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(54) **METHODS AND DEVICES FOR DELIVERY AND MONITORING OF TOBACCO, NICOTINE, OR OTHER SUBSTANCES**

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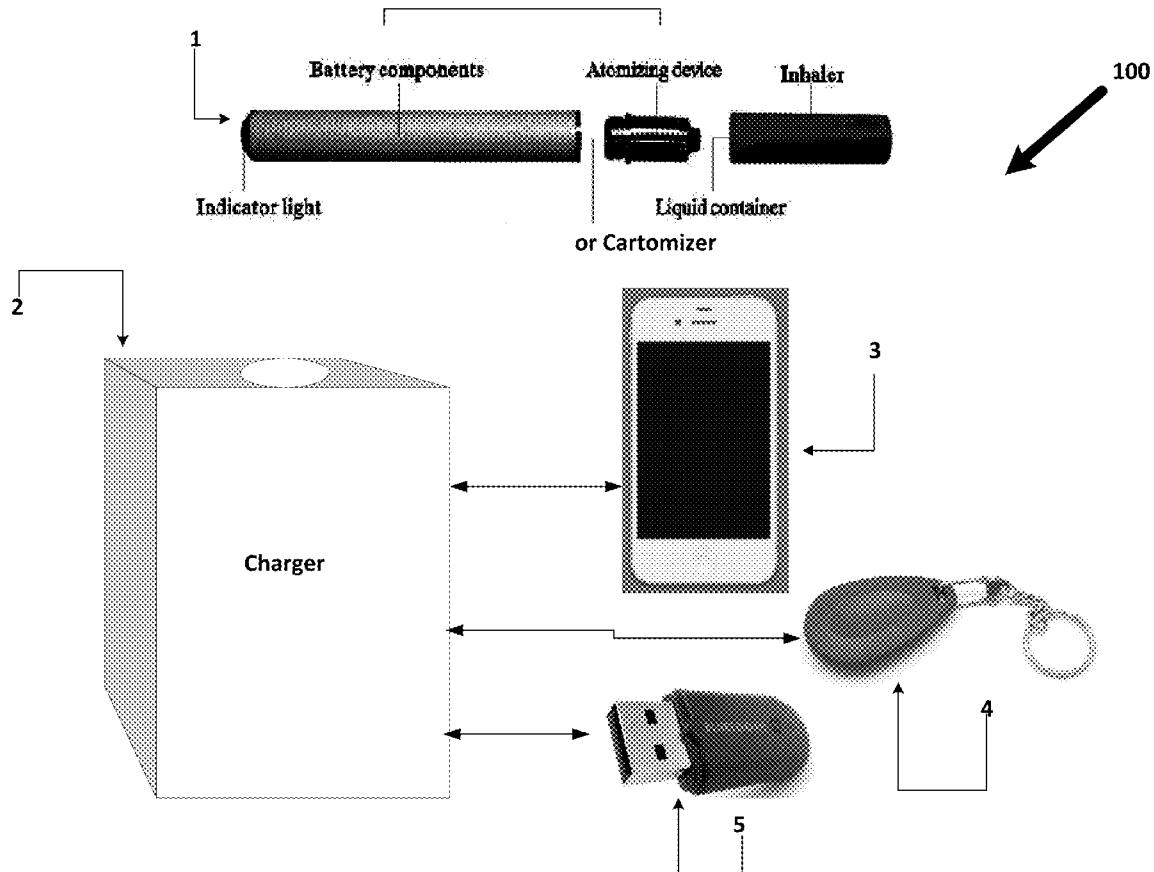
**ABSTRACT**

(22) **Filed: Aug. 28, 2013**

**Related U.S. Application Data**

(60) **Provisional application No. 61/694,046, filed on Aug. 28, 2012.**

Methods, systems, and devices are described for providing risk evaluation and mitigation strategies for use with modified risk products, and in particular, associated with nicotine and tobacco products.



