greatest for shared INN
- Survey found that additional eductaion is needed regarding biologics, biosimilars, and interchangeable products

Broad Stakeholder Educational Campaign

- AMCP seeks support and partners for a Biosimilars Resource Center to provide education to stakeholders on biosimilars
  - Differing levels of education from basic information to advanced
  - Continuing education as well as general education
  - Links and other resources

Mary Jo Carden, RPh, JD
Vice President, Government & Pharmacy Affairs
AMCP
mcarden@amcp.org

AMCP Biologics and Biosimilars Collective Intelligence Consortium (BBCIC)

January 13, 2016
JCPP

Bernadette Eichelberger, PharmD, Program Director, BBCIC

BBCIC
Biologics & Biosimilars
Collective Intelligence Consortium

Agenda

- AMCP Surveillance Strategy: BBCIC
  - Why the AMCP BBCIC Is Needed
  - Progress to Date
  - 2016 Research Scope
  - Governance structure & participants
- BBCIC Foundations: Distributed Research Networks (DRN)
  - DRN Surveillance Examples
  - DRN Research Methods
  - DRN Processes (Mini-Sentinel Example)

Why the AMCP Biosimilar Strategy

Generics saved the US $1 trillion in past decade *but it took 20 years*

The Generic Experience We Don't Want to Replay

- While some MCOs sped generic penetration through UM strategies, GFR penetration in the 2000's was frequently 30-50 percentage points lower in significant sectors (e.g., unions, employer groups, self-funded groups)
  - Slow growth of aggressive GFR strategies was influenced by anecdotal reports that got wide coverage in the press
  - Surveys of physicians and patients still show questions about *generic* drug safety and comparability
    - *Generic* drugs, physician survey: 23% express concern about efficacy, 50% about quality (Shrank et al. Ann Pharmacotherapy. 2011;45(1):31-8)
    - For *biosimilars*, 2015 survey of physicians: 78% were very concerned about biosimilar safety/immunogenicity (http://www.gastro.org/press_releases/2015/7/29/national-survey-reveals-gastroenterologists-views-on-biosimilar-drugs)
- The AMCP BBCIC strategy provides a unique opportunity for pharmacy to not allow anecdotal reporting to be the public's only source of information

AMCP BBCIC Overview

- We know that we don't have a **reliable system for actively monitoring and investigating** what we don't know.
- With the advent of biosimilars in the U.S., physicians, patients and other stakeholders will have questions about the safety and effectiveness of these products, similar to what was experienced with the introduction of generics more than a generation ago.
- As biosimilars come to market, the BBCIC will actively monitor biosimilars and their innovator products, using anonymous data from more than 100 million patients.
  - The BBCIC will use data and analytic methods that have been well tested to help ensure the safe passage of biosimilars. This improves the efficiency and cost-effectiveness of post-marketed observational studies
  - The multi-stakeholder consortium model allows for a larger voice with more credibility. A consortium of MCOs, IDNs, PBMs, medical societies, researchers and biopharma is less easily ignored
  - The consortium has the potential to address data challenges

AMCP BBCIC Progress To Date

- An AMCP task force recommended establishing a multi-stakeholder consortium for biologics & biosimilars post-approval evidence generation.
  - The task force included MCOs, IDNs, PBMs, Pharma & Research Institutions
- Feasibility study and business plan completed in 2014
- BBCIC officially kicked off in April 2015
  - 15 founding participants including managed care and integrated delivery organizations, PBMs, research institutions and pharmaceutical companies
  - 6 month organizing phase finished December 2015 (charter, policy & research plan, signed contracts)
  - Research protocol development starts 4Q2015
- Research commences January 2016

