FDA’s Science Needs

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Food and Drug Administration
Legislative Assumptions

- History of Safe Use
- Public Health Benefit
- Significant or unreasonable risk under conditions of use
## Regulatory Framework

<table>
<thead>
<tr>
<th></th>
<th>Supplements</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regulation</strong></td>
<td>Food</td>
<td>Drug</td>
</tr>
<tr>
<td><strong>Users</strong></td>
<td>General; healthy</td>
<td>Sick; symptomatic</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Risk</td>
<td>Risk/benefit</td>
</tr>
<tr>
<td><strong>Claims</strong></td>
<td>Risk reduction; Structure/ function</td>
<td>Treat, cure, mitigate, prevent</td>
</tr>
</tbody>
</table>
Who Bears the Burden?

Concept

Manufacturer

Market

FDA Review????

FDA

FDA action
What is the Starting Point?

Null hypothesis

Not effective → Effective

Not safe → Safe

Body of evidence
What is the Starting Point?

Assume
Unsafe

Same evidence

Safe

Conclude
Unsafe

Safe
What is the Starting Point?

Criteria

Risk

Risk/benefit

Conclude

Unsafe

Same evidence

Safe
What is the Starting Point?

Assume

- Effective
- No effect

Conclude

- Effective
- Not effective

Same evidence
“Usual” Scientific Process

Pre-Clinical

Clinical Studies

For substance to be marketed under anticipated conditions of use
“Reality” – Scientific Evidence

- History of use
  - Efficacy studies
  - Observational data

Safe
“Reality” – Scientific Evidence

History of use
- Drug efficacy study
- Observational data

Effective as a supplement
“Reality” -- Available Evidence

- Generalize:
  - Single high dose to lower dose
  - Short term to long term use
  - High risk to general population
  - One product to all products
Post-market Safety Challenges

- Under- and incomplete-reporting
- Product composition
- Consumer:
  - Use patterns
  - Individual sensitivities
- Causality
- Biological plausability
### Ephedra: Adrenergic activity

<table>
<thead>
<tr>
<th></th>
<th>α</th>
<th>β₁</th>
<th>β₂</th>
<th>CNS</th>
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<tr>
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<td>++</td>
<td>++</td>
<td>++</td>
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<tr>
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<td>+</td>
<td>+</td>
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<td>+</td>
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</tbody>
</table>
Interactions: Soy Protein

- Net Effect?
  - Daidzen
  - Genistein
  - Equol
  - Gut flora
  - Soy protein matrix
Interactions

- **Active Ingredients/Product:**
  - Mean: 22
  - Range: 1 to >50
- Multiple products used
Use Conditions

- Concurrent rapid weight losses
- Physical exertion/dehydration
- Concurrent illnesses
- Interactions with drugs and foods
- Interactions within individual products
Evaluation strategies

- Generic vs. product specific
- Pre-market systematic approaches
- Post-market monitoring and surveillance
  - Biomarkers
  - Product composition and use patterns
Research Needs

- Relevance to supplement use as a food
- Individual sensitivities/idiosyncrasies
- Drug and food interactions
- How use conditions alter potential for toxicity
Research Needs

- Validation of analytical methods
- Validation of rapid screening tests
- Validation of animal models
- Validation of “interpretable” biomarkers for population monitoring and surveillance
- Relative effects
Safety Research Needs

- Link to adverse events
- Relevant to conditions of use
- Biological plausibility
- Relative toxicities
Summary

- General population
- Risk reduction, not treatment etc.
- Risk, not risk/benefit
- Research:
  - Pre-market
  - Post-market