Integration of Pre- and Post-Market Reviews

IOM Recomm. 3.4 / 4.4 / 4.5 / 4.13 / 5.4

Industry's role in the institution of a lifecycle approach to drug safety review

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Answers That Matter.

Industry's role in lifecycle approach to drug safety review

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Conclusions / Ways Forward

Collaboration – standards! and systematic coordination for the following:

- Acknowledge that risk cannot be totally eliminated – optimize B/R
- Establish explicit standards for B/R – reduce re-dos (Right the first time!)
- Compel consistent transparency – reduce duplications across sponsor vs. regulator
- Pioneer, validate and utilize standard B/R definitions process and models – reduce post-hoc debates and resource churn
- Cycle (plan) for continuous improvements
- Improve communications – reduce confusion
  - benefit/risk (not safety)
  - stakeholders coordination
  - to patients / HC providers dispel “myths” and use their language
    - Drugs are NOT 100% safe
    - PDUFA co-opts FDA? NOT ! (ala BMV)
  - restore “trust”

Introduction / framing

- **What's in a word? (layman view ala Wiktionary)**
  - safety: a feeling of being secure; certainty; the condition of being protected against failure, damage, error, accidents or harm (Expectation of 100% protection/safety?)
  - risk: the possibility something will go wrong; probability of potential harm
    - * existence / analysis / evaluation of risks
    - * alternatives
  - benefit/risk (i.e., balance)
  - resources - human / economic / other ("raw" vs. capabilities)

Great Expectations

"…… any technology powerful enough to improve life radically is also capable of abuse and prone to serious, unanticipated side effects. Mix new technologies with the wide variations in how organizations and individuals behave and you often have a recipe for explosion."

Why Things Bite Back: Technology and the Revenge of Unintended Consequences

- Edward Tenner

From one sponsor's perspective – Status/ Issues (general)

- Inventory of current resources – FDA, industry, etc. (issue is moreso "coordination" than capacity); identify complementary disciplines (epidemiology, etc.) and best practices
- Lifecycle concept – what is the bridge between pre & post approval (rope bridge or 6 lane superhighway ?) –

  Issues are - standards for benefit/risk non-existent

  - common data sources post-approval (i.e., dueling databases)

  - is NDA dataset the best baseline value?

  (i.e., at launch, average age of patient in practice vs. CT goes up 1 decade, and concurrent meds double)

- LifeCYCLE implies defined feedback loops

Comments on specific IOM recommendations

- **Sect. 3.4 (designated OSE staff to work with OND staff at and after approval)**
  - **Important that OSE/OND processes and interactions be integrated to ensure timely review**
  - **What will be common standards for B/R criteria and review (regardless of compound/division/agency role/etc.)?**
  - **What about new indications/line extensions?**
  - **What will be process for reconciling disagreements?**

ACTION: defined processes (RACI)

Comments on specific IOM recommendations (cont'd.)

- **Sect. 4.4 (CDER assures timely, scientifically valid Risk MAP evaluations)**
  - **What concepts will drive quality checks/oversight?**
  - **How will MAP incorporate benefit/risk over time?**
  - **Since virtually no entities in healthcare capture postapproval drug benefit, how to assure balance (or counterbalance looking only at new risk data)? - rename as B/R map?**

ACTION: plan for benefit data capture

Comments on specific IOM recommendations (cont'd.)

- **Sect. 4.5 (CDER to develop and continuously approve a systematic approach to benefit-risk analysis pre & post approval)**
  - **BRAVO ! Assuring rigor and balance – clear standards**
  - **Best opportunity to communicate and reclarify B/R to public (use integrated B/R NDA summary as springboard)**
  - **Why not B/R statement in all product labels?**

Comments on specific IOM recommendations (cont'd.)

- **Sect. 4.13 (CDER regularly reviews all post approvals and disseminates B/R assessments)**
  - **Chance to avoid risk communication in isolation (the Bill Buckner phenomenon) – which in some cases has frightened as much as warned (ex.: pediatric SSRI warnings and unintended consequences)**
  - **How to capture benefit data**
  - **Burden of proof for --**
    - *** safety (1 new case?)**
    - *** benefit (2 RCTs?)**

Comments on specific IOM recommendations (cont'd.)

- **Sect. 5.4 (FDA re-evaluates all data on NMEs 5-yr. post approval)**
  - **Why not line extensions also? Why not generics? What is role of generic companies in all of this -- e.g.; Fluoxetine / Cefaclor**
  - **What would be actions based on review – restricted access, withdrawal, etc.?**
  - **Critical to establish standards pre-hoc**

Overall resource impact of preceding issues (and value for investment)

- **Less a matter of resource mass; moreso a need for prioritization, coordination and expertise (i.e., epi)**
  - **must fund PDUFA renewal**
- **Resources to capture benefit data in practice settings (long march – not quick win; changing SOPs at care level)**
- **Potential use of "surrogate markers" for benefit and risk (dB)**
- **Much depends on standards established and on access to postapproval data (major groups – Wellpoint, Kaiser, etc.)**
- **Foreseeing unintended consequences (on patients, innovation)**
- **Possible confounders**

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