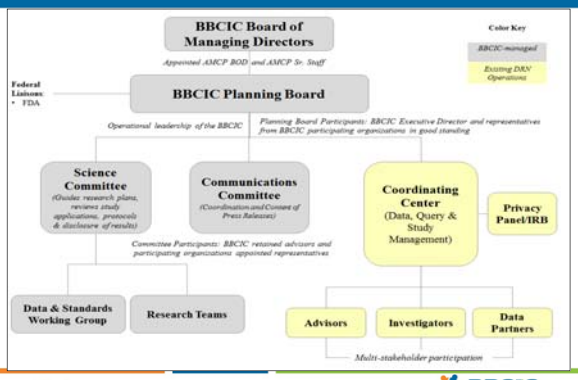
Draft 2016 Research Scope

- Comparative Safety and Effectiveness Research
  - G-CSF Agents (Including Neupogen, Neulasta, TBO-filgrastim, filgrastim and pegfilgrastim biosimilars)
- Descriptive Analyses
  - Infliximab, Epoetin Alfa, Insulin glargine and lispro, rituximab, adalimumab, abciximab, cetuximab, palivizumab
- Process:
  - BBCIC Participants submit topics (i.e., key questions of interest) for the Annual Research Plan
  - Quarterly update process for Annual Research Plan

Draft 2016 Research Scope—Another View

Biologic/Biosimilar Product	Disease Indications
G-CSF Agents (Neupogen, Neulasta, TBO-filgrastim, Zarxio)	Febrile Neutropenia risk reduction in non-myeloid malignancies treated with myelosuppressive anti-cancer drugs associated with a febrile neutropenia and/or undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT); in AML following induction or consolidation chemotherapy; in patients with nonmyeloid malignancies; and in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia. For mobilizing autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; For increasing survival in Hematopoietic Syndrome of Acute Radiation Syndrome.
Adalimumab (Humira), infliximab (Remicade), rituximab (Rituxan), and optional tocilizumab (Actemra), abatacept (Orencia), etanercept (Enbrel), certolizumab (Cimzia), golimumab (Simponi), tofacitinib (Xeljanz)	RA, JRA, Psoriasis, PsA, Ankylosing Spond, SJIA, PJIA
Adalimumab (Humira), infliximab (Remicade), and optional: certolizumab (Cimzia), natalizumab (Tysabri), golimumab (Simponi)	Ulcerative Colitis, Crohn's Disease
Insulin glargine (Lantus, Toujeo), insulin lispro (Humalog), and optional: insulin determir (Levemir), insulin degludec (Ryzodec, Tresiba), insulin degludec+liraglutide (Xultophy)	Diabetes Mellitus 1 and 2
Epoetin alfa (Epogen, Procrit)	Anemia (CKD, chemo)
Palivizumab (Synagis)	Respiratory Syncytial Virus (RSV)
Rituximab (Rituxan)	NHL, CLL, WG/MPA
Abciximab (Reopro)	adjunct PCI (percutaneous coronary intervention), unstable angina

BBCIC Governance Overview



BBCIC: Capitalizing on Investments

Some distributed networks

- CDC's Vaccine Safety Datalink (VSD)
- HMO Research Network
- Cancer Research Network
- Meningococcal Vaccine Safety Study
- EU-ADR
- FDA Mini-Sentinel
- NIH Health Care Systems Collaboratory
- PCORI National Clinical Research Network (PCORnet)

BBCIC –FDA's Next Generation Surveillance

At the 2015 Sentinel Public Workshop, FDA signaled:

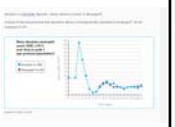
Janet Woodcock, FDA Director CDER:

- "Through Mini-Sentinel we've shown we can obtain rapid responses to [safety] signals – these questions that arise after marketing and get everyone in a twist …"
- We're going to transfer Sentinel to our safety office so we can **institutionalize the use of Sentinel as part of our safety tool kit.** As we see a problem – and the OSE is dealing with a myriad of safety signals at any given time – this is one of the tools they can easily reach for."

