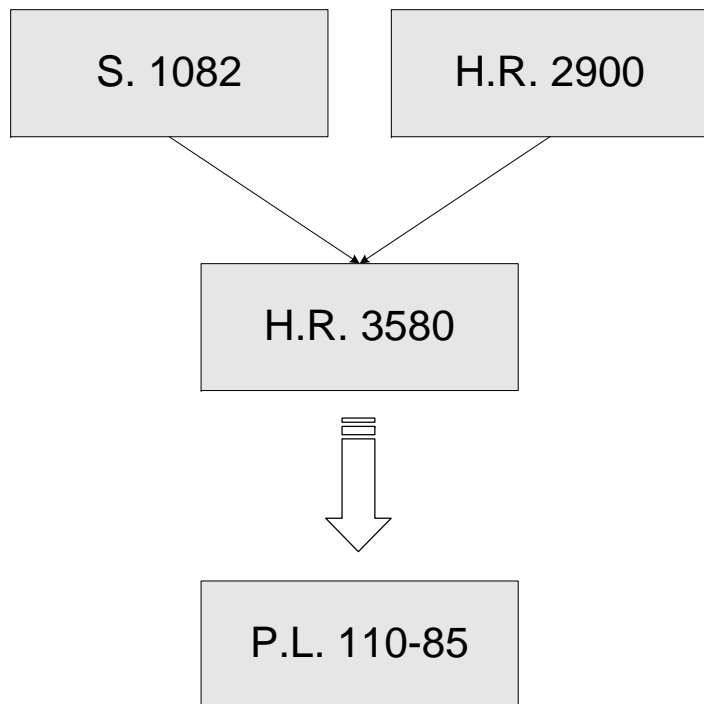


*Optimally Leveraging Epidemiologic and
Observational Studies in the Development of an
Appropriate RiskMAP or REMS*

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FDAAA Structure



- Tit. I – PDUFA IV
- Tit. II – MDUFA
- Tit. III – Device Peds
- Tit. IV – PREA 207
- Tit. V – BPCA 2007
- Tit. VI – Reagan-Udall
- Tit. VII – Conflicts of Interest
- Tit. VIII – Clinical Trial D-base
- Tit. IX – Drug Safety
- Tit. X – Food Safety
- Tit. XI – Other

Title IX of FDAAA

Subtitle A “Post Market Studies and Surveillance”

Empowers the FDA to:

- Require post-approval studies or clinical trials
- Request that safety information be included in labeling
- Require an applicant to submit and execute a REMS
- Require pre-review of DTC Advertisements

Potpourri

Subtitle B “Other Provisions to Ensure Drug Safety and Surveillance”

- Addresses various issues, including: antibiotic clinical trial guidance; foods to which biologics or drugs are added; pharmaceutical security (protect against counterfeit, misbranded or expired drugs); citizen petition modification (generic drugs); dissemination of post-market drug safety information (easily searchable database) ; etc.

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Greatest Impact Found in Title IX, Subtitle A

Post-market Studies and Surveillance

- 1. Post-market Studies and Clinical Trials
 - **FDAAA creates new FDC Act §505(o) which grants FDA authority to require post-approval studies and clinical trials from a “responsible person” for a “covered application” (NDA or BLA)**

FDC Act §505(o)(1) and FDC Act §505(o)(2) as amended by FDAAA §901(a)

FDA can Now Require Post Market Studies

Post-market Studies and Surveillance

- 1. Post-market Studies and Clinical Trials
 - **FDA can require post-market studies or clinical trials** on the “basis of scientific data deemed appropriate by [the Agency], including information regarding chemically-related or pharmacologically-related drugs” to “**assess a known serious risk or signals of a serious risk related to the drug**”, or to “**identify an unexpected serious risk when available data indicates the potential for a serious risk.**”
 - **FDA can apply FDC Act §505(o) to previously approved** “covered applications” if such determination is based on post-approval safety information.
 - In order for FDA to require a post-market study, however, the **Agency must first determine that currently required post-market reports will be insufficient to assess or identify the risk.**

FDC Act §505(o)(3) as amended by FDAAA §901(a)

Risk Evaluation and Mitigation Strategies

“REMS”

- Continuation of FDA’s risk management guidance initiatives
- **FDA now has authority to require a proposed REMS** *with a marketing application* if determined that such a strategy “is necessary to ensure that the benefits of the drug outweigh the risks of the drug.”
- **FDA may also require a REMS of a marketed drug** if new safety information becomes available that meet the above criteria (120 days to submit a proposed REMS).

