Dissolvable Tobacco Products: Chemistry & Toxicology

Tobacco Products Scientific Advisory Committee

July 21-22, 2011

Charles D. Garner, Ph.D., DABT, CIH

Sr. Director, Regulatory Oversight

RJReynolds

Presentation Objectives

- Overview of RJRT Stewardship principles and process for the assessment of smokeless tobacco products
- Describe Stewardship evaluation to support dissolvable tobacco products (Sticks, Strips and Orbs)

Outline

RJRT Stewardship Principles

Stewardship Approach for Smokeless Products

- Ingredient Assessment
- Chemistry
- *In vitro* studies
- *In vivo* studies

Child Resistant Packaging

Product Stewardship Guiding Principles

- The primary objective of the product stewardship program at RJRT is to ensure that product changes do not increase the biological activity of our products.

- We work to ensure that nothing we do or add to our products will increase the inherent risks associated with their use.

Product Stewardship
Product Changes - Examples

- Design parameters outside predicate universe
  - Materials not previously used
  - Materials in significantly greater amounts
- New or modified manufacturing processes
- Non-traditional products (for RJRT)

Product Stewardship

- RJRT has applied the product stewardship model in one form or another for at least 20 years to evaluate changes in cigarette design that have the potential to modify the quantity and/or quality of cigarette smoke.
- More recently, this concept has been extended to smokeless products.
- The corresponding FDA terminology for the RJRT approach to product stewardship is the concept of substantial equivalence.

RJRT Product Stewardship

- RJRT's approach to Product Stewardship is based on a tiered testing strategy
- Is based on the premise that the degree of effort expended to evaluate the use of an additive or process should relate logically to the likelihood that the modification might pose a public health risk.
- Entails product and process review by board certified toxicologists and assignment of a "Level of Concern" ("LOC") ranging from I (low) to V (high).
- Any LOCs greater than LOC I require chemical and/or biological testing in an escalating tiered testing strategy.

Ingredient Assessment

- Ingredients added to tobacco are evaluated in order to determine whether the use of an ingredient might pose an adverse health effect.

- This determination is conducted by evaluating the potential hazard(s) associated with the ingredient and the potential exposure of the consumer to the ingredient in question.

Smokeless Tobacco Product Ingredient Assessment

An ingredient added to tobacco is generally approved for use if one or more of the following is true:

(a)currently used by R.J. Reynolds at comparable levels;

(b)considered to be a food or food product by Food and Drug Administration (FDA) and/or U.S. Department of Agriculture (USDA);

(c)approved as a food additive by FDA or; given the status Generally Recognized as Safe (GRAS) by FDA, other expert committees or international regulatory bodies;

(d)adequate information is available in the public-access open-literature to support a lack of expected adverse health effects at the proposed inclusion levels and intended conditions of use.

Ingredient Assessment-Conclusion

- RJRT scientists reviewed the literature on the non-tobacco ingredients used in Orbs, Sticks and Strips.
- All materials are food-grade or pharmaceutical-grade ingredients.

Chemistry Evaluation

- Evaluating product chemistry is one part of the battery of tests RJRT used to compare dissolvable tobacco products to a range of smokeless tobacco products currently in the market.

- Through its chemical characterization program, RJRT compared the levels of toxicants in dissolvable tobacco products to existing smokeless tobacco products.

Chemistry Evaluation

Swedish Match GothiaTek® Limits

- Swedish Match has developed its own quality standard, GothiaTek®.
- Includes chemical evaluation of potentially harmful constituents

Constituent	Unit	Limit* (50%)	Limit (Dry wt.)
Nitrite	µg/g	3.5	7.0
TSNA	µg/g	5	10
NDMA	ng/g	5	10
BaP	ng/g	10	20
Cadmium	µg/g	0.5	1.0
Lead	µg/g	1.0	2.0
Arsenic	µg/g	0.25	0.5
Nickel	µg/g	2.25	4.5
Chromium	µg/g	1.5	3.0

*GothiaTek® standards are based on Swedish moist snus with 50% water content. The value is adjusted when considering constituents on a dry weight basis.

Chemistry Evaluation

Current RJRT Smokeless Chemical Constituent Target List:

Heavy Metals	**Polycyclic Aromatic Hydrocarbons**
Arsenic	Benz[a]anthracene
Cadmium	Benzo[a]pyrene
Lead	Benzo[b]fluoranthene
Nickel	Chrysene
Chromium	Dibenz[a,h]anthracene
N-Nitrosamines	Indeno[1,2,3-cd]pyrene
N-nitrosonornicotine (NNN)	Naphthalene
N,N-nitrosodiethylamine (NDEA)	**Others**
4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK)	Acrylamide
N,N-nitrosodimethylamine (NDMA)	Nitrite
N,N-nitrosoethylmethylamine (NEMA)	Nicotine
N'-nitrosopyrrolidine (NPYR)	
N-nitrosoanabasine (NAB)	
N-nitrosoanatabine (NAT)	