Michael Nguyen, FDA Center for Biologics Evaluation & Research

- BBCIC-type effort "Substantially expands postmarket safety monitoring options to allow more strategic and tailored surveillance of new drugs and biologics"
- FDA Advisory Committees are likely to look favorably on surveillance plans that include Sentinel level (e.g., BBCIC) active prospective surveillance.
- FDA Post-Approval Committees (PAC)s will be looking for "near real-time active surveillance for prespecified outcomes"
- FDA is "Working to apply Sentinel to all classes of CBER-regulated products

http://www.brookings.edu/events/2015/02/05-fda-sentinel-initiative-workshop



DRNs: Assessing Risk

Active Surveillance of Vaccine Safety

A System to Detect Early Signs of Adverse Events

Robert L. Davis,† Margarette Kolczak,‡ Edwin Lewis,† James Nordin,§ Michael Goodman,§ David K. Shay,‡ Richard Platt,¶ Steven Black,# Henry Shinefield,† and Robert T. Chen‡*

Background: There currently are no population-based systems in the United States to rapidly detect adverse events after newly introduced vaccines. To evaluate the feasibility of developing such systems, we used 5 years of data from 4 health maintenance organizations within the Centers for Disease Control and Prevention (CDC) Vaccine Safety Datalink.

Methods: Within every year, each week's vaccinated children were followed for 4 weeks, and rates of adverse events were compared with rates among children of similar ages before the introduction of the new vaccine. We assessed risks for intussusception after rotavi-

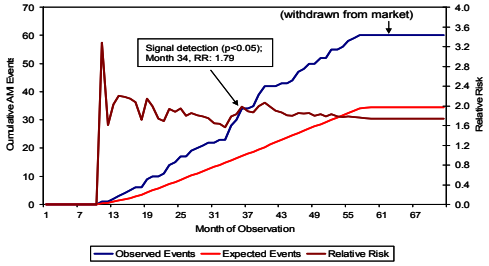
Conclusions: We conclude that it is feasible to develop systems for rapid and routine population-based assessments of new vaccine safety.

(*Epidemiology* 2005;16: 336–341)

Recent events in the United States have underscored the need for surveillance systems that detect adverse events as soon as possible after the introduction of new vaccines (eg,

DRNs: Assessing Risk

Observed and expected events for rofecoxib versus naproxen users: 2000-2005

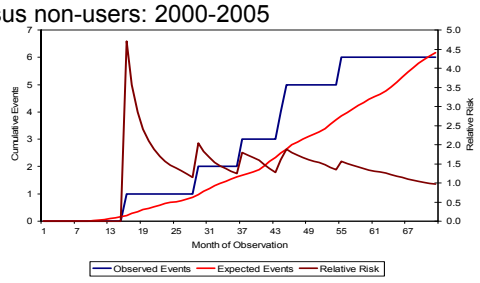


Signal after 28 events (16 expected) among new users of drug

Brown *et al.* (2007) PDS; Adjusted for age, sex, health plan. Outcome: AMI.

DRNs: Assessing Risk

Observed and expected events for cetirizine users versus non-users: 2000-2005

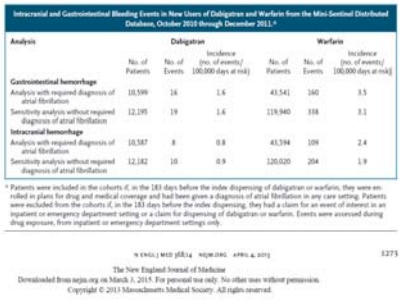


Negative control;6 observed and 6.1 expected. > 5 million exposed days.

Brown *et al*. (2007) PDS; Adjusted for age, sex, health plan. Outcome: Thrombocytopenia.

DRNs: Assessing Risk

Dabigatran and Post-Marketing Reports of Bleeding



Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database, October 2010 through December 2011.*

Analysis	Dabigatran			Warfarin		
	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)	No. of Patients	No. of Events	Incidence (no. of events/ 100,000 days at risk)
Gastrointestinal hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,599	16	1.6	43,541	160	3.5
Sensitivity analysis without required diagnosis of atrial fibrillation	12,195	19	1.6	119,940	338	3.1
Intracranial hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,587	8	0.8	43,594	109	2.4
Sensitivity analysis without required diagnosis of atrial fibrillation	12,182	10	0.9	120,020	204	1.9

* Patients were included in the cohorts if, in the 183 days before the index dispensing of dabigatran or warfarin, they were enrolled in plans for drug and medical coverage and had been given a diagnosis of atrial fibrillation in any care setting. Patients were excluded from the cohorts if, in the 183 days before the index dispensing, they had a claim for an event of interest in an inpatient or emergency department setting or a claim for dispensing of dabigatran or warfarin. Events were assessed during drug exposure, from inpatient or emergency department settings only.