Factors to Consider In Determining the Need for a REMS

- FDA must consider several factors when determining to require a REMS for a drug:
 - Estimated size of the population likely to use the drug
 - Seriousness of the disease or condition to be treated
 - Expected benefit with respect to such disease or condition
 - Expected or actual duration of treatment
 - Seriousness of any known or potential adverse events and the background incidence of such events in the likely population to use the drug
 - Whether the drug is a new molecular entity

FDAAA §901(b)

How do the RiskMAP Factors Compare?

When Should a RiskMAP be Considered?

- Types, magnitude and frequency of risks and benefits
- Population who benefits versus population at risk
- Existence of treatment alternatives and their risks and benefits
- Reversibility of adverse events observed
- Preventability of adverse effects by appropriate prescribing
- Will a RiskMAP encourage appropriate use

“FDA recommends that RiskMAPs be used judiciously to minimize risks without encumbering drug availability or otherwise interfering with the delivery of product benefits to patients” “FDA RiskMAP Guidance March 2005”

EXAMPLES: Benefit and Risk in At-Risk Population

- **ISOTRETINOIN**
 - Severe, recalcitrant nodular acne
 - Not life threatening
 - Treatment of last resort
 - Teratogenic (Category X)
 - Younger Population
 - Medication not authorized if all requirements are not met
- **ENDOTHELIN RECEPTOR ANTAGONISTS (bosentan, ambrisentan)**
 - Pulmonary Arterial Hypertension (PAH)
 - Life threatening
 - No alternative therapy
 - Teratogenic (Category X)
 - Population less likely to become pregnant (pregnancy contraindicated in PAH)
 - Patient can get Rx if testing requirements not met (through override mechanism)

Additional Tools within REMS

A REMS *may* include....

- MedGuide
- Patient Package Insert (PPI)
- Communication plan with healthcare providers about risks of the drug
- Procedures to assure safe use (ie. periodic monitoring or tests).

Reporting

- A REMS must include assessments at 18 months, 3 years and 7 years after strategy approval, *at a minimum*.

RiskMAPS for Patient Populations

- **Appropriate Professional Labeling**
 - Black box warning
- **Targeted Education and Outreach**
 - Health care practitioner letters
 - Training programs
 - Focused or limited promotional techniques
 - Continuing education for healthcare practitioners
 - Patient labeling
- **Reminder Systems**
 - Patient agreement or acknowledgement forms
 - Certification programs for practitioners (buprenorphine)
 - Special product packaging (Actiq)
- **Performance Linked Access Systems**
 - Prescription only by certified health practitioners

Assuring Access and Minimizing Burden

- For drugs that are effective but also have serious risks, FDA can establish a REMS to mitigate those risks.
 - FDA must post a statement on the Agency's website within 30 days of imposing a REMS explaining how the strategy will mitigate the risk.
 - When imposing a REMS under this provision, FDA must ensure that the strategy is commensurate with the risks involved.
 - **This includes considering whether the strategy will be unduly burdensome on patient access to the drug, particularly for patients with life-threatening diseases or patients with reduced access to healthcare.**
 - FDA must also issue regulations explaining how a physician may provide a REMS drug under the FDC Act's expanded access provisions at §561.

FDAAA §901(b)

Assuring Safe Use

- Training or Certification of health care providers (Dofetilide, Suboxone)
- Certification of pharmacies, practitioners or health care settings that dispense the drug (Dofetilide)
- Drug dispensed only in certain settings, such as hospitals (Dofetilide, Ionsys, Tysabri)
- Drug dispensed to patients with evidence or documentation of safe use conditions, such as lab tests (clozapine, isotretinoin, Tysabri, ERAs)
- Patients be subject to certain monitoring
- Patients be enrolled in a registry (Thalidomide)

Public Law 110-85 121 STAT. 930

Modifying a REMS

- Assessment of and modification to a REMS
 - May be submitted by a responsible person at any time
 - Assessments are required when:
 - submitting an application for a new indication of the drug,
 - required based on the agreed plan
 - requested by FDA based on new information, or
 - within 15 days of notification by FDA that withdrawal of approval may be appropriate under FDC Act §505(e).
 - Disputes arising from a REMS upon the initial approval of a drug will be handled under FDA's dispute resolution procedures. Other cases, handled by a Drug Safety Oversight Board.