**User Verification for Modified Risk Product Mitigation and Tracking**

## Elements of a Risk Evaluation and Mitigation Program

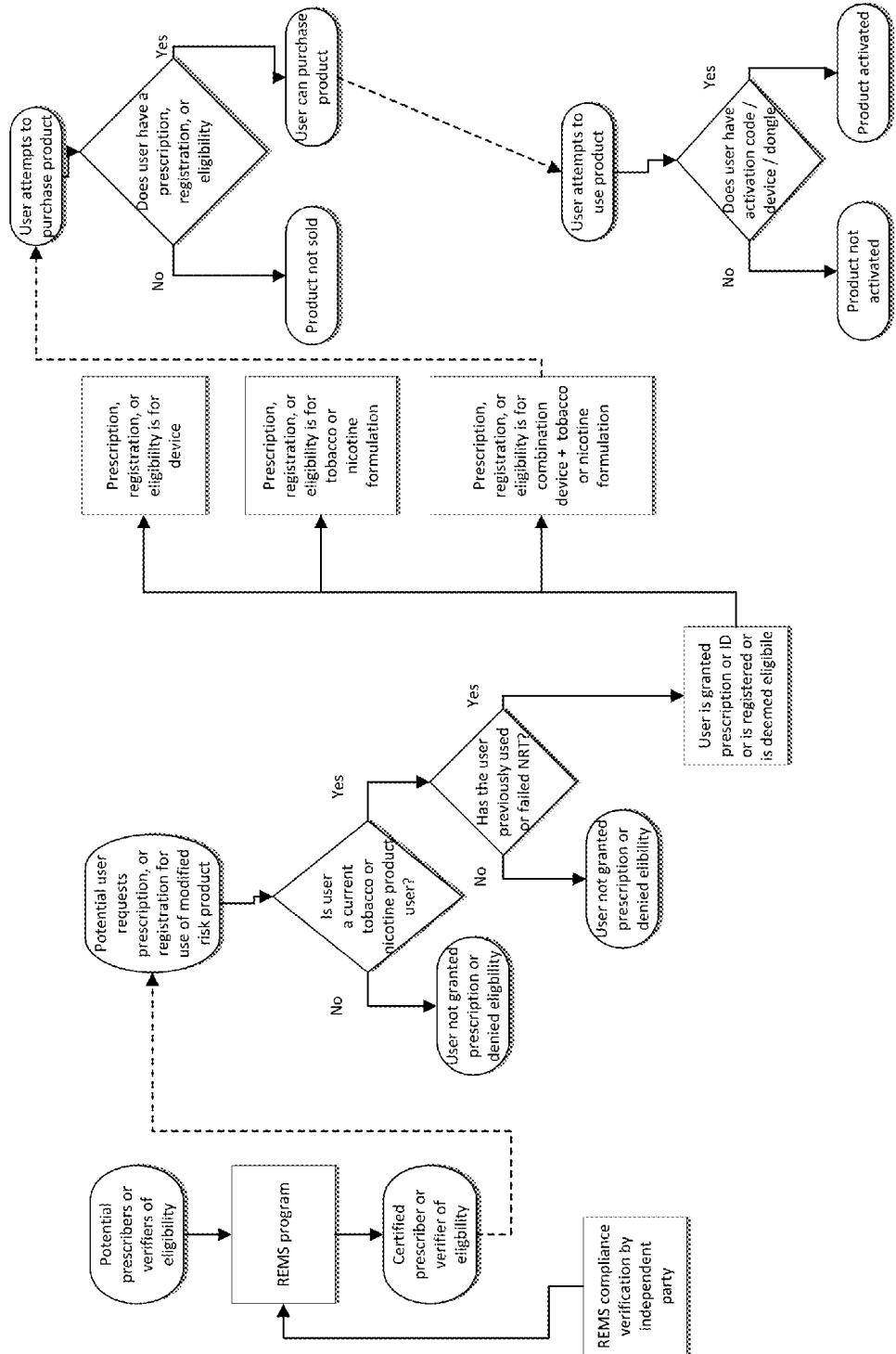


Fig. 1A

### Elements of a Risk Evaluation and Mitigation Program

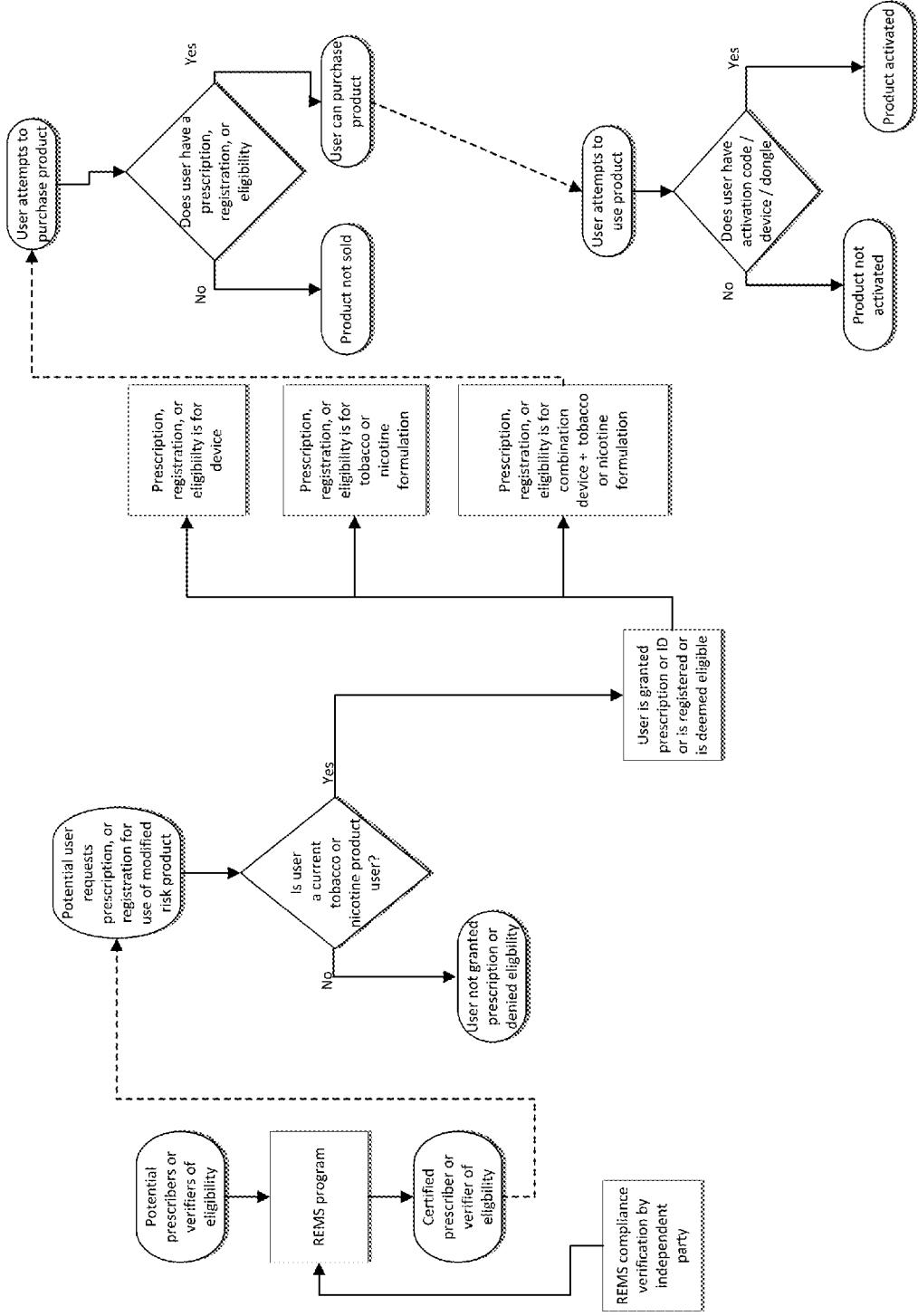
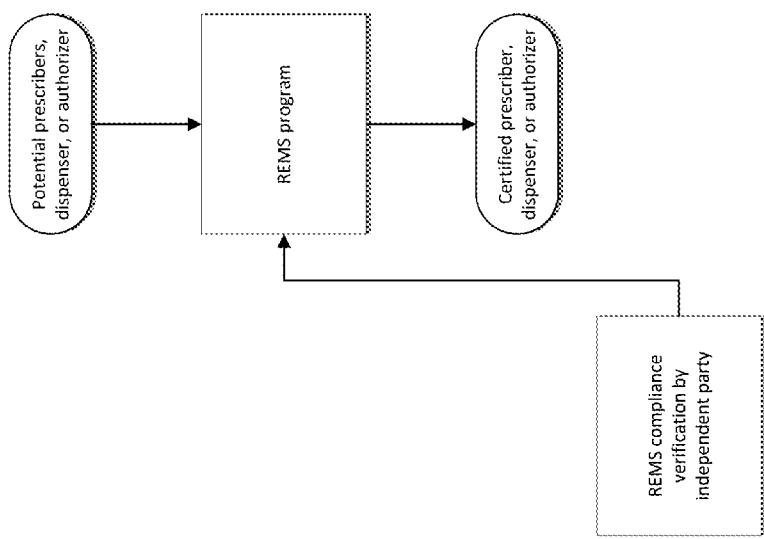
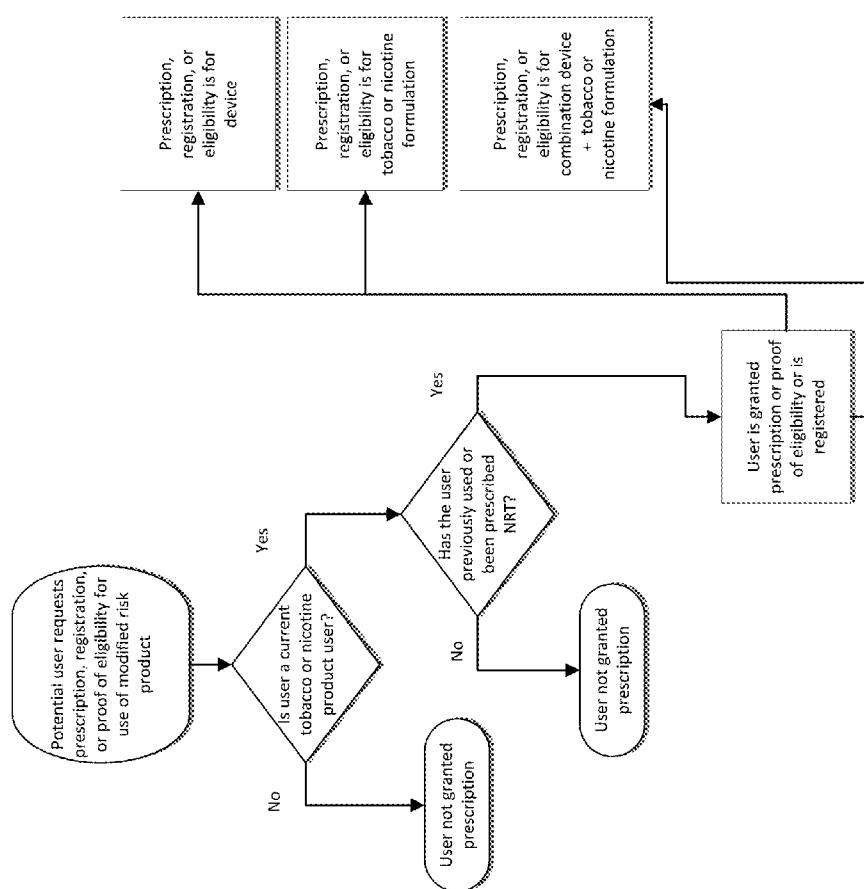