DRNs: Assessing Risk

The NEW ENGLAND JOURNAL of MEDICINE

FEBRUARY 6, 2014

Intussusception Risk after Rotavirus Vaccination in U.S. Infants

W. Katherine Yih, Ph.D., M.P.H., Tracy A. Lieu, M.D., M.P.H., Martin Kulldorff, Ph.D., David Martin, M.D., M.P.H., Cheryl N. McMahill-Walraven, M.S.W., Ph.D., Richard Platt, M.D., Nandini Selvam, Ph.D., M.P.H., Manu Selvan, Ph.D., Grace M. Lee, M.D., M.P.H., and Michael Nguyen, M.D.

ABSTRACT

BACKGROUND

International postlicensure studies have identified an increased risk of intussuscep-

From the Department of Population

CONCLUSIONS

RV5 was associated with approximately 1.5 (95% CI, 0.2 to 3.2) excess cases of intussusception per 100,000 recipients of the first dose. The secondary analysis of RV1 suggested a potential risk, although the study of RV1 was underpowered. These risks must be considered in light of the demonstrated benefits of rotavirus vaccination. (Funded by the Food and Drug Administration.)

Distributed Research Networks: Methods

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2007; **16**: 1275–1284
Published online 22 October 2007 in Wiley InterScience (www.interscience.wiley.com) **DOI**: 10.1002/pds.1509

ORIGINAL REPORT

Early detection of adverse drug events within population-based health networks: application of sequential testing methods[†,‡]

Jeffrey S. Brown PhD[1,2*], Martin Kulldorff PhD[1], K. Arnold Chan MD, MPH, ScD[3,4], Robert L. Davis MD, MPH[5], David Graham MD[6], Parker T. Pettus MS[1,2], Susan E. Andrade ScD[2,7], Marsha A. Raebel PharmD[2,8], Lisa Herrinton PhD[2,9], Douglas Roblin PhD[2,10], Denise Boudreau PhD[2,11], David Smith PhD[2,12], Jerry H. Gurwitz MD[2,7], Margaret J. Gunter PhD[2,13] and Richard Platt MD, MSc[1,2]

Distributed Research Networks: Methods

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2013
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3412

ORIGINAL REPORT

Near real-time adverse drug reaction surveillance within population-based health networks: methodology considerations for data accrual[†]

Taliser R. Avery[1,2*], Martin Kulldorff[1,2], Yury Vilk[1], Lingling Li[1], T. Craig Cheetham[2,3], Sascha Dublin[2,4], Robert L. Davis[2,6], Liyan Liu[2,5], Lisa Herrinton[2,5] and Jeffrey S. Brown[1,2]

Purpose: Practical considerations for implementation of real-time drug safety surveillance using safety of generic versus branded divalproex as use case

Methods: Near real time surveillance at 4 health plans; monthly data extracts

Results: Data quality review process for each extract at each site is crucial. Data lags exists but can be accounted for.

Conclusions: Near real-time sequential safety surveillance is feasible, but several barriers warrant attention. …differential accrual between exposure and outcomes could bias risk estimates towards the null, causing failure to detect a signal.

Distributed Research Networks: Methods

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2009; **18**: 226–234
Published online 15 January 2009 in Wiley InterScience (www.interscience.wiley.com) **DOI**: 10.1002/pds.1706

ORIGINAL REPORT

Early adverse drug event signal detection within population-based health networks using sequential methods: key methodologic considerations[†]

Jeffrey S. Brown PhD[1,2*], Martin Kulldorff PhD[1], Kenneth R. Petronis PhD[3], Robert Reynolds ScD[3], K. Arnold Chan MD, MPH, ScD[4,5], Robert L. Davis MD, MPH[6], David Graham MD[7], Susan E Andrade ScD[2,8], Marsha A. Raebel PharmD[2,9], Lisa Herrinton PhD[2,10], Douglas Roblin PhD[2,6], Denise Boudreau PhD[2,11], David Smith PhD[2,12], Jerry H. Gurwitz MD[2,8], Margaret J. Gunter PhD[2,13] and Richard Platt MD, MSc[1,2]

…alternative specifications tend to result in earlier signal detection by 10–16 months, a likely consequence of more exposures and events entering the analysis.

