Star
Scientific, Inc.

February 7, 2012

VIA FEDERAL EXPRESS
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane,
Room 1061
Rockville, MD 20852

Re: Star Scientific, Inc. Response to FDA Request for Comments; Docket No. FDA-Docket #FDA-2011-N-0867

Dear Sir or Madam:

In response to the publication in the Federal Register (Federal Register, Volume 76, No. 240, pgs. 77837-77838 December 14, 2011) of a request for comments on the "Experimental Study on the Public Display of Lists of Harmful and Potentially Harmful Constituents", Star Scientific submits this letter to set forth its position on the type of information that the Food and Drug Administration ("FDA" or "Agency") may wish to focus its attention on in considering disclosure of harmful or potentially harmful constituents under Section 904(d)(1) of the Food, Drug and Cosmetic Act ("FD&C Act"). On September 30, 2011, we provided comments in FDA Docket No.FDA-2011-N-0271 on the initial list of potentially harmful constituents developed by the Tobacco Products Scientific Advisory Committee ("TPSAC") Tobacco Product Constituents Subcommittee. (A copy of those comments is attached as Appendix "A").

In the September 30, 2011 comments, we pointed out that the quantified and undisputed constituent elements in tobacco products known to be toxic are:

1. For all Tobacco Products:

   Nicotine
   NNN (N-nitrosonornicotine)
   NNK (1-N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone)
   Benzo[a] pyrene (alon and as marker for polycylic aromatic hydrocarbons)

2. For smokeless tobacco products:

   Cariogenic sugars; and

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3. For smoked (combusted) tobacco products:

   Respirable smoke particles
   Carbon monoxide

In the comments we also pointed out the potential for confusion if the public were presented with an undifferentiated list of potential toxicants that were not subject to any ranking, assessment or evaluation with respect to their relative or probable hazard. Further, we noted that the list of harmful and potentially harmful constituents assembled by the Tobacco Products Constituents Subcommittee included compounds that currently are not added to tobacco, compounds reported as harmful in only a single peer-reviewed article, compounds that are found in tobacco at levels below those found in meat, milk or cereal grains, and compounds currently sold as dietary supplements. (Comments pp. 12-13)

To address the large number of compounds identified by the Tobacco Products Constituents Subcommittee, we recommended that the initial list of constituent elements be limited to those compounds whose role in human health is "known, quantified and undisputed."

In preparing to conduct an extensive survey of current smokers and others in order to gather information to assist FDA in determining the appropriate format for the public display of Harmful and Potentially Harmful Constituents, we would urge the Agency to carefully consider the impact and potential adverse effect of quantity over quality in identifying potentially harmful constituents. At a minimum, we would urge the Agency, as part of its information collection process, to carefully assess and analyze the amount of information that can be reasonably absorbed about potentially harmful constituents - and the point at which providing more information results in diminished understanding and appreciation of known risks.

Studies conducted to date have shown that there is significant misunderstanding about the relative harm of various forms of tobacco products; such misinformation may cause current tobacco users to not seek out products that may be less hazardous. The development of a list of potentially harmful constituents that is easily understandable and, that could be used to compare different tobacco products simply and effectively may go a long way to correcting longstanding misimpressions. We believe that the process by which the Agency's collection of information is conducted can be enhanced by carefully considering the quantity and presentation of information on constituent elements. At the end of the day, the overarching goal is to facilitate comprehension and understanding of constituents that pose a real and significant danger.

Designing the collection processes to measure the extent to which individual consumers are able to easily comprehend the extent to which such constituents are present in various tobacco would significantly facilitate that goal.

We trust that FDA will consider these comments in connection with the formulation of its plan for the collection of information relating to Harmful and Potentially Harmful Constituents.

Respectfully submitted,

Robert E. Pokusa
General Counsel

cc: Paul L. Perito, Esquire
President, Chairman and COO
Star Scientific, Inc.
Curtis Wright IV, MD, MPH
Medical/Clinical Director and Sr. Vice
President Rock Creek Pharmaceuticals, Inc.

