Tobacco Manufacturers Panel Discussion I – Introduction & Pre-Clinical Study Standards

IOM Committee “Scientific Standards for Studies on Modified Risk Tobacco Products”

May 9, 2011

Michael W. Ogden, Ph.D.
Sr. Director – Regulatory Oversight
Agenda

• Panel Overview
• Introduction
• Pre-Clinical Study Standards for Tobacco Products
  – Product Chemistry
  – Toxicity Studies
    • In Vitro
    • In Vivo
Panel Overview

- **R. J. Reynolds Tobacco Co.**
  - Introduction
  - Standards for pre-clinical studies
- **British American Tobacco (Investments) Ltd.**
  - Standards for studies on in vitro models of disease
- **Altria Client Services**
  - Standards for clinical studies and biomarkers
- **Swedish Match**
  - Population effects, risk communication & perception
- **Lorillard Tobacco Co.**
  - Summary
- **Discussion**
Modified Risk Tobacco Products

Introduction
**Modified Risk Tobacco Products (MRTP)**

**HOW THE FSPTCA DEFINES “MODIFIED RISK” PRODUCTS (Sec. 911)**

- “Modified risk tobacco product” means any tobacco product sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercial tobacco products.
- Includes products where labeling or advertising indicates (explicitly or implicitly):
  1. Less risk or less harmful;
  2. Reduced level of a substance or presents a reduced exposure to a substance;
  3. The product does not contain or is free of a substance;
  4. Use of descriptors such as “light”, “mild”, or “low” or similar descriptors.

**• A modified risk product may be commercially marketed only if FDA determines the applicant has demonstrated that product will**

- Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users;
- Benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products.

**• Scientific Evidence: Not later than 2 years after enactment, FDA will issue regulations and/or guidance on the scientific evidence required for assessment & ongoing review of modified risk tobacco products**

- The minimum standards for studies necessary prior to issuing an order (i.e., clearance) will be established;
- The requirements of post-market surveillance studies mandated by the Act will be defined.
MRTP Claim Spectrum*

- No Claim
- Reduced Level of a Substance
- Does Not Contain a Substance
- Reduced Exposure
- May Present Less Risk
- Reduced Risk

*For illustrative purposes only
Scientific Evidence Required for MRTP Claims

- Evidence required is claims-dependent
- Some claims will be far easier to support than others
  - Inter-category claims (e.g., Cigarettes vs. Smokeless)
    - Epidemiology already exists
  - Intra-category claims (e.g., within Cigarettes or Smokeless)
    - Comparative testing will be key
Harm Reduction

• The development of products to address health concerns is termed “harm reduction” and has been reviewed by the Institute of Medicine (IOM)*

• IOM coined the term PREP (potentially reduced exposure product) to describe products that have the potential to reduce exposure to one or more toxicants present in smoke

• Harm reduction potential can be assessed when a PREP product has been used by enough consumers for a period of time sufficient to assess the health impact of the product

*IOM, 2001: Clearing the Smoke - Assessing the Science Base for Tobacco Harm Reduction
IOM* Guidelines

1. No evidence of unintended consequences
   - It is essential that manufacturers ensure that product modifications do not increase the biological activity of cigarettes

2. Evidence of reduced exposure
   - Evidence of reduced exposure may include data from multiple types of studies

3. Biological plausibility
   - Sufficiently compelling argument to support the conclusion that a demonstrated reduction in exposure would be anticipated to result in a measurable reduction in morbidity and/or mortality in subsequent clinical or epidemiological studies

4. Independent scientific verification
   - All evidence is verified and validated by an external, preferably government appointed body

Details

- Smoke Chemistry yield data under multiple machine regimens
- In Vitro Toxicology
- Animal Toxicology
- Comprehensive preclinical toxicology
- Short-term biomarkers of effect data in smokers
- Quantitative risk assessment
- Biological plausibility evidence

Potential Data

- Evidence of reduced exposure may include data from multiple types of studies
- No evidence of unintended consequences
- Evidence of reduced exposure

*IOM, 2001: Clearing the Smoke - Assessing the Science Base for Tobacco Harm Reduction
It is essential that manufacturers ensure that product modifications do not increase the biological activity of cigarettes.

Evidence of reduced exposure may include data from multiple types of studies.

Sufficiently compelling argument to support the conclusion that a demonstrated reduction in exposure would be anticipated to result in a measurable reduction in morbidity and/or mortality in subsequent clinical or epidemiological studies.

All evidence is verified and validated by an external, preferably government appointed body.