Fig. 1B



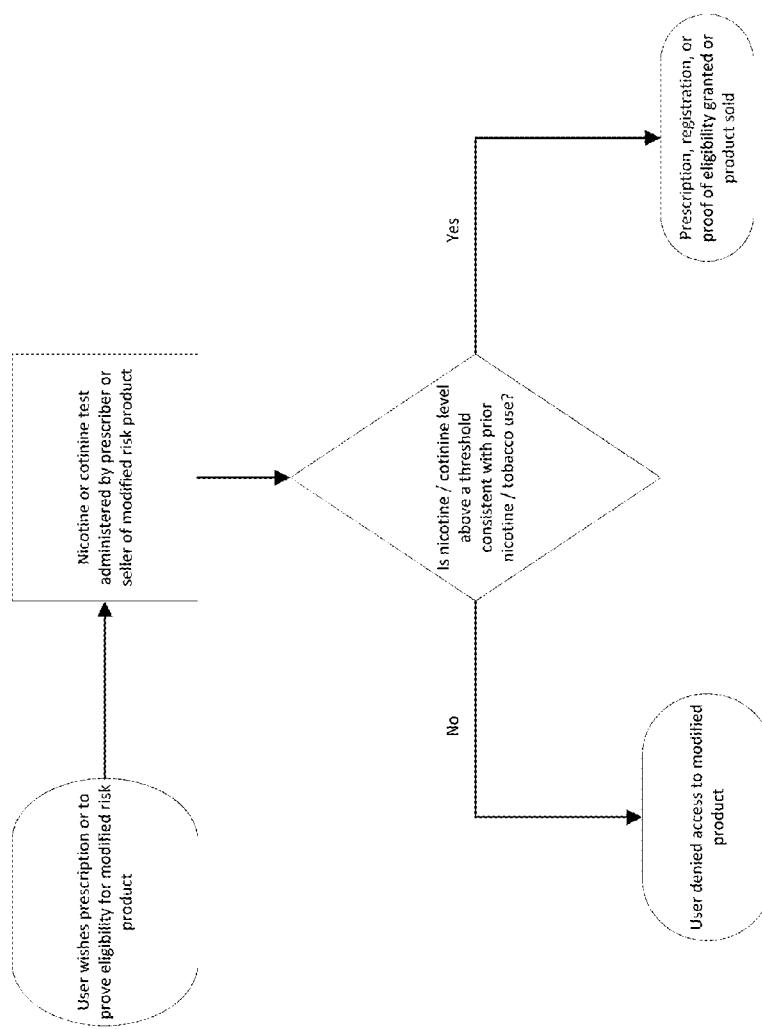
Prescriber / Dispenser Authorization and Verification