APPENDIX "A"

Star Scientific, Inc.
Comment on
FDA Docket No. FDA-2011-N-0271 Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Request for Comments

September 30, 2011

Contents

List of Abbreviations

CDC	Centers for Disease Control and Prevention
FDA	Food and Drug Administration
HPHC	Harmful and Potentially Harmful Constituents
MMWR	Morbidity and Mortality Weekly Report
NNK	1-(*N*-methyl-*N*-nitrosamino)-1-(3-pyridyl)-1-butanone
NNN	*N*-nitrosonornicotine
TPSAC	Tobacco Products Scientific Advisory Committee
TSNAs	Tobacco-Specific Nitrosamines

1.0 Introduction

Star Tobacco, Inc., a subsidiary of Star Scientific, Inc., has been making and selling low-nitrosamine tobacco products for over a decade. These products have been developed, manufactured, promoted and sold to provide smokers and users of smokeless tobacco with the least toxic tobacco products that current technology could produce.

Star was first among American tobacco companies in explicitly discussing the dangers of tobacco use, the addictive nature of tobacco products, and the toxin content of our products. Star Tobacco has over a decade of experience in the design, manufacture and responsible promotion of these products, and both internal and external scientific studies have demonstrated that the users of Star's products are exposed to less toxins (Stepanov et al. 2006), absorb less toxins (Mendoza-Baumgart et al. 2007), and that the majority of users have selected the products for just these reasons (Parascandola et al. 2009).

Given our experience and our commercial interest in this area, we submitted comments to the Tobacco Products Scientific Advisory Committee's (TPSAC) Tobacco Product Constituents Subcommittee meeting on harmful and potentially harmful constituents in tobacco. We attended and made an oral public presentation at the June 2010 meeting, and then reviewed the materials and draft list that came out of the August 2010 meeting as well as in the notice published in the Federal Register in August 2011.

We were disappointed by the overall substance of the subcommittee meetings, and by the eventual list of Harmful and Potentially Harmful Constituents (HPHC) that came out of those meetings. We do not believe that the process at the TPSAC subcommittee meetings met the minimal standards for ordinary science, and the TPSAC process entirely failed to meet established risk assessment standards for the Federal Government.

Most importantly, the exhaustive list so compiled buries the meaningful and significant toxins among a flood of minor and non-contributory toxins, making the list so dense and impermeable that it will have no anticipated consumer impact. The list as currently constituted provides little useful information to either the Congress or the consumer.

The Agency and its representatives bear a great burden owing to the power of the Agency and the effects its actions can have on both commerce and the well being of the public. While this may be self-evident, we give as an example the bankruptcy of Dow Corning following the Agency's premature ban on silicone breast implants based on unsubstantiated science (Angell 1997).

For this reason, the Center for Tobacco Products should move with caution on its list of HPHC in tobacco products and ensure that such a list is supported by sound toxicology, and more importantly, that it provides users of the list with valuable information as to the toxin content of any products they may use.

As will be discussed below, it is not enough to identify a compound as hazardous. Modern methods of analytical chemistry are so sensitive that toxic or carcinogenic

compounds can be shown to exist in the food we eat, the air we breathe and the water we drink - fortunately at levels that pose no known risk.

No discussion of the harm or potential harm of any compound, be it food, drugs, tobacco constituents or environmental pollutants, is meaningful without some discussion of the dose, dose response, route of exposure, extent of absorption and consequent population exposure and risk of harm.

Many common essentials of life such as oxygen, water, and table salt are toxic to man under certain circumstances. In reviewing the list of HPHC compounds we note that some are essential nutrients, some are present at levels below those found in the air we breathe or the food we eat, and some are not toxic at any tolerable exposure.

The FDA is tasked under the Family Smoking Prevention and Tobacco Control Act ("Tobacco Control Act") to **"publish a list of harmful and potentially harmful constituents, including smoke constituents, to health in each tobacco product by brand and by quantity in each brand and sub-brand"**. We interpret this to mean that following the publication of the final HPHC list, every constituent on the list will have to be tested for, in all products, at the expense of the manufacturer, and reported to the FDA.

