

# Section IX. All Documents Related to Research Findings

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## IX. All Documents Related to Research Findings

### A. Summary

This section contains scientific information related to the application. An external literature search was performed to identify possible publications that relate to VLNC cigarettes.

This search identified about 70 possibly responsive articles. These articles were reviewed, and

many are included in Section VII. Scientific Studies and Analyses. In the review of the potentially responsive articles, additional potentially responsive articles were identified that were not identified in the original literature search. When relevant, these documents were included in this application. The cited documents are linked from the bibliography that appears at the end of the MAIN document for each Section of this application. Documents relevant to studies that the Company is sponsoring include the name of the company that conducted the research in the file name; MARC Research (MARC is used in the filenames), Altasciences (Altascience or Altasciences is used in the filenames), and Certara Strategic Consulting (Certara is used in the filenames).

In addition to the search of the public literature, the Company performed an electronic search and a physical search of its records to find responsive documents. (b) (4)

(b) (4)

(b) (4) The document listing the electronic files is titled [Section IX AllDocs Appx 17 Index of Electronic Docs.xlsx](#). There are approximately (b) (4) A search of physical files was also performed. The document index of “paper” records is titled [Section\\_IX\\_AllDocs\\_Appx\\_16\\_Index of Physical Docs.xlsx](#). Electronic images of the documents are included with this application and are of the file names noted in the index document, “Section\_IX\_AllDocs\_Appx\_16\_Index of Physical Docs.xlsx,” as well as in the List of Files.

## B. External Document Search

A literature search was performed by (b) (4) looking for all studies related reduced nicotine cigarettes published through May 2018. The detailed search criteria and results are provided in Section IX.B.3.i.

## 1. Search Strategy

Search Topics: Nicotine, Cigarette, Reduced Nicotine Cigarettes, Compensation, Cigarettes per day, Smoking, Dependence, Cessation, Quit, Attempt, Cease, Cut Down, Intake, Urge Rate, Frequency, Topography, Withdrawal, Puff, Craving, Behavior, Consumption, Crave or Craving, CPD, Abuse, Abuse liability, Toxicity (and related terms), PK (and related terms). Specific search terms for each major concept are included in Section IX.B.3.i with Boolean truncation and proximity connectors included.

(b) (4)

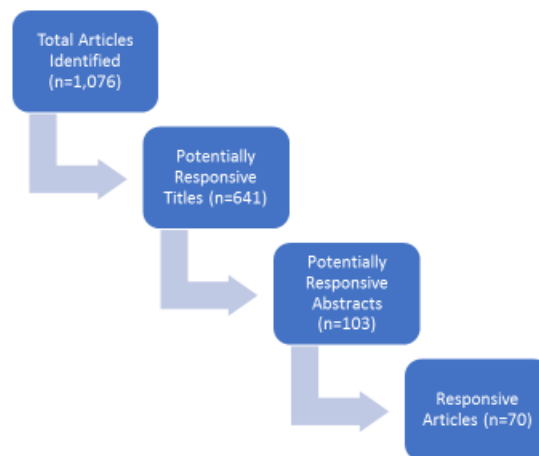
Comment: A comprehensive search of the scientific literature was initiated with articles published since 1960 and continued through all current publications (May 2018) and was performed to identify nonclinical and clinical research related to VLN™ published in (b) (4)

## 2. Methodology

A total of 1076 citations/article titles pertaining to VLN™ were identified by the literature search and reviewed by (b) (4) ) for relevancy to this PMT application. Of the 1076 citations reviewed, 641 citations were determined to be potentially relevant to this application and abstracts of these citations were further evaluated. Of these 641 abstracts, 103 were considered as being potentially related to VLN™ nonclinical and clinical effects. Figure IX.B-1. *External Article Review and Results*, outlines the external document review process and results.

Figure IX.B-1. External Article Review and Results

## External Document Search



In addition, a number of the articles cited in this document were derived from general literature searches (b) (4) in areas that were related to VLN™, and did not necessarily appear on the direct literature search. Any articles that were found through reviews of identified articles were also included in the list. All of the cited articles are listed in the bibliography that appears at the end of the MAIN document for each Section of this application.