MEAN CONSTITUENT LEVELS IN 7 CLASSES OF SMOKELESS TOBACCO PRODUCTS INCLUDING CAMEL DISSOLVABLES

Product Type (n)	Moisture %	pH	Nicotine mg/g	NNN µg/g	NNK µg/g	NAT µg/g	NAB µg/g	Benzo[a] pyrene ng/g	Benzo[a] anthracene ng/g	Cd µg/g	Cr µg/g	Ni µg/g
MS (31)	53.6	7.68	25.5	6.5	1.9	6.7	0.53	80.5	463	1.4	1.4	2.0
Snus (9)	35.5	6.96	16.0	0.8	0.2	0.5	0.05	2.9	8	0.6	1.8	2.3
LL (9)	24.3	5.66	6.0	1.8	0.4	0.7	0.09	8.5	33	0.6	0.8	1.1
DS (5)	7.8	6.04	14.7	11.2	6.8	7.7	1.19	51.8	252	1.3	2.6	4.3
Plug (4)	19.6	5.56	12.7	2.0	0.4	1.1	0.09	7.0	27	0.7	1.3	1.8
Twist (5)	15.2	5.22	34.5	3.3	0.4	3.3	0.19	6.7	44	1.2	1.6	1.6
DS (6)	7.4	7.64	4.4	0.2	0.2	0.2	0.03	1.0	2	0.4	1.2	1.1
DS-C (4)	8.9	7.84	3.3	0.3	0.3	0.2	0.03	1.2	2	0.4	0.9	0.8

Chemistry Evaluation-Conclusion

Chemistry results for RJRT dissolvable tobacco products demonstrate that:

- Chemical constituents fall within the market range for several categories of smokeless tobacco products
- In most cases, the chemical constituents represent the lower end of the market range for smokeless tobacco products

In Vitro Evaluation

- There is no current consensus in the scientific community regarding standardized procedures and protocols for *in vitro* testing of smokeless tobacco products, including dissolvable tobacco products.
- Lacking such guidance, RJRT continues to investigate and evaluate appropriate *in vitro* testing methodologies for smokeless and dissolvable tobacco products.

The products were compared to extracts obtained from:

2S3 (moist snuff reference product)
Camel Snus Frost
Ariva Wintergreen
Copenhagen Long Cut

Assessment Metrics for *In Vitro* Evaluation

- Normalization on a per gram dry weight of product is most appropriate*:
  - Most suitable metric for comparing products among category
  - Consumer use patterns vary widely across category
  - No standardization of packaged amounts / product size
  - Mitigates uncertain influence of product moisture on analyses
  - Long-accepted method and abundant available data using per gram dry weight

* WHO Study Group on Tobacco Product Regulation: Report on the Scientific Basis of Tobacco Product Regulation: 3rd Report of a WHO study group.

Geneva, World Health Organization, 2009 (WHO Technical Report Series, No. 955)

In Vitro Evaluation Results

Ames Mutagenicity

- In general, the responses for all smokeless tobacco product extracts (including Camel dissolvables) were weak or non-existent (depending on the strain), indicating, at most, low levels of mutagenic activity in some strains.
- Notably, no mutagenicity was observed for many of the testing conditions (strain ± metabolic activation).
- The Ames assay consistently showed that where there was mutagenic activity in a given strain of bacteria, the Camel dissolvable tobacco products all showed either *equivalent or statistically significantly less* mutagenic activity in that strain than the other smokeless tobacco products.

In Vitro Evaluation Results

Micronucleus Assay

- All Camel dissolvable tobacco products were *equivalent to, or statistically significantly less* genotoxic than, the other smokeless products tested.

Neutral Red Assay

- All Camel dissolvable products were *equivalent or less cytotoxic* than the other smokeless products.

In Vitro Evaluation Results-Summary

- Using standard *in vitro* assays, the overall assessment indicates that all three Camel dissolvable products are *equivalent or less active* than the other smokeless products.

In Vivo Evaluation

•In May 2003, Star Scientific, the manufacturer of the Stonewall and Ariva dissolvable tobacco products, provided an unrestricted grant to fund the creation of an expert consensus development panel to answer questions on the relative risks of smokeless tobacco products.

•The committee made several recommendations regarding research to characterize the risk of low-nitrosamine smokeless tobacco products; however, they did not recommend animal testing to address any of the “unanswered questions”.