Fig. 2



Prescription Process and Verification

Fig. 3A



**Prescription Process and Verification**

**Fig. 3B**

## Nicotine / Cotinine Test

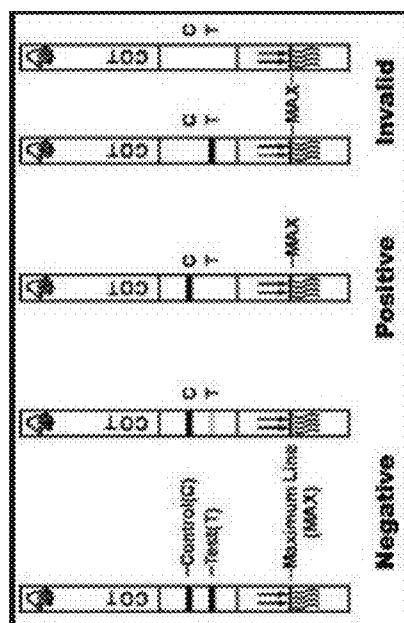


Fig. 3C

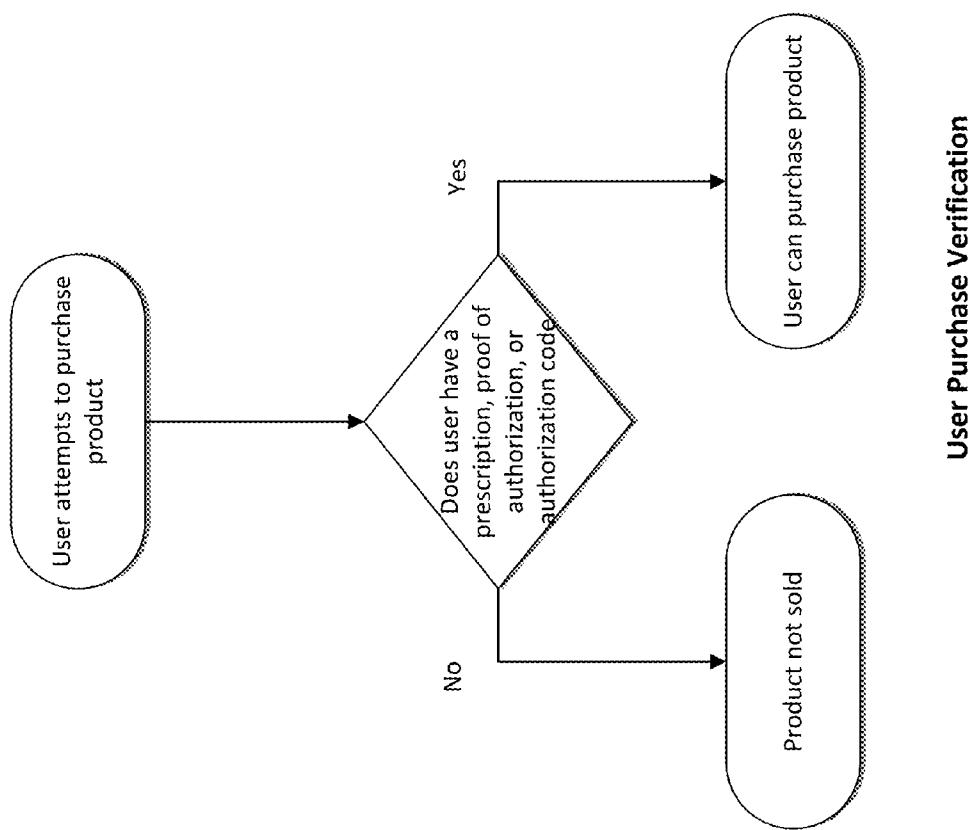


Fig. 4

User Purchase Verification

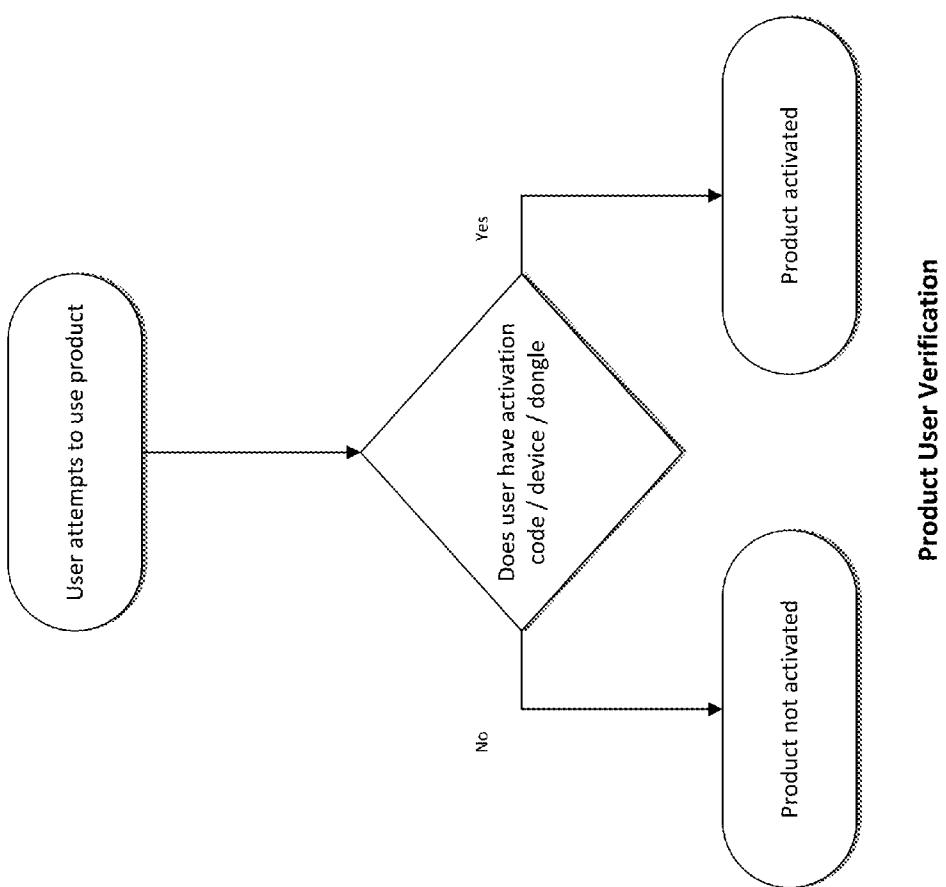
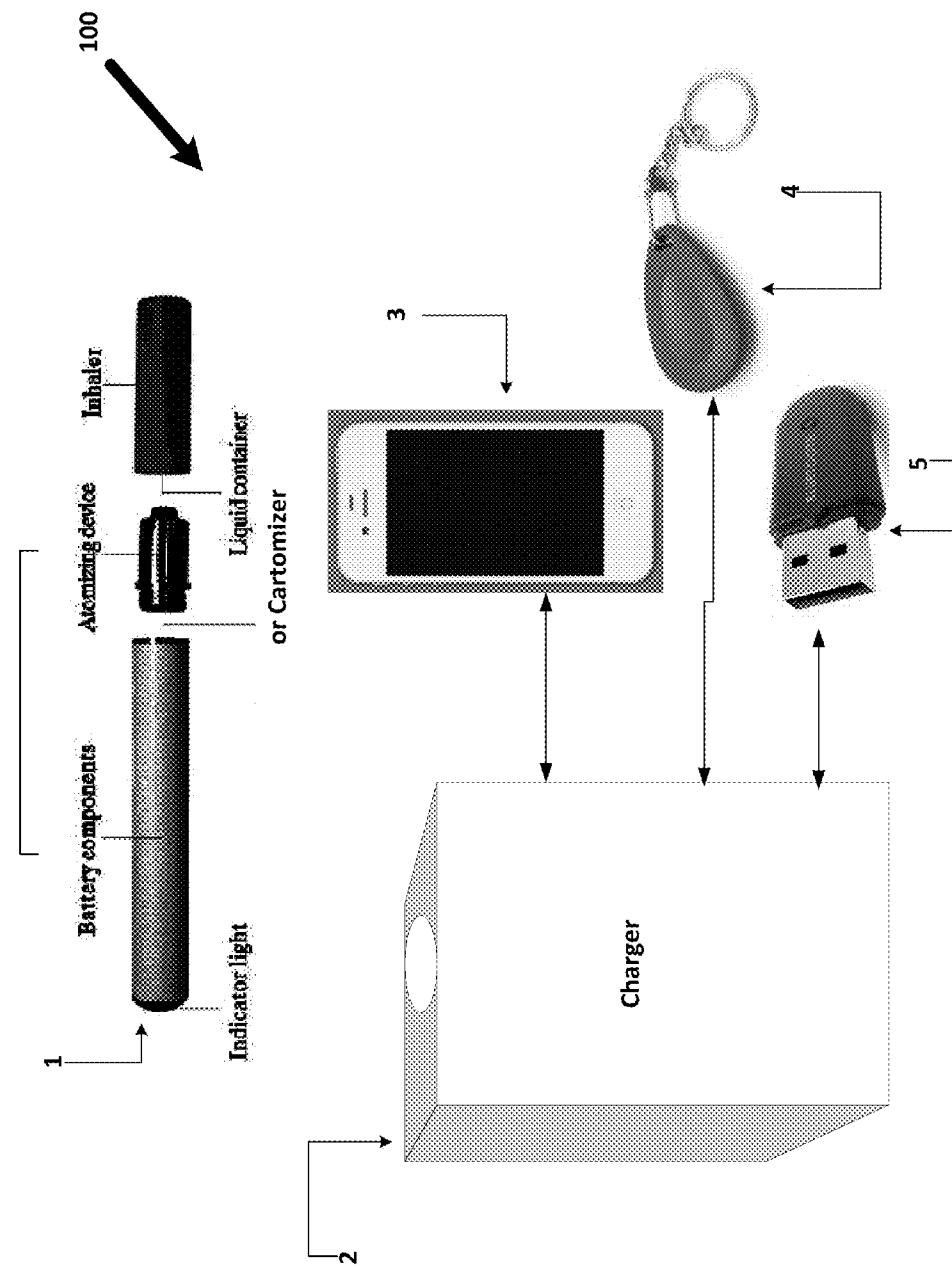
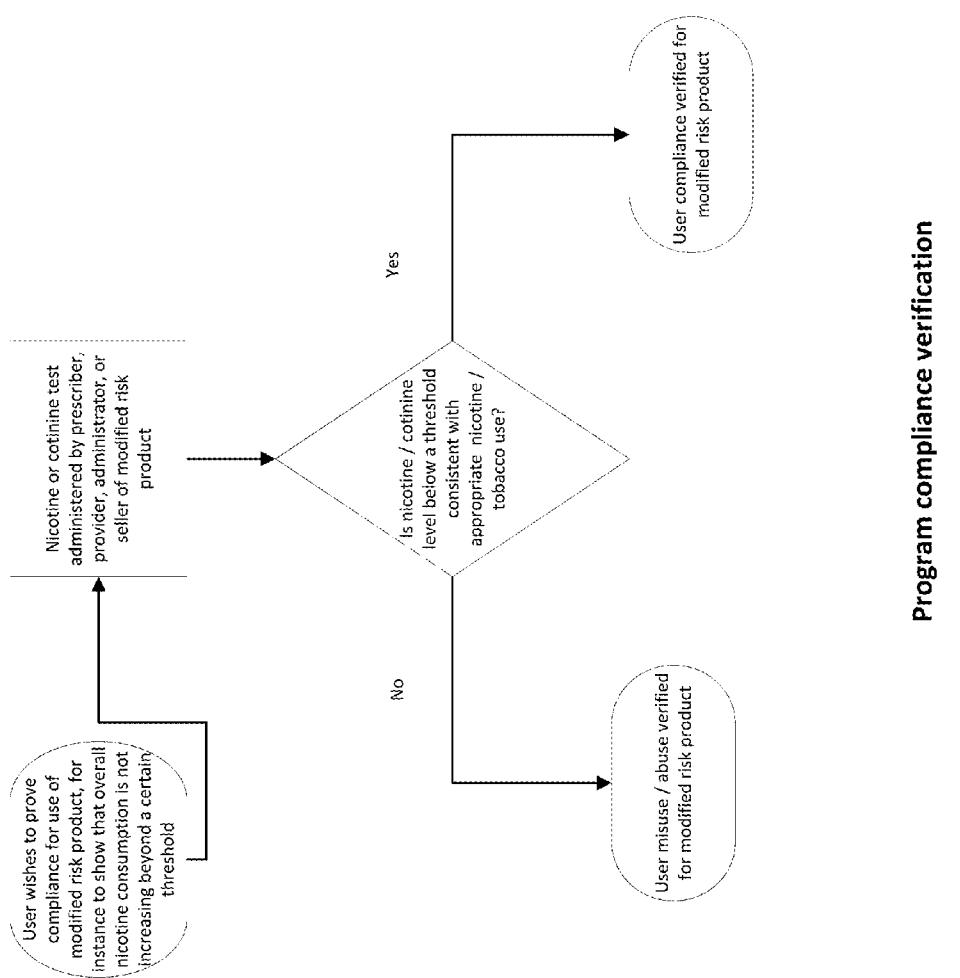