While this may be a trivial exercise for a major tobacco company, this burden may prove ruinously expensive to small tobacco manufacturers, who will either have to leave the business (to the benefit of the major tobacco companies), or litigate. It means, in fact, establishing regulations that benefit the larger manufacturers by imposing potentially ruinous costs on smaller ones. This list as currently constituted confers a prohibitive tariff which will result in lost jobs in the small business sector and with no consequent benefit to the public health.

If litigation were to ensue over the HPHC list, the quality of the risk assessment used, and the toxicological soundness of the analyses used to establish that list will figure prominently. Therefore, the science must be sound and consonant with such rule making by other Federal agencies. To date, the work of the TPSAC subcommittee, as reflected by the meeting transcript, does not meet such standards.

This is a potential tragedy for the American public. The establishment of valid, useful, and meaningful standards in this area is needed, and has been needed for over 50 years. Failing to establish any useful, implementable standards will be to continue a current and grievous disservice to the public. Users of tobacco products should be told the level of **major and meaningful** known toxins in the products they use. The HPHC list should be the principal tool to shape labeling requirements to provide them with such information.

It is in no one's interest to turn this area into a decades-long legal battle. It is better that the list focuses on the principal known and proven toxins and results in meaningful reductions of those toxins in existing or future products.

2.0 The Risk of Bad Faith in Tobacco Science

"There is a technique a good lawyer learns early on. The empty beer cans were scattered all over the front seat of your client's car, he was barreling down the wrong side of the highway before he hit the lamppost. What do you do? You talk about the massive conspiracy to suppress airbags, about Lee Iaccoca's salary, and about anything else you can think of- except your client's blood alcohol test."

Peter Huber, *Galileo's Revenge: Junk Science in the Courtroom*, Basic Books, 1991

Making tobacco products, promoting tobacco products, researching tobacco products, litigating over tobacco-related harm, campaigning against tobacco products, and regulating tobacco products have all become very profitable activities in the United States. They have also become areas where large sums of money have been spent in the generation of scientific data and test results, some good, some bad, and some overtly duplicitous. Most of those involved in this field are aware of the infamous quote from the Brown and Williamson "Smoking and Health Proposal":

"Doubt is our product, since it is the best means of competing with the body of fact that exists in the minds of the general public. It is also the means of establishing a controversy."

David Michaels, *Doubt is Their Product,* Oxford University Press, 2008

Doubt, and efforts to generate doubt, are part and parcel of the conflict among the tobacco industry, anti-tobacco activists, legislators, regulators and scientists involved in this area. As in most "wars", truth is the first casualty, as both sides adopt each other's tactics in an ever more strident conflict.

We think this poses a particular problem for the FDA, and especially for the Center for Tobacco Products. The extreme polarization in this area, as well as the financial dependence of anti-tobacco science on tobacco-related controversies, means that the Agency is hard pressed to find experts and advisors in this area who do not financially depend on the tobacco industry, the "anti-tobacco" industry or the pharmaceutical industry. Many, if not most of the FDA's "experts" on the TPSAC sub-committee that generated the HPHC list are dependent, financially and professionally, either on "anti-tobacco" money, whether from government grants, anti-tobacco organizations or pharmaceutical interests who sell nicotine replacement products.

We ask that the Agency be fair, balanced and impartial. We advise the agency that there are concerns over the quality, reproducibility, and accuracy of the data presented by all parties to the tobacco regulation dialogue.

We hope that the Center for Tobacco Products shares Marcia Angell's (*Science on Trial*, 1997) concern that we are in the midst of a groundswell of anti-scientific feeling, and will recognize that the reputation of the Agency for scientific integrity has never been more at risk than it is at present. We ask that the Agency look carefully at the data, for science can only survive if built on a solid foundation of facts.

Star Scientific's position is clear. We believe that most of the harmful effects of tobacco products on health are due to a small number of known toxic agents whose identities are well-established, that the toxicity of tobacco products can be reduced to the direct benefit of users, and that it is past time that information about the toxicity of these products be made available to the public in clear and meaningful labeling. To be candid, Star hopes to make a profit making and selling less toxic tobacco products to tobacco users who desire to use them as our company's mission is to reduce tobacco-related harm.

