Biomarkers: Dynamic “Tools” For Health And Safety Risk Assessments

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Biomarkers: Dynamic “Tools” For Health And Safety Risk Assessments

Tasks:
- Discuss how regulatory agencies use biomarkers in developing public health policy
- Identify key weaknesses in current available biomarkers
- Identify barriers to validating additional biomarkers applicable to public health policy

Resources:
1. Toxicologic Biomarkers, Anthony DeCaprio (Editor), Taylor and Francis, 2007.
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Task

-Discuss how regulatory agencies use biomarkers in developing public health policy
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Terminology and Definitions

**Biomarker**: “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to an intervention”

**Analytical Validation**: “assessing an assay and its measurement performance characteristics, determining the range of conditions under which the assay will be reproducible and accurate data”

**Surrogate Endpoint**: “a biomarker that is intended to substitute for a clinical endpoint. … expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence”

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Biomarker Types, Applications, Uses

Types
- Lipids
- Proteins: Protein Modifications
- Nucleic acids: DNA (SNPs; modifications), RNA (mRNAs; microRNAs)
- Metabolites: Carbohydrates, Vitamins/Nutrients
- Hormones
- Cells: Stem Cells, Microparticles
- Physiological Responses
- Xenobiotics
- Bioimaging

Applications
- Efficacy
- Exposure
- Toxicity
- Susceptibility
- Health Status
- Disease Status: Detection, Monitoring, Prognosis, Diagnosis
- Personalized Medicine

Use(s)
- Biomonitoring
- Safety
- Risk Assessment
- Risk Management
- Risk vs. Benefit

Regulatory Decisions
- EPA
- FDA
- Etc.

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Public, Ecology, and Environmental Health

Risk Assessment

Risk Management

Dose-Response Assessment
Hazard Identification
Risk Characterization
Exposure Assessment
Statutory and Legal Considerations
Public Health Considerations
Social Factors
Risk Management Options
Economic Factors
Political Considerations
Risk Management Decision

*Adapted from:
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EPA, CSPC, CDC: Biomarkers of Exposure, Toxicity, Susceptibility and Air Pollution/Toxics & Consumer Products Standards

CSPC - The Consumer Product Safety Improvement Act (CPSIA), August 2008, makes it illegal to sell children's products with more than 600 ppm total lead. The total lead limit will drop to 300 ppm in August 2009 and to 100 ppm in 2010.

EPA (TSCA) - April 22, 2010, regulations require certification of renovation firms under the Agency's “Renovation, Repair and Painting Rule” (RRP), 40 CFR Part 745. Under the new standards, lead is considered a hazard when equal to or exceeding:

- 40 micrograms of lead in dust per square foot on floors;
- 250 micrograms of lead in dust per square foot on interior window sills;
- 400 parts per million (ppm) of lead in bare soil in children's play areas;
- 1200 ppm average for bare soil in the rest of the yard.

EPA (NAAQS) - October, 2008, NAAQS for Lead, 0.15 µg/m³ (rolling 3 month ave.)
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EPA: Biomarkers of Exposure, Toxicity, Susceptibility and Air Pollution Health Risk

NAAQS Particulate Matter (PM)

<1990, particle effects were focused on pulmonary system with alterations on lung function, allergy, asthma and infection being the primary focus of PM health effects research.

This changed in 1993 with the publishing of Harvard Six City Epidemiology Study reporting increased mortality occurring at or below the NAAQS PM standard that was in place over the previous 10 year period.
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EPA: Biomarkers of Exposure, Toxicity, Susceptibility and Air Pollution Health Risk

“Translatable Responses”

('04 - '12) Epidemiology

('00 - '12) Clinical Studies

('97 - '12) Animal Studies

(Healthy and Susceptible Cardiovascular Compromised Rodent Models)
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EPA: Air Pollution Health Effects Risk Management

1971 - Issued the first National Ambient Air Quality Standard for Air Particulate Pollution:
- Total Suspended Particles (TSP), ~25 - 45 µm, 260 µg/m³ (24h ave.)
- 75 µg/m³ (annual mean)

1987 - Replaced TSP with PM₁₀ to target inhalable particles < 10 µm:
- 150 µg/m³ (24h ave.); 50 µg/m³ (annual mean).

