

# **Public Meeting**

## ***Sentinel Network to Promote Medical Product Safety***

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- *What are the current gaps in postmarket medical product safety data collection and risk identification and analysis?*

## **Spontaneous Reports: Limitations**

- Adverse event recognition
- Underreporting
- Biases
- Lack of population exposure data
- Report quality

- *How can postmarket medical product safety data collection be integrated into workflow of clinical practice at point-of-care while avoiding imposition of undue burdens on HCPs, patients, and health care institutions?*
- *How readily can existing systems be used or be modified to serve as dynamic surveillance loops (e.g., constant integration of data collection from, analysis, and feedback of information to health care practitioners and patients at the point-of-care)?*

- Multiple educational programs shown to improve AE recognition, AE reporting and report quality
  - MD reporting at Massachusetts General Hospital<sup>1</sup>
  - Rhode Island ADR Reporting Project<sup>2</sup>
  - Clinical pharmacist rounds (Switzerland)<sup>3</sup>
  - Morning report (US)<sup>4</sup>
  - Targeted outreach program (Portugal)<sup>5</sup>

<sup>1</sup>Koch-Weser J, et al. *NEJM* 1969;280:20-26

<sup>2</sup>Scott HD, et al. *R I Med J* 1988;71:179-184

<sup>3</sup>Schlienger RG, et al. *Pharm World Sci* 1999;21:110-115

<sup>4</sup>Welsh CH, Pedot R, Anderson RJ. *J Gen Intern Med* 1996;11:454-460

<sup>5</sup>Figueiras A, et al. *JAMA* 2006;296:1086-1093

# *MedWatch*

- Quality of pharmacist reports and total proportion of serious direct ADE reports increased after MedWatch launch<sup>6</sup>
- Conference on recognition and management of drug-induced disease<sup>7</sup> and clinically-oriented CE articles distributed nationally well-received<sup>8-10</sup>

<sup>6</sup>Piazza-Hepp TD, Kennedy DL. *Am J Health Syst Pharm* 1995;52:1436-1439

<sup>7</sup>Goldman SA, Lieberman R, Kausal DJ. *J Clin Pharmacol* 1996;36:386-396

<sup>8</sup>Goldman SA, Kennedy DL, Lieberman R (eds). *Clinical therapeutics and the recognition of drug-induced disease*. FDA, 1995.

<sup>9</sup>Goldman SA. *J Clin Pharmacol* 1999;39:1126-1135

<sup>10</sup>Goldman SA. *The clinical impact of adverse event reporting*. FDA, 1996

# Other Successful Interventions

- *US*: Multidisciplinary ADR committee formed<sup>11</sup>
  - ↑ ADR reporting after simplifying process and implementing ADR newsletter & in-service educational program
  - Pharmacist investigated suspected ADRs
    - Report to forwarded to P & T Committee and clinical departments
- *Australia*: Community physicians received regular CE “visits” on therapeutics (NSAIDs)<sup>12</sup>
  - 70% reduction in GI disorder-related hospital admissions over 5-year period (since “visits” began) in service area without significant change in comparison area hospitalization rates

<sup>11</sup>Etzel JV, Brocavich JM, Rousseau M. *Hosp Pharm* 1995;30:1083-1087

<sup>12</sup>May FW, et al. *Med J Aust* 1999;170:471-474

# Report Quality

- High quality AE information critical to medical product safety system and related initiatives
  - If data quality poor, enhanced electronic databases and applied techniques will make no difference
- Directed questioning enhances report quality
  - Full clinical information (“Off-Service Note” format)
  - AE/AR-specific questions when designated serious AE/AR suspected to be associated with medical product

# FDA Proposed Rule: “*Always Expedited Reports*”<sup>13</sup>

- Specific SADRs, regardless of expectedness/seriousness, to be reported on expedited basis due to medical gravity:

Congenital anomalies

Acute respiratory failure

Ventricular fibrillation

Torsades de pointe

Malignant hypertension

Seizure

Agranulocytosis

Aplastic anemia

Toxic epidermal necrolysis

Liver necrosis

Acute liver failure

Anaphylaxis

Acute renal failure

Sclerosing syndromes

Pulmonary hypertension

Pulmonary fibrosis

<sup>13</sup>[www.fda.gov/OHRMS/DOCKETS/98fr/03-5204.pdf](http://www.fda.gov/OHRMS/DOCKETS/98fr/03-5204.pdf)

# *“Always Expedited Reports”*<sup>13</sup>

- Given significant morbidity/mortality and known association with pharmaceuticals, questionnaires have been developed for some of these ADRs
- Consensus query documents for use by any company suspecting occurrence of these ADRs?
- Perceived need for development of
  - Clinically relevant, internationally accepted case definitions
  - Clinically relevant, internationally accepted series of questions designed to acquire optimal quality data for each of these serious ADRs

# Correlational Analysis: Felbamate

- Epidemiology group performed extensive examination of first 31 putative cases of aplastic anemia in felbamate-treated patients reported to FDA, including
  - Review of pathology reports
  - Review of bone marrow biopsies/aspirates (when available)<sup>14</sup>
- Noting case report utility enhanced by augmentation with such data, authors reported confirmation of association between felbamate and aplastic anemia
  - Ten-fold difference between “best case” and “worst case” estimated incidence rates among users

<sup>14</sup>Kaufman DW, et al. *Epilepsia* 1997;38:1265-1269

# Clinical Practice Guidelines: Noncompliance Intervention

- In large Belgian university hospital, 44% noncompliance with Infectious Diseases Society of America guidelines for treatment of catheter-related bloodstream infection (CRBSI) over 52 consecutive episodes<sup>15</sup>
- Physicians caring for next 46 CRBSI patients received semiautomatic standardized treatment advice by e-mail
  - Simple, non-labor-intensive intervention
  - Guideline noncompliance ↓ from 44% to 15% (P<.01)

<sup>15</sup>Rijnders BJ, et al.; Infectious Diseases Society of America. *Clin Infect Dis* 2003;37:980-983

# Clinical Practice Guidelines: Prescribing Behavior

- In France, OncoDoc (non-automated guideline-based decision support system that allows interpretation flexibility for best patient-specific recommendations) used in breast cancer management<sup>16</sup>
- Treatment decisions measured before/after system use to assess impact upon physician prescribing
  - After 4 months, 127 decisions recorded
    - Physician compliance with OncoDoc improved ( $p < .0001$ ) to 85.03%
    - Comparison of initial/final decisions showed physicians modified prescription in 31% of cases

<sup>16</sup>Bouaud J, et al. *Medinfo* 2001;10(Pt 1):420-424

# Lessons Learned

- Educational activities related to medical product AE recognition, reporting and analysis optimally provided in point-of-care setting, preferably by HCPs
- Relevance of safety-related activities enhanced when linked to other important activities, e.g.,
  - Quality Assurance
  - Joint Commission accreditation
  - P & T Committee

# Lessons Learned

- If postmarket safety data collection activities perceived as clinically relevant, HCPs VERY receptive
- If clinically relevant feedback provided on safety data collection and resultant analysis, HCPs VERY receptive
- If clinically relevant treatment advice (including safety) provided in user-friendly format at point-of-care, HCPs VERY receptive