Distributed Research Networks: Processes

See Appendix DRN Processes

Questions?

BIOSIMILARS

Source: Sarah Palin – mistydawnphoto / Shutterstock.com

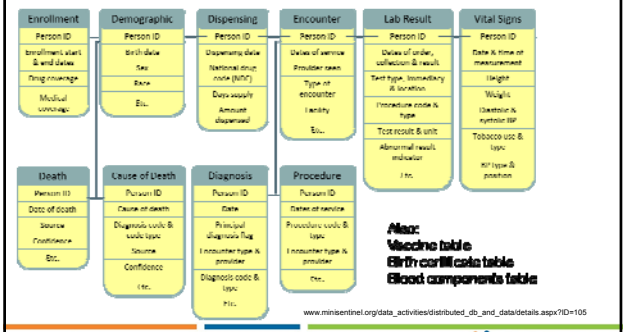
Email comments and questions to Bernadette Eichelberger, beichelberger@BBCIC.org

BBCIC Contacts

- Bernadette Eichelberger, Pharm.D.
  - beichelberger@BBCIC.org
  - (703) 684-2646

Appendix: DRN Processes

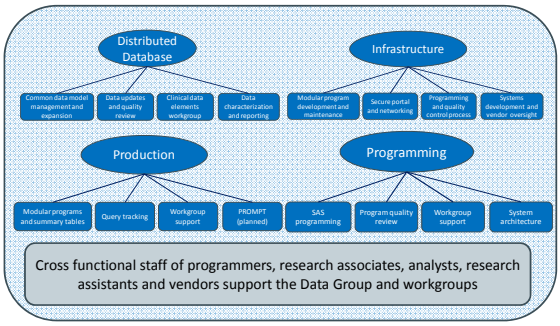
DRN : Mini-Sentinel's Common Data Model



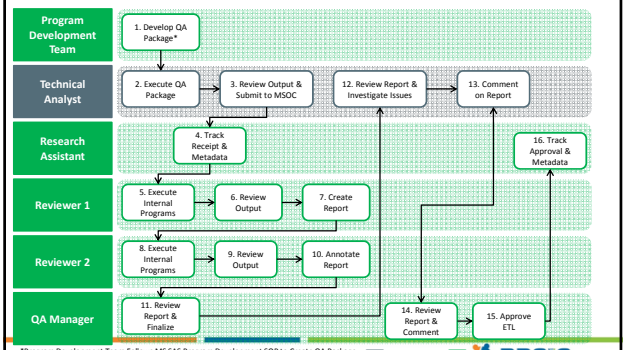
www.minisentinel.org/data_activities/distributed_db_and_data/details.aspx?ID=105

DRN Process: Mini-Sentinel Coordinating Center

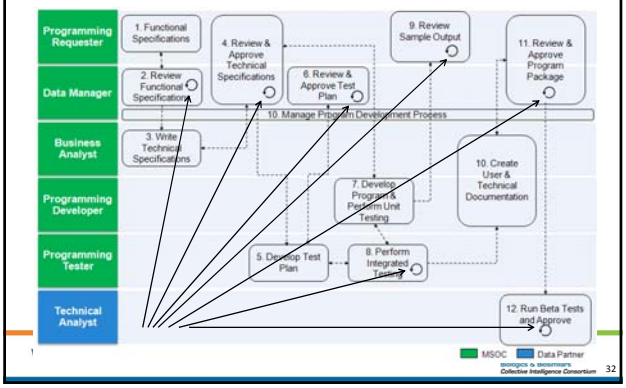
Scientific and technical infrastructure



DRN Process : Data QA and Characterization



DRN Process : New Program Development



DRN Process: Query Fulfillment