### 3. Search Results

A total of 1076 articles were retrieved. The titles of the articles were reviewed using the following generalized criteria:

- Include primary studies that report the testing VLN™ cigarettes in humans, animals, or smoke chemistry. VLNC cigarette nicotine approximately equal to 0.4 mg/g tobacco was included. Other nicotine levels were included if they also included the VLN™ tobacco.

- Exclude reports that discuss the Proposed Nicotine Standard unless they appear to present actual new data.
- Exclude reports that discuss nicotine policy unless they appear to present actual new data.
- Exclude reports of analysis of internal tobacco industry documents as they are not relevant to VLN™ cigarettes.
- Duplicate reports were struck
- Exclude reports on Nicotine that do not mention VLN™.
- Exclude reports on De-Nic cigarettes as they are not the same as VLN™.
- Exclude nicotine inhalers.
- Exclude studies on low tar low nicotine cigarettes. The VLN™ product is regular tar low nicotine.
- Studies listed on Clinicaltrials.gov were excluded unless they listed data. Reports of study protocols only were excluded.
- Low tar/ low nicotine cigarettes were excluded since our product is regular tar low nicotine.
- Exclude nicotine as a pesticide.
- Exclude nicotinamide.
- Exclude other tobacco forms like snus, oral tobacco, e-cigarettes, cigars as they are not relevant to this submission.

Articles considered not relevant or out of scope were “struck” and the results of the review may be found in Section IX.B.3.ii. Abstracts of the potentially relevant articles were ordered and reviewed using the following criteria:

- Include primary studies that report the testing VLN™ cigarettes in humans, animals, or smoke chemistry. VLNC cigarette nicotine approximately equal to 0.4 mg/g tobacco was included. Other nicotine levels were included if they also included the VLN™ tobacco.
- Reports published before about 1998 were excluded since the technology was developed about that time.
- Exclude reports that discuss the Proposed Nicotine Standard unless they appear to present actual new data.
- Exclude reports that discuss nicotine policy unless they appear to present actual new data.
- Exclude reports of analysis of internal tobacco industry documents as they are not relevant to VLN™ cigarettes.
- Duplicate reports were struck.
- Exclude reports on nicotine that do not mention VLN™.
- Exclude reports on de-nic cigarettes as they are not the same as VLN™ cigarettes.
- Exclude nicotine inhalers.

- Exclude studies on low tar low nicotine cigarettes. Our product is regular tar, low nicotine.
- Studies listed on Clinicaltrials.gov were excluded unless they listed data. Reports of study protocols only were excluded.

Articles considered not relevant or out of scope were “struck” and the results of the review may be found in Section IX.B.3.ii. A bibliography, for all referenced published articles cited in this application, appears at the end of the MAIN document for each Section of this application in which the articles were referenced. Copies of the articles are included with this application and are generally named by the last name of the main author and the publication year.