Fig. 5



User Verification for Modified Risk Product Mitigation and Tracking

Fig 6



## Nicotine / Cotinine Test

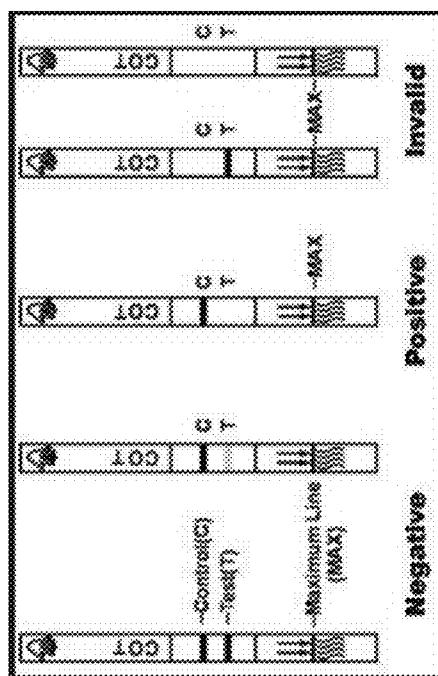


Fig. 7B

## METHODS AND DEVICES FOR DELIVERY AND MONITORING OF TOBACCO, NICOTINE, OR OTHER SUBSTANCES

### CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 61/694,046, filed Aug. 28, 2012, which application is incorporated herein by reference.

### BACKGROUND OF THE INVENTION

[0002] The use of tobacco products and the harmful side effects of smoking tobacco and nicotine consumption continue to gain increasing attention worldwide. As more regulations come into effect regarding smoking in the work place or in public, interest in developing alternative methods of protecting public health and providing cessation products and methods is growing significantly. As with most new therapies or drugs, the federal government has issued regulations intended to protect the public, with enforcement authority granted to the U.S. Food and Drug Administration (FDA).

### SUMMARY OF THE INVENTION

[0003] It is generally understood that the mission of the US Food and Drug Administration (FDA) is to advance the public health by helping to speed the innovations that make medicines and most foods more effective, safer, and more affordable; and help the public get accurate, science-based information they need to use those medicines and foods to improve their health.

[0004] In June, 2009, The Family Smoking Prevention and Tobacco Control Act was signed into law, creating "The Center for Tobacco Products", a tobacco control center within the FDA, having the authority to regulate tobacco industry in the U.S., by regulating the content, commercial marketing, sale and distribution of tobacco products within the United States. The law also requires tobacco companies and importers to reveal all product ingredients and seek FDA approval for any new tobacco products.

[0005] Under its new-found, expanded authority, the FDA now has the ability to control the commercial sale and distribution of traditional tobacco products, including cigarettes, pipe tobacco, and cigars, as well as new tobacco and nicotine related products, including; electronic nicotine vaporizers, (e.g. the electronic cigarette); and products with potentially modified safety risk relative to cigarettes. These products have new regulatory pathways associated with them, including those proscribed under Section 911 (modified risk tobacco products.)

[0006] When considering whether to allow the marketing of modified risk products, FDA must consider the benefit to health of individuals and the population as a whole, including: "the increased or decreased likelihood that existing users of tobacco products who would otherwise stop using such products will switch to the tobacco product that is the subject of the application; the increased or decreased likelihood that persons who do not use tobacco products will start using the tobacco product that is the subject of the application; and the risks and benefits to persons from the use of the tobacco product that is the subject of the application as compared to the use of products for smoking cessation approved under chapter V to treat nicotine dependence."

[0007] One potential approach for FDA to address the benefits to health of individuals and the population could be to

require Risk Evaluation and Mitigation Strategies (REMS) be put in place for modified risk products or other tobacco products as a prerequisite for marketing approval.

[0008] There are essentially three components to a REMS program: 1. A medication guide or patient insert; 2. A communication plan for healthcare providers; and 3. Elements to assure safe use, (ELASU). A drug's REMS program may not require the provision of all three components, as the specific components a REMS program employs will vary based on the severity of the risks, the population likely to be exposed, and other factors. In fact, the most common REMS only require the provision of a medication guide.

[0009] While REMS components are not uniform, some currently do, or in the future, may contain new provisions and requirements for physicians and other certified health care providers. For REMS requiring ETASU, clinicians may be required to: Obtain and dispense drugs through specific distribution channels; Possess specific training, education, experience, or certification(s) in order to prescribe these drugs; Enroll patients in registry programs; and, Issue mandatory, time-sensitive reports of patient responses to treatment.

[0010] It is possible that one's ability to prescribe and dispense certain medications, even some that have been on the market for years, could be contingent upon compliance with these REMS provisions.

[0011] Applicant has developed novel methods and devices for the delivery and monitoring of tobacco, nicotine and other substances that will meet or exceed any potential federal regulation in this field.

[0012] Provided herein is a method of protecting public health comprising: increasing the likelihood that a first subject or a second subject will stop using a tobacco product by providing a modified risk product for administration to the first subject addicted to the tobacco product wherein the first subject has previously failed nicotine replacement therapy.