In Vivo Evaluation-Previous Studies

Homburger *et al*.,1976

Chronic carcinogenicity/co-carcinogenicity tobacco feeding study

- 2 PAH-sensitive Syrian hamster strains
- Diet - 20% methylcellulose,
  - 20% snuff (powdered tobacco)
- 5 and 0.5 mg treatments of 2-methylcholanthrene (MC)

Absence of carcinogenic effects of chronic feeding of snuff in inbred Syrian hamsters; Homburger *et al.* Toxicology and Applied Pharmacology, 35:3, 1976

In Vivo Evaluation-Previous Studies

Homburger *et al*., 1976, contd.

- This chronic carcinogenicity/co-carcinogenicity feeding study failed to reveal any carcinogenic or cocarcinogenic effects of tobacco ingestion.
- Presence in serum of cotinine together with food consumption and body weights, showed adequate tobacco intake.
- Tumors in the MC-treated animals demonstrated the susceptibility of the two inbred lines of Syrian hamsters used in this study (i.e. positive control worked as expected).
- The authors' conclusion is that administration of 20% tobacco in the diet induced neither carcinogenic nor co-carcinogenic effects in these animals.

In Vivo Evaluation-Previous Studies

Brown and Williamson conducted a 14-day palatability and 90-day dietary toxicity study in male and female Sprague-Dawley rats.

The following groups were included in the studies

Normal diet (control)
Nicotine – low, mid, high (positive control)
Tobacco pellet prototype – low, mid, high (test)
Non-tobacco ingredients – low, mid, high (reference)

In Vivo Evaluation-Previous Studies

Study Results

- The major finding from the B&W 90-day study consisted of a dose-dependent reduction in body weight gain for the tobacco test groups and nicotine control groups.
- Reduced food consumption correlated with observed reduced body weight gains.
- No apparent effects on organ weights were observed, other than those related to lower terminal body weights.
- No gross or histopathological changes were attributed to the control, test or reference articles.

In Vivo Evaluation-Study Design

RJRT *In Vivo* Stewardship Studies

•Rodent feeding studies commenced in June 2008 in order to determine whether ingestion of 'whole' tobacco differs from the ingestion of tobacco extract.

•The test battery reflects ICH guidelines for the carcinogenicity testing of pharmaceuticals and consists of 4 sets of studies:

- 14-day Palatability Study
- 28-day Toxicity Range-Finding and Pharmacokinetics Study
- 90-day Toxicity Range-Finding Study
- 2-year Chronic Toxicity/Carcinogenicity Study

•The 14, 28 and 90-day studies were conducted in both rats and mice.

•The 2-year study was initiated in 2009 in Wistar Han rats.

In Vivo Evaluation

2-Year Chronic/Carcinogenicity Study

- Assess comparative toxicity of tobacco ingestion vs. extract ingestion (i.e. dissolvable vs. snus).
- Interim sacrifice (12 months) is a useful predictive metric for chronic toxicity results.
- Data collected in the study included:
  - Plasma concentrations of nicotine and cotinine at various time points
  - Clinical Observations
  - Body and Organ Weights
  - Feed Consumption
  - Clinical Pathology
  - Histopathological examination

In Vivo Evaluation

Chronic/Carcinogenicity Study-1 Year Interim Results

Food Consumption/Body weight (Blend=Extract=Nicotine<Control)

Spontaneous Lesions:

- Non-neoplastic lesions are of:
  - Low incidence
  - Minimal severity ≤0.4 (0 to 5 severity scale)
  - Typical of historical control findings in this strain
- Neoplastic lesions within 2-year Wistar Han historical data

Most importantly, no dose or treatment related effects observed

Child Resistant Packaging

- Case studies report minimal adverse symptoms in children who accidentally consume products that contain nicotine (whole cigarettes, moist snuff, NRTs etc.).
- Given the paucity of poison-control data on dissolvable tobacco products already in market, RJRT decided to employ child-resistant (CR) packaging
- Product Stewardship established CR packaging requirements such that access to the products by children is substantially limited.
- CR packaging has been instituted for all dissolvable products.
- Packaging is tested by a third-party testing facility for compliance with the regulations specified in 16CFR§1700.20.

POISINDEX® Information System and Reporting

- Poisindex® is maintained by Micromedex, Inc. in Greenwood Village, Colorado. To obtain listing in Poisindex®, a product manufacturer need only complete a “Product Information Form” and mail the completed form to Micromedex, Inc.
- RJRT has submitted appropriate forms regarding its dissolvable products to Micromedex.
- To date, RJRT has not received any calls from Poison Control stating that a person had become ill from using a dissolvable product.

Overall Summary

- Product chemical evaluations show that constituents for dissolvable tobacco products fall within the market range (low end) for several categories of smokeless tobacco products.
- *In vitro* results show that dissolvable tobacco products are equivalent or less active than the other smokeless products.
- Previous tobacco feeding studies have not shown any significant effects from ingestion of tobacco.
  - RJRT interim (1-year) results from the current study confirm this finding.
- Based on the above conclusions, dissolvable tobacco products are substantially equivalent to US smokeless tobacco products.