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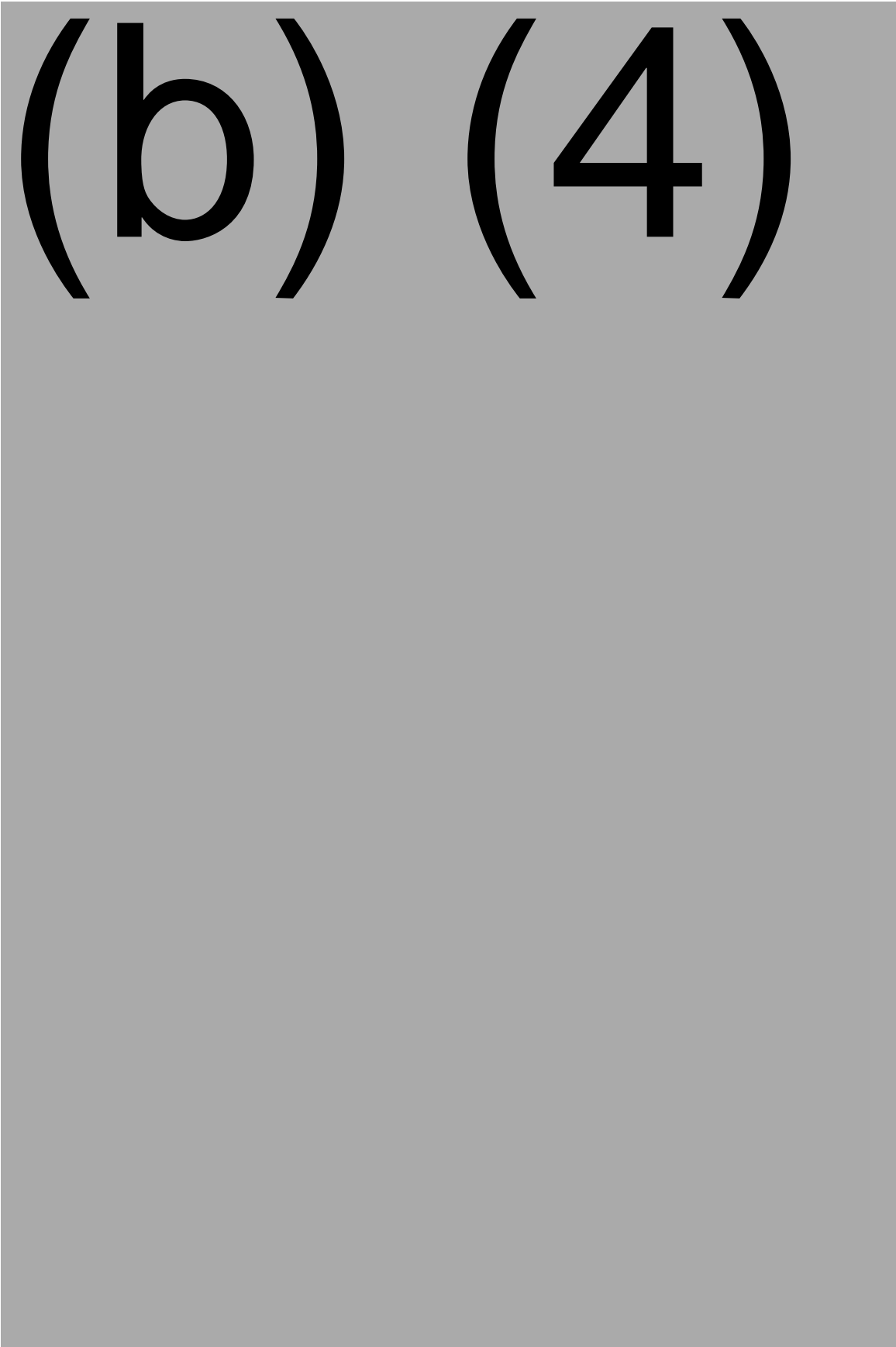
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## C. Internal Document Search

### 1. Strategy

22<sup>nd</sup> Century believes that a majority of, if not all internal documents that are responsive to the “all documents” requirement is/are stored electronically. 22nd Century engaged an outside regulatory counsel, (b) (4) to search, review, and produce responsive emails and attachments. In addition, all employees were instructed to review their physical files and provide copies of any responsive documents for inclusion in this submission.

### 2. Emails - Strategy

(b) (4) reviewed all electronic documents (b) (4)

(b) (4)

#### Document Custodians Included:

<u>Employee Name</u>	<u>Position</u>
(b) (6)	Operations Manager
(b) (6)	President and Chief Executive Officer
(b) (6)	Director of Communications
(b) (6)	Past Employee, Senior Vice President of Science and Regulatory Affairs

<u>Employee Name</u>	<u>Position</u>
(b) (6)	Past Employee, Founder and Previous CEO
(b) (6)	Vice President Research and Development
(b) (6)	Tax Compliance Manager
(b) (6)	Patent Librarian
(b) (6)	Retired, Vice President Research and Development
(b) (6)	Director of Marketing & Special Projects
(b) (6)	Vice President of Plant Biotechnology
(b) (6)	Vice President, General Counsel and Secretary
(b) (6)	Vice President of Business Development
(b) (6)	Past Employee, Previous Director of Regulatory Affairs
(b) (6)	Marketing Coordinator
(b) (6)	Administrative Assistant
(b) (6)	Regulatory Affairs
(b) (6)	Manufacturing Factory Manager
(b) (6)	Former Manufacturing Factory Manager