[0013] In some embodiments the modified risk product comprises; an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, and/or a tobacco or nicotine product, used in combination with a risk evaluation and mitigation strategy and may involve subject eligibility verification, subject compliance verification to a risk mitigation strategy and overall validation of the success of said risk evaluation and mitigation strategy.

[0014] In some embodiments the previously failed nicotine replacement therapy comprises abstinence, nicotine gum, nicotine oral spray, nicotine inhaler, nicotine nasal spray, nicotine lozenge, nicotine dermal patch, bupropion (which includes 3-chloro-N-tert-butyl- $\beta$ -ketoamphetamine, a derivative thereof, an analogue thereof, a bupropion metabolite, a pharmaceutically acceptable salts thereof, R,R-hydroxybupropion, S,S-hydroxybupropion, threo-hydrobupropion, erythro-hydrobupropion, 1-(3-chlorophenyl)-2-[(1,1-dimethyl) amino]-1-propanone hydrochloride, 2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol, 1-(3-chlorophenyl)-2-[(1,1-dimethyllethanol)amino]-1-propanol and 1-(3-chlorophenyl)-2-[(1,1-dimethyl ethanol)amino]-1-propanone or combinations thereof), varenicline or 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine or a pharmaceutically acceptable salt thereof, varenicline tartrate or 7,8,9,10-tetrahydro-6, 10-methano-6H-pyrazino[2,3-h][3]benzazepine, (2?;3?)-2,3-dihydroxybutanedioate (1:1) or 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine tartrate or a pharmaceutically acceptable salt thereof, or comparable oral

nicotine replacement product. Varenicline is sold by Pfizer under the brand name CHANTIX® (see, for example, WO2010023561, incorporated by reference herein in its entirety.)

[0015] In some embodiments, the product is prescribed, provided, or a subject's eligibility is verified by a physician, a nurse, a pharmacist, an accredited healthcare provider, or an employee of a convenience or retail store.

[0016] In some embodiments, the product is prescribed, provided, or a subject's eligibility is verified by an internet or wireless based application, service or business, or by a call center or phone based application service or business.

[0017] In some embodiments, the subject eligibility verification comprises collecting samples and measuring nicotine levels in blood samples, in expelled breath samples, in saliva samples, in hair samples, and in urine samples to verify that the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user.

[0018] In some embodiments, the subject compliance verification comprises collecting and sending samples, taken before and after being provided a modified risk product, for analysis to an accredited testing facility, and measuring the difference between said samples for nicotine levels in blood, expelled breath, saliva, hair, and in urine.

[0019] In some embodiments, components of the subject compliance verification may be performed by a physician, a nurse, a pharmacist, an accredited healthcare provider, or an employee of a convenience or retail store.

[0020] Provided herein is a method of protecting public health comprising: increasing the likelihood that a first subject or a second subject will stop using a tobacco product by providing a modified risk product for administration to the first subject addicted to the tobacco product only after at least one failed attempt by the first subject to quit using such tobacco product.

[0021] In some embodiments, the modified risk product comprises; an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, and/or a tobacco or nicotine product, used in combination with a risk evaluation and mitigation strategy and may involve subject eligibility verification, subject compliance verification to a risk mitigation strategy and overall validation of the success of said risk evaluation and mitigation strategy.

[0022] In some embodiments, the previously failed at least one attempt to quit using said tobacco product comprises, abstinence, nicotine gum, nicotine oral spray, nicotine inhaler, nicotine nasal spray, nicotine lozenge, nicotine dermal patch, bupropion (which includes 3-chloro-N-tert-butyl- $\beta$ -ketoamphetamine, a derivative thereof, an analogue thereof, a bupropion metabolite, a pharmaceutically acceptable salts thereof, R,R-hydroxybupropion, S,S-hydroxybupropion, threo-hydrobupropion, erythro-hydrobupropion, 1-(3-chlorophenyl)-2-[(1,1dimethyl) amino]-1-propanone hydrochloride, 2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol, 1-(3-chlorophenyl)-2-[(1,1-dimethyl-ethanol)amino]-1-propanol and 1-(3-chlorophenyl)-2-[(1,1-dimethyl ethanol)amino]-1-propanone or combinations thereof), varenicline or 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino [2,3-h][3]benzazepine or a pharmaceutically acceptable salt thereof, varenicline tartrate or 7,8,9, 10-tetrahydro-6, 10-methano-6H-pyrazino[2,3-h] [3] benzazepine, (2i?,3i?)-2,3-dihydroxybutanedioate (1:1) or 7,8,9,10-Tetrahydro-6,10-methano-6H $\gamma$ -pyrazino[2,3-h][3]benzazepine

tartrate or 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino [2,3-h][3]benzazepine tartrate or a pharmaceutically acceptable salt thereof, or comparable oral nicotine replacement product. Varenicline is sold by Pfizer under the brand name CHANTIX® (see, for example, WO2010023561, incorporated by reference herein in its entirety.)

[0023] In some embodiments, the product is prescribed, provided, administered, or subject eligibility verified by a physician, a nurse, a pharmacist, or an accredited healthcare provider, or an employee of a convenience or retail store.

[0024] In some embodiments, the subject eligibility verification comprises collecting samples and measuring nicotine levels in blood samples, in expelled breath samples, in saliva samples, in hair samples, and in urine samples to verify that the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user.

[0025] In some embodiments, the subject compliance verification comprises collecting and sending samples taken before and after being provided a modified risk product, for analysis to an accredited testing facility, and measuring the difference between samples for nicotine levels in blood, expelled breath, saliva, hair, and in urine.

[0026] In some embodiments, components of the subject compliance verification may be performed by a physician, a nurse, a pharmacist, an accredited healthcare provider, or an employee of a convenience or retail store.

[0027] Provided herein is a method of protecting public health comprising increasing the likelihood that a first subject or a second subject will stop using a tobacco product by providing a modified risk product for administration to the first subject addicted to the tobacco product only after the modified risk product is prescribed to the first subject.

[0028] In some embodiments, the modified risk product comprises; an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, and/or a tobacco or nicotine product, used in combination with a risk evaluation and mitigation strategy and may involve subject eligibility verification, subject compliance verification to a risk mitigation strategy and overall validation of the success of said risk evaluation and mitigation strategy.

[0029] In some embodiments, the subject eligibility verification comprises collecting samples and measuring nicotine levels in blood samples, in expelled breath samples, in saliva samples, in hair samples, and in urine samples to verify that the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user.

[0030] In some embodiments, the product is prescribed by a physician, a nurse, a pharmacist, or an accredited healthcare provider.

[0031] In some embodiments, the risk evaluation and mitigation strategy incorporates a means of subject compliance verification.

[0032] In some embodiments, the subject compliance verification comprises collecting and sending samples taken before and after being provided a modified risk product, for analysis to an accredited testing facility, and measuring the difference between samples for nicotine levels in blood, expelled breath, saliva, hair, and in urine.

[0033] In some embodiments, components of the subject compliance verification may be performed by a physician, a nurse, a pharmacist, an accredited healthcare provider, or an employee of a convenience or retail store.

[0034] Provided herein is a method of protecting public health comprising decreasing the likelihood that a second subject not using a tobacco product will start using the tobacco product by providing a modified risk product for administration to the first subject addicted to the tobacco product wherein the first subject has previously failed nicotine replacement therapy.