<table>
<thead>
<tr>
<th>Details</th>
<th>Potential Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>No evidence of unintended consequences</td>
<td>Smoke Chemistry yield data under multiple machine regimens</td>
</tr>
<tr>
<td>Evidence of reduced exposure</td>
<td>In Vitro Toxicology</td>
</tr>
<tr>
<td>Biological plausibility</td>
<td>Animal Toxicology</td>
</tr>
<tr>
<td>Independent scientific verification</td>
<td>Comprehensive preclinical toxicology</td>
</tr>
<tr>
<td></td>
<td>Short-term biomarkers of effect data in smokers</td>
</tr>
<tr>
<td></td>
<td>Quantitative risk assessment</td>
</tr>
<tr>
<td></td>
<td>Yield-in-use data</td>
</tr>
<tr>
<td></td>
<td>No evidence of unintended consequences</td>
</tr>
<tr>
<td></td>
<td>Evidence of reduced exposure</td>
</tr>
<tr>
<td></td>
<td>Biological plausibility evidence</td>
</tr>
</tbody>
</table>
## IOM Guidelines

<table>
<thead>
<tr>
<th>Details</th>
<th>Potential Data</th>
<th>Evidence of reduced exposure</th>
<th>Biological plausibility</th>
<th>Independent scientific verification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No evidence of unintended consequences</td>
<td>Evidence of reduced exposure may include data from multiple types of studies</td>
<td>Sufficiently compelling argument to support the conclusion that a demonstrated reduction in exposure would be anticipated to result in a measurable reduction in morbidity and/or mortality in subsequent clinical or epidemiological studies</td>
<td>All evidence is verified and validated by an external, preferably government appointed body</td>
</tr>
<tr>
<td></td>
<td>It is essential that manufacturers ensure that product modifications do not increase the biological activity of cigarettes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Evidence of reduced exposure may include data from multiple types of studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Biological plausibility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Independent scientific verification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Smoke Chemistry yield data under multiple machine regimens</td>
<td>Smoke Chemistry yield data under multiple machine regimens</td>
<td>Comprehensive preclinical toxicology</td>
<td>No evidence of unintended consequences</td>
</tr>
<tr>
<td></td>
<td>In Vitro Toxicology</td>
<td>Biomarker of exposure data in smokers</td>
<td>Short-term biomarkers of effect data in smokers</td>
<td>Evidence of reduced exposure</td>
</tr>
<tr>
<td></td>
<td>Animal Toxicology</td>
<td>Yield-in-use data</td>
<td>Quantitative risk assessment</td>
<td>Biological plausibility evidence</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pre-Clinical Study Standards for MRTPs

Brief Overview of RJRT Perspective
Risk Reduction Assessment

• Philosophical Approach
  – An integrated extension of RJRT’s product stewardship program
  – Same initial focus on establishing that proposed modifications will not increase risk to the consumer
  – Additional focus on assessing risk reduction potential
Guiding Principles and Beliefs

• An individual’s level of risk for serious disease is significantly affected by the
  – Type of tobacco product used
    • Non-clinical (laboratory) studies
  – Manner and frequency of use
    • Clinical (human) studies
Product Stewardship

- Currently there is no standardized approach to the evaluation of tobacco products
- RJRT employs a tiered-testing approach that is based on evaluation strategies employed by U.S. industry and regulatory agencies to evaluate other consumer products
- The approach has been presented at scientific conferences and described in the peer-reviewed literature
- Similarities exist in evaluation strategies among major U.S. and international tobacco companies
No Single Test Provides the Answer

- The specific tobacco/smoke constituents associated with observed risks are not known with certainty
- There are no in vitro or animal models that are direct measures of tobacco-related diseases
- Lack of clear mechanisms makes it difficult to focus on specific compound reductions or a single biological endpoint
Suitability of Pre-Clinical Assessment Methods

• Suitable pre-clinical tobacco test methods must be
  – Relevant to tobacco-related disease
  – Responsive to the relevant test matrix (cigarette smoke, smokeless tobacco extract)
  – Sufficiently sensitive to differentiate between products within a tobacco category (cigarettes, smokeless)
Exposure / Risk Assessment Approach

- **Product chemistry assessment**
  - Reduction in content/yield

- **Pre-clinical toxicology**
  - Reduction in toxicity

- **Clinical studies**
  - Reduced exposure/effects in adult tobacco consumers

- **Quantitative risk assessment**
  - Biological plausibility
Smoke Chemistry

• **Standard smoke measures**
  – Machine tests with standardized smoking conditions
    • ISO tar, nicotine and carbon monoxide yields
    • Other smoke regimens as deemed appropriate

• **Specific Compound Determinations**
  – Specific toxicant yields reportedly associated with risks of smoking
    • E.g., formaldehyde, cadmium, benzo[a]pyrene, NNK, etc.