#### Search Terms Included:

Very low nicotine	Initiate	Stepanov
VLN	Magic 0	Girdhar
Low nicotine	Quest 3	Chen
Modified risk	T-value	Lin
M RTP	Degrees of	Naik
Exposure modification	freedom	Skott
Exposure	P-value	Catanzaro
Bridging	Effect size	Xie
Abstract	Initiation	Song
Population	Hatsukami	Nap
IOM	Walker	Bijvoet

Institute of Medicine	Benowitz	Leffingwell
Toxic	Henningfield	Arista
Toxicity	Hammond	Gu
MARC	O'Connor	McClernon
Testing method	Ding	Strasser
Sampling plan	Donny	Filtrona
Regimen	Fiore	Withdrawal
Smoking regimen	MacQueen	Dependence
Compensatory	Becker	Toxicant
Compensatory smoking	Walker	Perception
Pack and Ad	Dermody	Switch
Consumer model	Naqvi	Lindsey
HPHC	Mullins	King
Harmful and potentially	Barrett	Oliver
harmful	Lee	Harrell
Constituents	Penetar	Juliano
PARE	Perkins	Keleman
FDA	AhnAllen	Kaighobadi
Tobacco-related disease	Tidey	Dedert
Health-related	Rezaishiraz	Calhoun
Condition	Rose	Falcone
Study	Jones	Blendy
Studies	Darredeau	Brody
Compensatory smoking	Addicott	Karelitz
SPECTRUM	Vogel	Ray
X-22	Attwood	Rukstalis
Xodus	Pappas	T-test
Magic	Ramachandran	Statistical analysis
Program code	Stimuli	Raw data
Report	Images	Protocol
Enthalpy	Celerion	(b) (4)

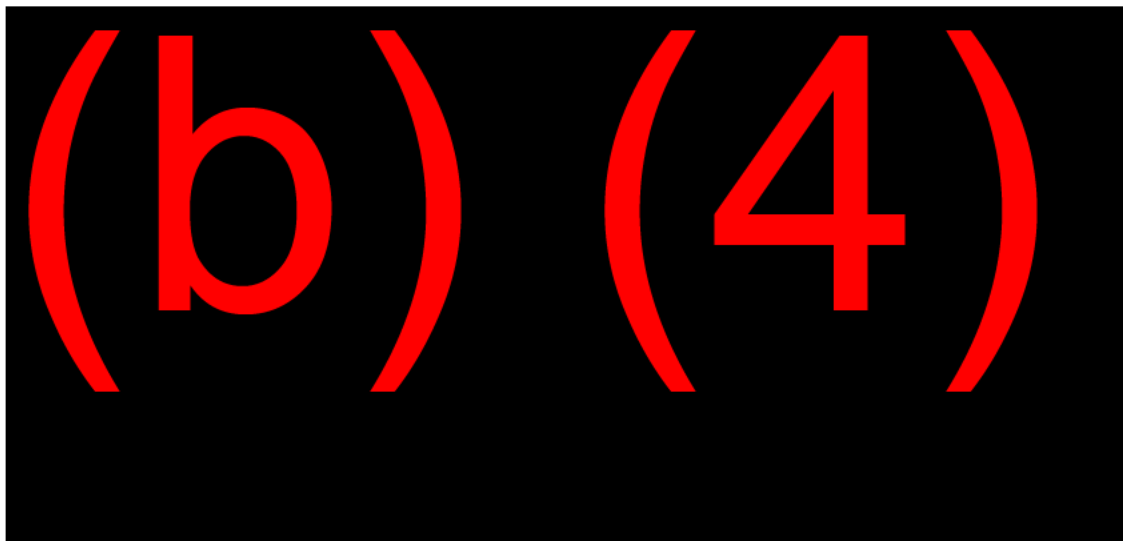
Vince and Associates	(b) (4)	(b) (4)
Altsciences	(b) (4)	(b) (4)
(b) (4)		

(b) (4) searched documents by each custodian identified above within the date range specified above. (b) (4) then applied the search terms above. After eliminating duplicate items, a total of (b) (4) documents remained. After application of the date filters and removal of documents that did not contain at least one of the search terms, (b) (4) documents remained.