1997 - Two size standards, fine and coarse particles:
- Fine PM₂.₅ - 65 µg/m³ (24h ave.); 15 µg/m³ (annual mean)
- Coarse PM₂.₅-₁₀ - 150 µg/m³ (24h ave.); 50 µg/m³ (annual mean);

2006 - Fine PM₂.₅ 35 µg/m³ (24h ave.); 15 µg/m³.
- Coarse PM₂.₅-₁₀ - 150 µg/m³ (24h ave.)

www.epa.gov/ttnnaaqs/standards/pm/s_pm_history.html
EPA (TSCA; FIFRA; OPPTS Harmonized Test Guidelines, Series 870 Health Effects)

It has been estimated that over 80,000 chemicals are in use in the US with an average of over 700 new ones introduced annually with the complete knowledge of their potential health effects for most of them unknown. In some cases such as novel engineered nanomaterials the risk to human health and environment are unknown.

> Systems Biology Approach
> High Throughput Technology
> Informatics/Modeling
> Testing Options:
  1. *In Vivo*
  2. Tiered *In Vivo*
  3. *In Vitro* and *In Vivo*
  4. *In Vitro*

> Establish biomarkers and alternative testing methods/approaches that predict chemical *in vivo* toxicity
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Biomarkers for Chemical: Prioritizing, Assessing, and Management

Toxicological Priority Index (ToxPi)
A new weight-of-evidence framework for profiling and prioritizing chemicals.

www.epa.gov/ncct

Endocrine Disruptor Screening
Endocrine profiling and prioritization of environmental chemicals using ToxCast data. PMID 20826373

ToxCast; Tox21 > Health Effects Data
ToxRfDB > Health Effects Data
ToxExpo > Exposure Data

ToxPi
(Vascular Disrupting Chemicals)

Validation → Translation → Extrapolation

> Biomarkers of Toxicity
> Alternative Tests/Approaches Predictive of In Vivo Toxicity
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Biomarkers for Drug Safety and Efficacy

Conceptual diagram illustrates the use of biomarkers in drug development. Biomarkers that guide full development and regulatory decisions require more rigorous validation and greater predictive power than biomarkers that support decisions during early development.

2. E. Floyd and T. M. McShane, Toxicologic Pathology, 32(Suppl. 1):106-115, 2004
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Biomarkers for Drug Safety