3.0 Smoke Toxicity: The Toxin Not on the HPHC List

Tobacco products are toxic, but slowly toxic, relative to most known toxic agents. Tobacco-related harm results in a significant number of casualties, but most of the morbidity and mortality takes place in the 7^{th} to 10^{th} decades of life, resulting in 5-8 years of life lost on average (Doll et al. 1994). Of the estimated 443,000 premature deaths from smoking in the US each year (CDC MMWR 2008), 128,000 are cardiovascular, 160,000 are due to cancer and 103,000 are due to pulmonary disease. The great majority of these casualties are due to cigarette smoking (Levy et al. 2004; RCP 2007) and result from the inhaling of large quantities of respirable smoke particles, toxic gases and both endogenous and combustion-generated carcinogens.

Cigarette smoke, both first-hand and second-hand, remains the most common and the most damaging non-industrial air pollutant for the US population. Pyrolysis of tobacco generates highly surface-active and toxic respirable aerosols that travel deep into the lung, establishing intra-alveolar and endovascular inflammation, which result in both lung and cardiovascular damage (Benowitz 2003; Pope et al. 2009). Carcinogens are both intrinsic to conventionally cured tobacco (TSNAs), and formed by combustion (polycyclic aromatic hydrocarbons and volatile nitrosamines). Carcinogen exposure can be measured in the lung, blood and urine of smokers (Ashley et al. 2010). The toxic role of combustion gases and other volatile organic compounds is less well understood, but clearly these are of concern as well.

Early attempts to quantify harm from smoking by measuring tar and nicotine failed as compensatory smoking (smoking more to reach the desired nicotine effect) by users of "light" tobacco products resulted in greater, rather than lesser toxin exposure (Lanier and Wright 2010).

Comment #1
The most harmful constituent of smoked tobacco products is respirable smoke particles, expressed as weight of particles per unit volume of air and weight of

particles per milligram nicotine in smoke. Exposure to such particles has been quantified, the dose response has been established, absorption by man has been documented and exposures generated by tobacco products have been shown to pose a demonstrable risk to man. Smoke is the most obvious and harmful constituent of tobacco products and is conspicuously absent from the HPHC list.

4.0 The Role of Testing and Labeling: The Three-Fold Requirements for Risk Assessment in the Federal Government.

If the Agency is to require testing of tobacco products for harmful and potentially harmful constituents in order to impose testing requirements on the industry as mandated by the Tobacco Control Act, that testing should meet the ordinary standards of toxicology and the established standards in this area of Federal regulation. Government-mandated testing, especially costly testing that would impose a restrictive and potentially prohibitive tariff on small business, should only be undertaken if it meets the established standards for Risk Assessment established by the Federal Government for the protection of the public (National Research Council, *Risk Assessment in the Federal Government*, 1983). There are three mandatory elements: Hazard Identification, Dose-Response Assessment and Exposure Assessment, which are then synthesized into a Risk Characterization.

Hazard Identification is the evaluation of epidemiological data, in vitro and in vivo bioassay data, short-term test data, and chemical structure similarity data to establish that a compound or class of compounds poses a risk to man or other elements of the biosphere.

Dose-Response Assessment uses epidemiological data, in vitro and in vivo bioassay data and short-term test data to evaluate the level of exposure required to induce a meaningful change in animals, man or the environment.

Exposure Assessment evaluates information on the use, quantities of use, distribution of use, frequency of use, route of exposure, or extent of absorption of a compound, in addition to evaluating biomarkers, metabolites or other data that indicate the extent of exposure of a population to the agent.

Risk Characterization is a synthesis of the information from hazard, dose-response and exposure assessment to determine if a significant level of risk exists, and to quantify that risk and the likely effectiveness of means of controlling that risk relative to background or other sources of exposure.