[0035] In some embodiments, the modified risk product comprises; an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, and/or a tobacco or nicotine product, used in combination with a risk evaluation and mitigation strategy and may involve subject eligibility verification, subject compliance verification to a risk mitigation strategy and overall validation of the success of said risk evaluation and mitigation strategy.

[0036] In some embodiments, the previously failed attempt to quit using said tobacco product comprises, abstinence, nicotine gum, nicotine oral spray, nicotine inhaler, nicotine nasal spray, nicotine lozenge, nicotine dermal patch, bupropion (which includes 3-chloro-N-tert-butyl- $\beta$ -ketoamphetamine, a derivative thereof, an analogue thereof, a bupropion metabolite, a pharmaceutically acceptable salts thereof, R,R-hydroxybupropion, S,S-hydroxybupropion, threo-hydrobupropion, erythro-hydrobupropion, 1-(3-chlorophenyl)-2-[(1,1dimethyl) amino]-1-propanone hydrochloride, 2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol, 1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-propanol and 1-(3-chlorophenyl)-2-[(1,1-dimethyl ethanol) amino]-1-propanone or combinations thereof), varenicline or 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino [2,3-h][3] benzazepine or a pharmaceutically acceptable salt thereof, varenicline tartrate or 7,8,9, 10-tetrahydro-6, 10-methano-6H-pyrazino[2,3-h] [3] benzazepine, (2i?,3/?)2,3-dihydroxybutanedioate (1:1) or 7,8,9,10-Tetrahydro-6,10-methano-6H<sup>+</sup>-pyrazino[2,3-h][3]benzazepine tartrate or a pharmaceutically acceptable salt thereof, or comparable oral nicotine replacement product. Varenicline is sold by Pfizer under the brand name CHANTIX®.

[0037] In some embodiments, the product is prescribed, provided or subject eligibility verified by a physician, a nurse, a pharmacist, or an accredited healthcare provider.

[0038] In some embodiments, the product is provided or subject eligibility verified by an employee of a convenience or retail store.

[0039] In some embodiments, the product is provided, or subject eligibility verified by an internet based application, service or business.

[0040] In some embodiments, the product is provided or subject eligibility verified by a call center or phone based application service or business.

[0041] In some embodiments, the subject eligibility verification comprises collecting samples and measuring nicotine levels in blood samples, in expelled breath samples, in saliva samples, in hair samples, and in urine samples to verify that the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user.

[0042] In some embodiments, the subject compliance verification comprises collecting and sending samples taken before and after being provided a modified risk product, for analysis to an accredited testing facility, and measuring the difference between samples for nicotine levels in blood, expelled breath, saliva, hair, and in urine.

[0043] In some embodiments, components of the subject compliance verification may be performed by a physician, a nurse, a pharmacist, an accredited healthcare provider, or an employee of a convenience or retail store.

[0044] Provided herein is a method of protecting public health comprising decreasing the likelihood that a second subject not using a tobacco product will start using the tobacco product by providing a modified risk product for administration to the first subject addicted to the tobacco product only after at least one failed attempt by the first subject to quit using such tobacco product.

[0045] In some embodiments, the modified risk product comprises; an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, and/or a tobacco or nicotine product, used in combination with a risk evaluation and mitigation strategy and may involve subject eligibility verification, subject compliance verification to a risk mitigation strategy and overall validation of the success of said risk evaluation and mitigation strategy.

[0046] In some embodiments, the previously failed attempt to quit using said tobacco product comprises, abstinence, nicotine gum, nicotine oral spray, nicotine inhaler, nicotine nasal spray, nicotine lozenge, nicotine dermal patch, bupropion (which includes 3-chloro-N-tert-butyl- $\beta$ -ketoamphetamine, a derivative thereof, an analogue thereof, a bupropion metabolite, a pharmaceutically acceptable salts thereof, R,R-hydroxybupropion, S,S-hydroxybupropion, threo-hydrobupropion, erythro-hydrobupropion, 1-(3-chlorophenyl)-2-[(1,1dimethyl) amino]-1-propanone hydrochloride, 2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol, 1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-propanol and 1-(3-chlorophenyl)-2-[(1,1-dimethyl ethanol) amino]-1-propanone or combinations thereof), varenicline or 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino [2,3-h][3] benzazepine or a pharmaceutically acceptable salt thereof, varenicline tartrate or 7,8,9, 10-tetrahydro-6, 10-methano-6H-pyrazino[2,3-h] [3] benzazepine, (2i?,3/?)2,3-dihydroxybutanedioate (1:1) or 7,8,9,10-Tetrahydro-6,10-methano-6H<sup>+</sup>-pyrazino[2,3-h][3]benzazepine tartrate or a pharmaceutically acceptable salt thereof, or comparable oral nicotine replacement product. Varenicline is sold by Pfizer under the brand name CHANTIX®.

[0047] In some embodiments, the product is prescribed, provided or subject eligibility verified by a physician, a nurse, a pharmacist, or an accredited healthcare provider.

[0048] In some embodiments, the product is provided or subject eligibility verified by or an employee of a convenience or retail store.

[0049] In some embodiments, the product is provided, or subject eligibility verified by an internet based application, service or business.

[0050] In some embodiments, the product is provided or subject eligibility verified by a call center or phone based application service or business.

[0051] In some embodiments, the subject eligibility verification comprises collecting samples and measuring nicotine levels in blood samples, in expelled breath samples, in saliva samples, in hair samples, and in urine samples to verify that the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user.

[0052] In some embodiments, the subject compliance verification comprises collecting and sending samples taken before and after being provided a modified risk product, for

analysis to an accredited testing facility, and measuring the difference between samples for nicotine levels in blood, expelled breath, saliva, hair, and in urine.

[0053] In some embodiments, components of the subject compliance verification may be performed by a physician, a nurse, a pharmacist, an accredited healthcare provider, or an employee of a convenience or retail store.

[0054] Provided herein is a method of protecting public health comprising decreasing the likelihood that a second subject not using a tobacco product will start using the tobacco product or an alternative tobacco product, by providing a modified risk product for administration to the first subject addicted to the tobacco product, only after the modified risk product is prescribed to the first subject.

[0055] In some embodiments, said modified risk product comprises; an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, and/or a tobacco or nicotine product, used in combination with a risk evaluation and mitigation strategy and may involve subject eligibility verification, subject compliance verification to a risk mitigation strategy and overall validation of the success of said risk evaluation and mitigation strategy.

[0056] In some embodiments, the product is prescribed by and subject eligibility verified by a physician, a nurse, a pharmacist, or an accredited healthcare provider.

[0057] In some embodiments, the product is provided or subject eligibility verified by or an employee of a convenience or retail store.

[0058] In some embodiments, the product is provided, or subject eligibility verified by an internet based application, service or business.

[0059] In some embodiments, the product is provided or subject eligibility verified by a call center or phone based application service or business.

[0060] In some embodiments, the subject eligibility verification comprises collecting samples and measuring nicotine levels in blood samples, in expelled breath samples, in saliva samples, in hair samples, and in urine samples to verify that the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user.

[0061] In some embodiments, the subject compliance verification comprises collecting and sending samples taken before and after being provided a modified risk product, for analysis to an accredited testing facility, and measuring the difference between samples for nicotine levels in blood, expelled breath, saliva, hair, and in urine.

[0062] In some embodiments, components of the subject compliance verification may be performed by a physician, a nurse, a pharmacist, an accredited healthcare provider, or an employee of a convenience or retail store.

