What Can the Pharmaceutical Industry Learn From the History of Risk Assessment?

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Select Milestones in Chemical Risk Assessment

1954: Lehmann’s article proposing the use of safety factors
1970: OSHA and EPA are created
1976: Low dose extrapolation model for carcinogens is adopted
1984: PB – PK* models begin to be used
1994: EPA cancer guidelines updated and become generally accepted
1994: Monte Carlo techniques often used for risk assessments
2006: OMB opens the dialogue asking:

“Where are we headed..and why?”

*PB – PK = Physiologically based pharmacokinetic models
Anticipated Role of Risk Assessment in 1983

• A systematic process for quantitatively characterizing chemical hazards
• An objective process which was “separate and distinct” from decision making
• A way to educate the public so they could participate in the decision making process
• Vision documented by the NAS – “Risk Assessment in the Federal Government” (the Red Book)
The Role as Envisioned in 1994

- Risk assessment had become integrated into most regulatory guidance and policy involving chemicals
- Although evolving, the confidence in the exposure assessment component had increased
- Confidence was eroding with respect to the accuracy of low-dose extrapolation models (but they remained in regulatory policy)
- Vision documented by the NAS: “Science and Judgment” (the Purple Book - 1994)
What Has 30 Years Taught Us in Risk Assessment?

• There was considerable conservatism in the early risk assessments of the 1970s and 1980s

• The traditional cancer bioassays were not very helpful at predicting low dose risks

• Movement has been away from an LMS model for carcinogens and towards recognition that some may act through a threshold
What Has 30 Years Taught Us in Risk Assessment?

- Over the past 10 years, biologically based risk assessments have been favored.
- Attempts have been made to harmonize approaches for carcinogens and non-carcinogens.
- Transparency is an absolutely crucial step in the process.
- A quantitative description of the uncertainties is very helpful for the public and regulatory agencies.
- A straightforward communication of the risks is critical to enjoy the support of the public.
Nine Suggestions for the Pharmaceutical Industry
Opportunities for Risk Assessment

Decision Point

Research → Manufacturing → Sales → Post-Sales Evaluation
Recommendation #1:

“Humility about the limits of science is critical to enjoy the trust and respect of the public”
What Does This Mean?

• The press and others have convinced the public that the scientific community doesn’t understand what causes disease (especially in certain population subgroups)

• Consequently, scientific analyses are often not trusted by the public

• Recent government studies involving HRT and role of diet have damaged credibility

• The public is suspicious of claims that “at a given dose, there should be no risk”
Recommendation #2:

“Transparency is absolutely critical to maintain the trust of the public and regulatory agencies... and to satisfy the expectations of trial attorneys”
What Does This Mean?

- Agencies, NGOs, trial attorneys and others want to be able to reconstruct the scientific analyses.
- These parties want to understand where professional judgment vs. objective quantitative methods were used.
- They also want to know the level of uncertainty in the analyses and their conclusions.
- Pharmaceutical companies, unfortunately, are increasingly being placed in the same “basket” as chemical companies.
Recommendation #3:

“Use quantitative techniques to describe the uncertainty in your risk estimates”
What Does This Mean?

• Today, it is usually possible to quantitatively describe the uncertainty using Monte Carlo methods

• The diversity of views among experts can be included and accounted for in such analyses
Recommendation #4:

“Acknowledge that genetic polymorphisms exist and that most have not been characterized”
What Does This Mean?

- As time passes, we have come to recognize that there may be more than one dose–response curve for some chemicals.
- Evidence of significant differential susceptibility is best illustrated by sensitizing agents (such as certain metals, isocyanates, acrylates).
- We now know of numerous biologic variations or deficiencies among persons:
  - Glucose 6 Phosphate Dehydrogenase (G6PD) deficiency
  - Differences in alcohol dehydrogenase activity, particularly in certain ethnic groups
  - Lactose intolerance
  - Cytochrome P450 families of enzymes
Recommendation #5:

“In chemical risk assessment, we are often confident that we can identify safe doses (because exposures are usually quite low). However, pharmaceutical agents often involve relatively high doses and human safety may be more difficult to pinpoint.”
What Does This Mean?

- Concentrations of chemicals in air, water and soil are usually quite low (i.e., rarely present an acute hazard)

- The risks associated with low level environmental exposures are usually quite low (involving theoretical risks of 1 in 100,000 or less)

- The margin of safety for many pharmaceutical agents is less than a factor of ten (certain seizure medications, chemotherapeutic agents, insulin, tricyclic antidepressants)
Recommendation #6:

“Clearly describe the benefits of taking the drug and compare with the possible risks”
What Does This Mean?

• Most Americans want to know the risk/benefit relationship and are taking a more active role in their medical decisions

• Most persons will accept higher levels of medication risk if they understand how it compares with the litany of risks they face in their daily lives

• Product inserts are probably not going to be considered adequate in the coming years...they are simply too technically dense
Recommendation #7:

“Discuss the risks of NOT taking the drug...that is, allowing the underlying disease to progress, or the symptoms to be untreated”
What Does This Mean?

• Consumers want to know, from their physicians and pharmaceutical companies, what will happen if they don’t take the recommended medications.

• For example, there may be a theoretically increased cancer risk of 1 in 10,000 of taking a particular blood pressure medication, but there may be a 1 in 100 chance that my life will be shortened by 15 years if I don’t take the drug.
Recommendation #8:

“Be clear about the risks and benefits of taking your drug with other pharmaceutical and recreational drugs, and the roles of diet, exercise and other factors with respect to the ‘total approach’ to dealing with the illness”
What Does This Mean?

- It will become increasingly important to remind the public about their role and responsibilities in helping to minimize the adverse impact of their disease process...or even how to prevent it from occurring.

- Except for alcohol, other confounding drugs, vitamins, alternative medicines and foods are usually not discussed in much detail for consumers.
Recommendation #9:

“The importance of strong federal agencies grounded in science cannot be underemphasized”
What Does This Mean?

• Strong, credible regulators effectively protect industry from public suspicion and tort litigation

• Pharmaceutical companies provide themselves with the best defense by combining this with proper industrial science, performed with integrity and diligence
Recommendation #10:

“Don’t try to hide the ball”
What Does This Mean?

• In recent years, Americans have insisted that they be informed of all possible risks to which they are exposed.

• Rarely, if the risk is clearly discussed and emphasized, will the public or an Agency get angry with a manufacturer.

• Over the past five years, regulatory agencies and the courts have decided that one almost has to advertise when they have concerns about an agent..and I don’t expect this to change.
“After 30 years, chemical risk assessors have learned that conducting good scientific analyses is not enough...one has to be transparent, direct, forthcoming, and willing to acknowledge uncertainties in our medical or scientific understanding.”
“Chance favors only the prepared mind.”

*Louis Pasteur*