FDA New Enforcement Power: CMP

Specific and Severe Penalties for Failure to Follow the Post Approval Requirements

- Penalties for Violations of FDC Acts:
 - §505(o), §505(p) and §505-1
- Civil Money Penalties are capped at \$250,000 per violation, up to maximum of \$1M for all violations in a single proceeding.
 - If such activity continues, additional \$250,000 for next 30-day period; \$500,000 for every 30-day period thereafter up to a max of \$1M for any 30-day period & \$10M for all violations in a single proceeding
- Misbranding

The Role of Epidemiologic Observational Studies in RiskMAPs or REMS

- **Detecting and evaluating known or suspected risks**
 - Quantifying the occurrence and severity of any known or potential adverse events as well as the background incidence of such events
 - Identifying previously unknown, rare, or delayed adverse effects

- **Quantifying the benefits associated with the drug and providing complementary data for evaluation of the drug's benefit-risk profile**
 - Assessing drug benefit in specific patient sub-populations

- **Evaluating the effectiveness of risk management interventions**
 - Assessing consumer and providers knowledge, attitudes and practices (thalidomide)
 - Assessing patient compliance and physician prescribing practices
 - Identifying and quantifying potential off-label use and medication errors

Epidemiologic Designs for Risk Evaluation and Management

■ **Descriptive Designs**

- Correlational studies (population-based analyses of drug utilization and market research data)
- Cross-sectional surveys
- Case reports and case series

■ **Analytic Observational Designs**

- Cohort studies (prospective and retrospective)
- Case-Control studies

■ **Registries**

- Patient registries
- Product registries
- Disease or condition registries
- Combinations of registry designs

Descriptive Studies

■ Purpose

- Describe the general characteristics of a disease or drug utilization patterns in relation to person, place, and time

■ Advantages

- Using population data that are readily available
- Can be done fairly quickly and easily

■ Limitations

- Exposure and outcome are assessed at the same point in time, therefore temporal relationship between them cannot be clearly determined
- Only useful for the formulation of hypotheses that can be tested subsequently using an analytic design

Analytic Observational Studies: Cohort Studies

■ Purpose

- Test a hypothesis of an association between the exposure (drug) and outcome (disease, adverse events, quality of life, etc.)

■ Advantages

- Subjects are classified on the basis of exposure, minimal selection bias
- Can establish the temporal sequence between exposure and outcome, thus make better inference on causality
- Allow the calculation of Relative Risk (RR)
- Allow for the examination of multiple effects of a single exposure

■ Limitations

- No randomization
- Involve following a large number of subjects for periods of time
- Loss to follow-up can seriously impact study results and validity
- Can be very time-consuming and expensive

Analytic Observational Studies: Case-Control Studies

■ Purpose

- Test a hypothesis of an association between the exposure (drug) and outcome (disease, adverse events, quality of life, etc.)

■ Advantages

- Subjects are classified on the basis of their disease/condition status thus this design allows the investigator to identify adequate number of diseased and non-diseased individuals
- Particularly useful for studying diseases with very long latency periods
- Optimal for evaluation of rare diseases or conditions
- More efficient than cohort studies in terms of both time and costs

■ Limitations

- No randomization
- More prone to various types of bias (selection, recall, interviewer, etc) than cohort studies
- Temporal sequence between exposure and outcome may be difficult to establish
- Cannot directly measure Relative Risk, odds of exposures are compared instead

Observational Studies: Registries

■ Purpose

- Used for a broad range of purposes but generally as “an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons who have either a particular disease, a condition (e.g. risk factor) that predisposes them to the occurrence of a health-related event, or prior exposure to substances known or suspected to cause AEs”¹

■ Advantages

- Not protocol bound or driven
- Data are collected in a naturalistic manner reflecting “real life” treatment practices, disease patterns, and patient compliance
- Can provide important post-marketing data on the incidence of SAEs (iPledge Pregnancy Registry)
- Can be used to evaluate the effectiveness of REMS and risk interventions
- Provide complimentary information about the real-world effects of treatments outside of the RCT settings

■ Limitations

- Potential for selection bias and confounding by indication
- Highly dependant on Physician’s interest
- Recruitment can pose serious ethical, logistical, and regulatory challenges

¹National Committee on Vital and Health Statistics, USDHHS

Questions?

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