• **Other measures as indicated**
  – Gross measures
    • A chemical or physical property of mainstream smoke particulate matter such as thermogravimetric analysis
  – Aggregate chemical measures
    • Evaluate the response of many smoke components in a single analysis such as chromatographic profiling
Smokeless Chemistry

• Standard measures
  – Moisture / oven volatiles, nicotine, pH, etc.

• Specific Compound Determinations
  – Specific toxicants reportedly associated with risks of smokeless tobacco use
    • Acrylamide, cadmium, benzo[a]pyrene, NNK, etc.
Pre-Clinical Toxicology

• Specific chemical reductions alone cannot predict reduced toxicity
• No single biological assay can directly measure disease risk
• A battery of pre-clinical studies must be used
  – To indicate the biological significance of the chemical changes
  – To demonstrate biologically relevant and significant exposure reductions
Pre-Clinical Toxicology
In Vitro Studies

• Mutagenesis (Ames Test)
  – Specific point mutations of one or a few DNA base pairs
    • Smoke condensate and smokeless extract

• Cytogenetics (Sister Chromatid Exchange or Micronucleus Test)
  – Modification of chromosome structure
    • Whole smoke, smoke condensate and smokeless extract

• Cytotoxicity (Neutral Red Assay)
  – Sensitive and integrated measure of cell integrity and growth
    • Whole smoke, smoke condensate and smokeless extract

• All tests
  – Have a long history in tobacco studies (especially cigarettes)
  – Are reproducible
Pre-Clinical Toxicology
In Vivo (Animal) Studies

Cigarettes

• Whole smoke
  – 90 day inhalation study in rats
    • Studies consistent with FDA-GLP and OECD Guidelines
    • Subchronic studies provide all necessary pathology data for comparative purposes
    • Chronic studies provide no additional information beyond changes observed at 90 days
  – Smoke tumorigenesis cannot be assessed using the inhalation model
    • Animal studies designed to model respiratory tract cancer in humans have met with limited, if any, success
    • Chronic inhalation studies do not form a sound basis to compare the tumorigenic effects of different cigarettes

• Cigarette smoke condensate (CSC)
  – Dermal tumor promotion study in mice
    • Scientific consensus (40+ years) supports the use of mouse skin model as an assessment of the tumorigenic potential of CSC
    • Substantial, statistically-significant and reproducible tumorigenic responses have been observed in mouse dermal-application studies with CSC

Smokeless tobacco

• Rodent feeding studies
  – Acute, subchronic and/or chronic
Scientific Judgment is used to Conclude Reduced Exposure

<table>
<thead>
<tr>
<th>Potential Data for Plausibility</th>
<th>Relevant Data</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comprehensive preclinical toxicology</td>
<td>At a minimum, a statistically significant decrease in toxicity must be achieved</td>
<td>Level of reduction must be biologically meaningful – which means it should be large enough to suggest the observed difference will manifest itself as decreased mortality and morbidity</td>
</tr>
<tr>
<td>Biomarkers of exposure</td>
<td>At a minimum, a statistically significant decrease in biomarkers of exposure must be achieved</td>
<td>Should reflect our existing knowledge of relevant epidemiology associated with disease modeled by the pre-clinical assay</td>
</tr>
<tr>
<td>Quantitative risk assessment</td>
<td>At a minimum, a statistically significant decrease in calculated risk must be achieved</td>
<td></td>
</tr>
</tbody>
</table>

- To establish plausibility, there should be directionally consistent data from multiple data types
- It is scientifically unsound to set a specific global reduction in activity level that must be achieved
Potential MRTP Case Studies

- **Low-TSNA Cigarettes**
  1. Chemical Analysis → Reduced TSNAs
  2. Toxicology Testing → No Difference
  3. Studies in Smokers → Not Tested*
     - MRTP application not warranted

- **Eclipse Cigarettes**
  1. Chemical Analysis → Significant Toxicant Reductions
  2. Toxicology Testing → Substantially Lower Toxicity
     - MRTP application may be warranted

*Steps 1 & 2 must show reductions to proceed to Step 3.
Conclusions

- Different MRTP claims are possible under the FSPTCA
- Previous IOM guidelines are still relevant and reasonable as a roadmap to required lines of scientific evidence
- Appropriate assays and methods are available to compare differences in
  - Chemistry
  - Toxicity
  - Product usage behavior
  - Exposure
  - Quantitative risk assessment
- The patterns of changes in chemistry, biology and exposure must be considered as a whole
- Experts must weigh the evidence and extrapolate to assess harm-reduction potential
  - Extrapolation is required prior to market entry
  - True harm reduction measurements in the population require that products are available and usage/exposure/risk are tracked with time