Drug Attrition/Withdrawal

<table>
<thead>
<tr>
<th>Phase</th>
<th>Ph I to III</th>
<th>Ph I</th>
<th>Ph II/III</th>
<th>Ph III, Market</th>
<th>Market</th>
<th>Market</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information</td>
<td>Attrition</td>
<td>Serious ADRs</td>
<td>Serious ADRs</td>
<td>ADRs</td>
<td>Serious ADRs</td>
<td>Withdrawal 1975-2007</td>
</tr>
<tr>
<td>Sample size</td>
<td>63 CDs</td>
<td>1,015 subjects</td>
<td>?</td>
<td>1,138 drugs</td>
<td>21,298 patients</td>
<td>47 drugs</td>
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<tr>
<td>CVS</td>
<td>34.9%</td>
<td>9.3%</td>
<td>6.4%</td>
<td>35.7%</td>
<td>25.0%</td>
<td>44.7%</td>
</tr>
<tr>
<td>Liver</td>
<td>28.6%</td>
<td>9.3%</td>
<td>0%</td>
<td>12.7%</td>
<td>10.5%</td>
<td>31.9%</td>
</tr>
<tr>
<td>Nervous system</td>
<td>1.6%</td>
<td>27.9%</td>
<td>2.3%</td>
<td>64.9%</td>
<td>30.2%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Genetic Tox</td>
<td>0%</td>
<td>-</td>
<td>-</td>
<td>(No terms)</td>
<td>-</td>
<td>0%</td>
</tr>
<tr>
<td>Dev Tox</td>
<td>3.2%</td>
<td>-</td>
<td>-</td>
<td>8.1%</td>
<td>-</td>
<td>0%</td>
</tr>
<tr>
<td>GI</td>
<td>1.6%</td>
<td>23.3%</td>
<td>10.8%</td>
<td>66.6%</td>
<td>14.2%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Renal</td>
<td>4.8%</td>
<td>4.7%</td>
<td>2.3%</td>
<td>18.5%</td>
<td>2.4%</td>
<td>0%</td>
</tr>
<tr>
<td>Immuno-tox</td>
<td>4.8%</td>
<td>2.3%</td>
<td>0%</td>
<td>5.0%</td>
<td>33.5%</td>
<td>2.1%</td>
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<tr>
<td>Testicular tox</td>
<td>1.6%</td>
<td>-</td>
<td>0%</td>
<td>2.5%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>3.2%</td>
<td>2.3%</td>
<td>6.3%</td>
<td>15.5%</td>
<td>0%</td>
<td>8.5%</td>
</tr>
<tr>
<td>Others</td>
<td>Up to 4.8%</td>
<td>Up to 14%</td>
<td>Up to 3.2%</td>
<td>-</td>
<td>Up to 26.3%</td>
<td>Up to 2.1%</td>
</tr>
</tbody>
</table>

1. HESI, Technical Committee on Cardiac Safety, Review 2009. (Jean-Pierre Valentin, Ph.D. AstraZeneca, France)

Toxicity Observed Mostly in Late Phase of Clinical Trials and Post-Market Surveillance

Toxicities/Adverse Drug Reactions:
- Cardiovascular
- Hepatic
- Neurological
- Renal
- Gastrointestinal
- Immune

Drug Cardiovascular Biomarkers:
- ICH Guidelines ICH S7A and ICH S7B
- HESI, Cardiac Safety Technical Committee Working Groups
- Critical Path Institute, Predictive Safety Testing Consortium

Chemical Cardiovascular Biomarker:
- US EPA, Chemical Safety for Sustainability Path Forward Program
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Weaknesses in Current Biomarkers

- Time and Resource Intensive
  (Discovery > Analytical Validation >> Qualification >>>> Surrogate Endpoint)

- Translational and/or Predictive Capability for Many Are Low
  - ideally preclinical <> clinical communications

- Early Detection of Adverse Effects Lacking
  - is it due to specificity and/or sensitivity of biomarkers and/or
  - lack of identifying the critical health endpoint(s)

- Biomarkers for Susceptibility and/or Life Stage Effects “?”

- Biomarkers for Chronic and/or Cumulative Effects “?”

- Lack of Exposure to Dose to Effect Linkages Often Lacking
  and Often Developed at High Doses\Exposures

- Not Keeping Pace with Technology
  (New Chemicals: Nanomaterials/Drugs)
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Challenges in Developing Future Biomarkers

- Develop New Biomarkers and Faster Capable of Detecting Early Toxicities
- Application of Biomarkers
  Y. Hao et al., Cancer Investigation, 29:318-324, 2011
  “Positive predictive value analysis of prostate cancer was increased from 40% to 87.5% by integrating patient PSA blood levels with miR-21 and miR-141 profiles”.
- Communication, Coordination and Harmonization in Biomarker Development
- Harmonizing Regulatory Use and Approval of Biomarkers
  Strength-of-evidence based criteria for evaluating and applying biomarkers
- Nomenclature and Hierarchically Categorized Biomarkers
  (Risk Assessors: how “good” is this biomarker?; what does it measure?)
- Biomarkers Derived From Alternative Methods Predictive of In Vivo Toxicity