In less formal language, to establish that a product or compound is probably hazardous, it is necessary to show that the product causes or is likely to cause a harmful effect, that you know how much exposure poses a risk, that the anticipated exposure is of a magnitude (dose) that is high enough to pose a risk, and that controlling the exposure is likely to be of benefit to the public relative to background and other exposures in the environment.

Mandatory testing of products for compounds that do not meet these risk assessment standards is not consonant with established Federal practice. Toxic compounds must be shown to be toxic, the dose response for toxicity must be established or estimated, the population must be exposed to toxic levels, and the means of control must be shown to be of probable value to the public.

We would characterize the activities of the TPSAC subcommittee as Hazard Identification, but we believe that the other essential elements are still required in order to compile and publish a meaningful list of HPHC of tobacco and tobacco smoke.

5.0 Smoked and Smokeless Tobacco

The list, as constituted in the Federal Register, fails to differentiate combusted (smoked) tobacco products from smokeless tobacco products. This failure, while possibly useful in expeditiously meeting the legal requirements of the Tobacc ControlAct, makes no sense toxicologically.

Smokeless tobacco contains far fewer toxins than combusted tobacco. Smoked products provide (in addition to the toxic respirable smoke described above) combustion gases, volatile organic compounds, and pyrolysis products that are not found in smokeless tobacco products. In addition, the pharmacokinetics of absorption, redistribution and elimination from the lungs are often markedly different than the absorption through the buccal or enteric mucosa. This leads to our second comment.

Comment #2
The HPHC list should be divided into two sections, one pertaining to combusted tobacco products and one pertaining to non-combusted tobacco products, owing to the recognized and significant differences between the method, extent and kinetics of absorption between these routes. Testing smokeless tobacco products for toxins known to be present only in smoked products is not reasonable.

6.0 Specific Compounds Known to be Toxic

There is a short list of known HPHC compounds that are generally accepted within the industry and in the scientific community as meeting the following tests: the compounds are of known toxicity, have an established dose-response in man, are known to be present in tobacco products in meaningful amounts, are proven to be absorbed in potentially toxic amounts by tobacco users and pose an established risk to the population.

These are:

For all Tobacco Products:

Nicotine
NNN
NNK
Benzo[a]pyrene (alone and as a marker for polycyclic aromatic hydrocarbon levels)

For Smokeless Products:

Cariogenic Sugars

Comment #3
One of the known, proven, significant, observed risks for addictive smokeless tobacco products is significant dental toxicity, periodontal disease, tooth loss and other oral health problems associated with added cariogenic sweeteners. Sugar (cariogenic sugars) in smokeless tobacco products is a harmful constituent.

For Smoked (combusted) products:

Respirable smoke particles (see above)
Carbon Monoxide

Comment #4
For the following compounds, the data provided by the FDA, the discussions at the TPSAC subcommittee meetings, and the Federal Register Notice were deficient in documenting one or all of the following areas:

1. **The levels present in cigarette smoke or tobacco products**
2. **The dose-response for animal or human toxicity**
3. **The extent of absorption by route of exposure (inhaled or ingested)**
4. **The metabolic clearance or disposition of the compound when inhaled/ingested**
5. **The magnitude of the risk posed to users or the general population**
6. **The magnitude of exposure relative to other environmental sources**

We note from the transcript that members of the subcommittee asked Agency staff if they were to evaluate the potential toxicants in terms of their relative importance, and were instructed only to identify compounds, with instructions to not conduct any ranking, assessment or evaluation of the relative or probable hazard.

