Adverse Event Reporting: Presentation to the IOM

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Overview

- Postmarketing Reporting of Adverse Drug Experiences (ADEs)
- Physicians and Adverse Event Reporting
- Reporting to IRBs
Postmarketing Reporting of Adverse Drug Experiences (ADEs)

• What is an ADE?
  – “Any adverse event associated with the use of a drug in humans, whether or not considered drug related . . . .” (21 CFR 314.80(a))
  – Examples in regulatory definition:
    • An adverse event occurring in the course of the use of a drug product in professional practice
    • An adverse event occurring from drug overdose whether accidental or intentional
    • An adverse event occurring from drug abuse
    • An adverse event occurring from drug withdrawal
    • Any failure of expected pharmacological action
Postmarketing Reporting of Adverse Drug Experiences (ADEs)

- A sponsor must **review** all adverse drug experience information obtained or otherwise received from any source.
- A sponsor must develop written **procedures** for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.
- A sponsor must **report** adverse drug experience information to FDA in accordance with the regulation:
  - Serious and unexpected adverse drug experiences: \( \leq 15 \) calendar days
  - FDA Form 3500A or comparable alternative.
- A sponsor must promptly **investigate** serious and unexpected adverse drug experiences and submit followup reports within 15 calendar days of receiving new information or as requested by FDA.
Postmarketing Reporting of Adverse Drug Experiences (ADEs)

• Periodic Reports
  – All adverse drug experiences not reported in 15-day reports must be reported to FDA
    • quarterly for the first 3 years from approval and then annually thereafter
    • FDA may reestablish a quarterly reporting requirement after a major supplement is approved
  – Periodic reporting does not apply to information obtained from postmarketing studies (see below), reports in the scientific literature, or foreign marketing experience
Postmarketing Reporting of Adverse Drug Experiences (ADEs)

- Periodic Reports
  - Contents:
    - Narrative summary and analysis of the information in the report
    - Analysis of the 15-day reports submitted during the reporting period
    - FDA Form 3500A for each adverse drug experience not reported as a 15-day report
    - Actions taken since the last report because of adverse drug experiences (e.g., labeling changes)
Postmarketing Reporting of Adverse Drug Experiences (ADEs)

- Patient privacy (21 CFR 314.80(h))
- Recordkeeping (21 CFR 314.80(i))
- Miscellaneous
  - Failure to establish and maintain records and make reports required under the regulation means FDA can withdraw approval
  - Submitting a report does not mean the sponsor or FDA has concluded the drug caused the adverse effect
Adverse Event Reporting by Physicians

- Dramatically underreport – FDA always assumes that only 1 in 10 AEs are reported
- Not required by FDA, or by any federal agency
  - Practice of medicine is regulated by states
- 20 states have mandatory reporting systems
  - types of events required to be reported vary widely
  - reports to mandatory systems
    - cumbersome and time-consuming
    - risk loss of license or loss of accreditation
    - invite fear of adverse effect on business, bad PR
    - raise liability risks
Suggestions for improving physician reporting

- Look to aviation safety reporting requirements
  - simple
  - no liability to pilots if report promptly
  - worthwhile

- Simple – single page on the internet

- No liability – pending federal legislation on this

- Worthwhile – FDA needs to act on information faster

- COMMUNICATE THE IMPORTANCE AND EASE!
Adverse Event Reporting to IRBs – case study of the limits of the system and of transparency

- IRBs must review studies at least annually
- IRBs must maintain records of continuing review activities
- Investigators must promptly report all unanticipated problems to IRB asap, or within 10 days
- Sponsors must report results of an evaluation of a reported effect to reviewing IRBs and investigators within 10 days
- IRBs must follow written procedures to ensure prompt reporting to IRB, appropriate officials, FDA
Problems in the current system

- IRB for single study site commonly receives AERs and other info from all other study sites
- Some IRBs receiving >12,000 reports/year
- HHS Sect’y Advisory Committee: “seldom contain adequate information”
- received in isolation, unaggregated and unanalyzed
- in blinded studies, reports might not even disclose treatment subject received
- range from serious to minor
- anticipated and unanticipated reporting
- reporting from other studies using same drug but not under same conditions (different doses, duration of therapy, subpopulations, etc.)
Some suggestions

• Summary based reporting, instead of unaggregated
• Reporting should be to local IRB only
• Protocol should specify reporting criteria
  – highlights need for uniform protocol
  – FDA needs to modify some regs and guidances
• Will actually put increased pressure on sponsors, who will have to summarize and analyze data
Some (obvious) lessons learned

• Too much “transparency” can have unacceptable costs
• Need manageable signal-to-noise ratio
• If no regulatory guidance\safe harbor, in this environment, all of the incentives are to overreport
• Serious questions about utility of learning about random events
  – If someone taking an investigational drug is hit by a bus, what is the IRB to do about that?
  – How can they investigate it?
Conclusions

• Understand the limits of FDA’s (and federal) authority and resources
• Understand the reluctance of physicians and the burdens on them
• Understand the limited utility of adverse event reporting as a scientific, decision-making tool
• Understand the need for liability protections