With the returned documents, (b) (4) implemented technology assisted or "predictive coding" review, whereby an attorney reviewed subsets of documents (b) (4) for responsiveness to the "all documents" requirement to train its e-discovery software (Relativity) regarding whether or not a document satisfies the "all documents" requirement. The responsive documents from the subset reviews were submitted to Relativity in order to categorize the entire set of returned documents. Through multiple subset reviews and training Relativity a total of (b) (4) potentially responsive documents were identified (b) (4) including attachments). The results produced by 22nd Century to the FDA are based on a 95 percent confidence level, with 3 percent margin of error (i.e., 95 percent certainty that they are responsive to the "all documents" requirement, plus/minus 3 percent). Figure IX.C-1. *Internal Document Search Process*, shows the document search process and results.

Figure IX.C-1. Internal Document Search Process

## Internal Document Search



This approach was submitted to the FDA in a letter dated January 25 ,2018. (See file [Section\\_IX\\_AllDocs\\_Appx\\_13\\_01252018\\_AllDocsProposal](#)). A revised submission was submitted February 28, 2018 (See file [Section\\_IX\\_AllDocs\\_Appx\\_14\\_02282018\\_AllDocsProposal-Rev](#)). The FDA responded on May 14, 2018 (See file [Section\\_IX\\_AllDocs\\_Appx\\_15\\_05142018\\_AllDocs-FDAResponse](#)). While the FDA could not determine whether the requirements will be met by the submission, the FDA concluded that the approach appeared reasonable. As shared with FDA in 22nd Century's January and February 2018 letters, the use of technology assisted review to evaluate responsiveness or potential responsiveness of large volumes of documents – like the process **(b) (4)** used in this matter – has been recognized by courts throughout the United States.<sup>1</sup>

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<sup>1</sup> See, e.g., *Rio Tinto Pie v. Vale S.A.*, 2015 WL 872294 (S.D.N.Y. Mar. 2, 2015) ("In the three years since *Da Silva Moore*, the case law has developed to the point that it is now black letter law that

### 3. Emails – Results

A table of the results of the electronic document search may be found in the file named [Section IX AllDosc Appx 17 Index of Electronic Docs.xlsx](#), and the individual documents are saved under the filenames appearing in the column titled “Filename” With regard to the Company e-mails and attachments produced in satisfaction of the “all documents” requirement, 22nd Century believes that all such documents are exempt from disclosure because internal company communications are, by their nature, confidential, nonetheless the files have been reviewed and the level of confidentiality noted for each in the Appendix 17 file, [“Section IX AllDosc Appx 17 Index of Electronic Docs.xlsx”](#). Based on the Company’s belief that all internal company communications are exempt from FOIA disclosure, all e-mails and attachments produced to the FDA in satisfaction of the “all documents” requirement are stamped with the following: “CONTAINS TRADE SECRETS OR OTHERWISE CONFIDENTIAL INFORMATION; EXEMPT FROM DISCLOSURE UNDER FOIA.”

### 4. Internal Printed Documents - Strategy

All employees were instructed to review their personal physical files and to provide copies of any relevant documents. A copy of the request may be found in the file named [Section IX AllDocs Appx 18 Company Memo-InternalDocSearch.pdf](#).

### 5. Internal Documents – Printed – Results

The documents that the employees found in their personal files were scanned and converted to pdf’s. A table of these documents may be found in the file named

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where the producing party wants to utilize TAR [technology assisted review] for document review, courts will permit it.”).

[Section\\_IX\\_AllDocs\\_Appx\\_16\\_Index of Physical Docs.xlsx](#). The documents are included in this application under the file names listed in the Index of Physical Docs as well as the List of Files for this Section IX.