7.0 Other Compounds

Acetaldehyde
Acetamide
Acetone
Acrolein
Acrylonitrile
Aflatoxin B1
4-aminobiphenyl
1-Aminonapthalene
2-Aminonapthalene
Ammonia
Anabasine
o-Anisidine
Arsenic
A-α-C (2-Amino-9*H*-pyrido[2,3-*b*]indole
Benz[a]anthracene
Benz[j]aceanthrylene
Benzene
Benzo[*b*]fluoranthrene
Benzo[*l*]fluroanthrene
Benzo[*b*]furan
Benzo[*c*]phenanthrene
Beryllium
1,3-Butadiene
Cadmium
Caffeic acid
Catechol
Chlorinated dioxins/furans
Chromium
Chrysene
Cobalt
Coumarin
Cresols (*o*-, *m*-, and *p*-cresol)
Crotonaldehyde
Cyclopenta[*c,d*]pyrene
Dibenz[*a,h*]acridine
Dibenz[*a,h*]anthracene
Dibenzo[*c,g*]carbazole
Dibenzo[*a,j*]pyrene
Dibenzo[*a,l*]pyrene
Dibenzo[*a,j*]pyrene
2,6-Dimethylanaline
Urethane
Ethylbenzene
Ethylene Oxide

Formaldehyde
Furan
Glu-P-1 (2-Amino-6-methyldipyrido[1,2-*a*:3'2'-d]imidazole)
Glu-P-2 (2-Aminodipyrido[1,2-*a*:3'2'-d]imidazole)
Hydrazine
Hydrogen Cyanide
Indeno[*1,2,3-cd*]pyrene
IQ(2-Amino-3-methylimidazo[*4,5-f*]quinoline
Isoprene
Lead
MeA-α-C(2-Amino-3-methyl)-9*H*-pyrido[*2,3-b*]indole
Mercury
Methyl Ethyl Ketone
5-Methylchrysene
Naphthalene
Nickel
Nitrobenzene
Nitromethane
2-Nitropropane
NDELA
N-Nitrosodiethylamine
NDMA
N-Nitrosomethylethylamine
NMOR
NPIP
NPYR
NSAR
Phenol
PhIP (2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine
Polonium-210
Proprionaldehyde
Propylene oxide
Quinoline
Selenium
Styrene
o-Toluidine
Trp-P-1(3-Amino-1,4-dimethyl-5H-pyrido[4,3-*b*]indole)
Trp-P-2(1-Methyl-3-Amino-5H-pyrido[4,3-*b*]indole)
Uranium-235
Uranium-238
Vinyl acetate
Vinyl chloride

This list includes some compounds that have not been added to domestic tobacco products for over a decade, compounds reported to be found only in a single peer-reviewed article, compounds <u>never</u> reported in peer-reviewed articles (that we could

find), compounds which are present in tobacco at levels far below those found in meat, milk or cereal grains, and compounds currently sold as essential dietary supplements.

The TPSAC list published in the Federal Register consists, in fact, of all known carcinogens ever reported to be present in tobacco or tobacco smoke from any source, regardless of amount, importance, or potential risk to the public. Some of these compounds may prove upon examination to be harmful or pose significant risk of harm, others will not; however, the report to Congress should meet the current standards of toxicological analysis.

8.0 Conclusion and Recommendation

Comment #5- Resolving the problem

We strongly recommend that the Center for Tobacco Products restrict the initial list of HPHC compounds to those described above whose role in human health is known, quantified, and undisputed. Since the Agency has the right and responsibility to update the list at any time, there is little to be lost by improving the quality of the scientific assessment to meet minimal standards. The HPHC list should consist only of compounds where a reasonable and complete risk assessment has been performed and presented for review and comment.

Comment #6- Requirement for Labeling

We strongly recommend that the Center for Tobacco Products restrict the HPHC list to compounds which are to be used in required labeling for tobacco products, and that the Agency proceed to mandate such labeling. Failure to provide information that is of value to the consumer or to bury such information among a list of dozens of complex chemical names does little service to the Congress and no service to the public.

9.0 References

Angell M. *Science on Trial: the Clash of Medical Evidence and the Law in the Breast Implant Case*. New York: W.W. Norton, 1997.

Ashley DL, O'Connor RJ, Bernert JT, et al. Effect of differing levels of tobacco-specific nitrosamines in cigarette smoke on the levels of biomarkers in smokers. Cancer Epidemiol Biomarkers Prev. 2010 Jun;19(6):1389-98.

Benowitz NL. Cigarette smoking and cardiovascular disease: pathophysiology and implications for treatment. Progress in Cardiovascular Disease, 2003:46(1) (July/August):91-111.