[0063] Provided herein is a method of treating a first subject addicted to a tobacco product, the method comprising administering to the first subject who has previously failed nicotine replacement therapy, a modified risk product.

[0064] In some embodiments the modified risk product comprises; an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, and/or a tobacco or nicotine product, used in combination with a risk evaluation and mitigation strategy and may involve subject eligibility verification, subject compliance verification to a risk mitigation strategy and overall validation of the success of said risk evaluation and mitigation strategy.

[0065] In some embodiments the previously failed nicotine replacement therapy comprises abstinence, nicotine gum, nicotine oral spray, nicotine inhaler, nicotine nasal spray, nicotine lozenge, nicotine dermal patch, bupropion (which includes 3-chloro-N-tert-butyl- $\beta$ -ketoamphetamine, a derivative thereof, an analogue thereof, a bupropion metabolite, a pharmaceutically acceptable salts thereof, R,R-hydroxybupropion, S,S-hydroxybupropion, threo-hydrobupropion, erythro-hydrobupropion, 1-(3-chlorophenyl)-2-[(1,1dimethyl) amino]-1-propanone hydrochloride, 2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethylmorpholinol, 1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-propanol and 1-(3-chlorophenyl)-2-[(1,1-dimethyl ethanol) amino]-1-propanone or combinations thereof), varenicline or 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine or a pharmaceutically acceptable salt thereof, varenicline tartrate or 7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine, (2i?3?)-2,3-dihydroxybutanedioate (1:1) or 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine tartrate or a pharmaceutically acceptable salt thereof, or comparable oral nicotine replacement product. Varenicline is sold by Pfizer under the brand name CHANTIX®.

[0066] In some embodiments, the product is administered by a physician, a nurse, a pharmacist, or an accredited healthcare provider.

[0067] In some embodiments, the product is administered by an employee of a convenience or retail store.

[0068] In some embodiments, the subject eligibility verification comprises collecting samples and measuring nicotine levels in blood samples, in expelled breath samples, in saliva samples, in hair samples, and in urine samples to verify that the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user.

[0069] In some embodiments, the subject compliance verification comprises collecting and sending samples taken before and after being provided a modified risk product, for analysis to an accredited testing facility, and measuring the difference between samples for nicotine levels in blood, expelled breath, saliva, hair, and in urine.

[0070] In some embodiments, components of the subject compliance verification may be performed by a physician, a nurse, a pharmacist, an accredited healthcare provider, or an employee of a convenience or retail store.

[0071] In some embodiments, the subject compliance verification comprises collecting samples and measuring nicotine levels in blood samples, measuring nicotine levels in expelled breath samples, measuring nicotine levels in saliva samples, measuring nicotine levels in hair samples, and measuring nicotine levels in urine samples.

[0072] In some embodiments, the subject compliance verification is performed by a physician, a nurse, a pharmacist, or an accredited healthcare provider.

[0073] In some embodiments, the subject compliance verification is performed by or an employee of a convenience or retail store.

[0074] Provided herein is a method of treating a first subject addicted to a tobacco product, the method comprising administering to the first subject a modified risk product only after at least one failed attempt by the first subject to quit using such tobacco product.

[0075] In some embodiments the modified risk product comprises; an electronic cigarette, an electronic pipe, an elec-

tronic cigar, an electronic water pipe, an electronic vaporizer, and/or a tobacco or nicotine product, used in combination with a risk evaluation and mitigation strategy and may involve subject eligibility verification, subject compliance verification to a risk mitigation strategy and overall validation of the success of said risk evaluation and mitigation strategy.

[0076] In some embodiments the previously failed nicotine replacement therapy comprises abstinence, nicotine gum, nicotine oral spray, nicotine inhaler, nicotine nasal spray, nicotine lozenge, nicotine dermal patch, bupropion (which includes 3-chloro-N-tert-butyl- $\beta$ -ketoamphetamine, a derivative thereof, an analogue thereof, a bupropion metabolite, a pharmaceutically acceptable salts thereof, R,R-hydroxybupropion, S,S-hydroxybupropion, threo-hydrobupropion, erythro-hydrobupropion, 1-(3-chlorophenyl)-2-[(1,1dimethyl) amino]-1-propanone hydrochloride, 2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol, 1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-propanol and 1-(3-chlorophenyl)-2-[(1,1-dimethyl ethanol) amino]-1-propanone or combinations thereof), varenicline or 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino [2,3-h][3]benzazepine or a pharmaceutically acceptable salt thereof, varenicline tartrate or 7,8,9, 10-tetrahydro-6, 10-methano-6H-pyrazino[2,3-h] [3]benzazepine, (2i?,3/?)2,3-dihydroxybutanedioate (1:1) or 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine tartrate or a pharmaceutically acceptable salt thereof, or comparable oral nicotine replacement product. Varenicline is sold by Pfizer under the brand name CHANTIX®.

[0077] In some embodiments, the product is administered by a physician, a nurse, a pharmacist, or an accredited healthcare provider.

[0078] In some embodiments, the product is administered by an employee of a convenience or retail store.

[0079] In some embodiments, the subject eligibility verification comprises collecting samples and measuring nicotine levels in blood samples, in expelled breath samples, in saliva samples, in hair samples, and in urine samples to verify that the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user.

[0080] In some embodiments, the subject compliance verification comprises collecting and sending samples taken before and after being provided a modified risk product, for analysis to an accredited testing facility, and measuring the difference between samples for nicotine levels in blood, expelled breath, saliva, hair, and in urine.

[0081] In some embodiments, components of the subject compliance verification may be performed by a physician, a nurse, a pharmacist, an accredited healthcare provider, or an employee of a convenience or retail store.

[0082] In some embodiments, the subject compliance verification comprises collecting samples and measuring nicotine levels in blood samples, measuring nicotine levels in expelled breath samples, measuring nicotine levels in saliva samples, measuring nicotine levels in hair samples, and measuring nicotine levels in urine samples.

[0083] In some embodiments, the subject compliance verification is performed by a physician, a nurse, a pharmacist, or an accredited healthcare provider.

[0084] In some embodiments, the subject compliance verification is performed by an employee of a convenience or retail store.

[0085] Provided herein is a method of treating a first subject addicted to a tobacco product, the method comprising administering a modified risk product to the first subject only after the modified risk product is prescribed to the first subject.

[0086] In some embodiments, said modified risk product comprises; an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, and/or a tobacco or nicotine product, used in combination with a risk evaluation and mitigation strategy and may involve subject eligibility verification, subject compliance verification to a risk mitigation strategy and overall validation of the success of said risk evaluation and mitigation strategy.

[0087] In some embodiments, the modified risk product is prescribed and administered by a physician, a nurse, a pharmacist, or an accredited healthcare provider.

[0088] In some embodiments, the product is administered by an accredited employee of a convenience or retail store, or an employee of an accredited convenience or retail store.

[0089] In some embodiments, the product is administered by an internet or wireless based application, service or business.

[0090] In some embodiments, the product is administered by a call center or phone based application service or business.

[0091] In some embodiments, the subject eligibility verification comprises collecting samples and measuring nicotine levels in blood samples, in expelled breath samples, in saliva samples, in hair samples, and in urine samples to verify that the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user.

[0092] In some embodiments, the subject compliance verification comprises collecting and sending samples taken before and after being provided a modified risk product, for analysis to an accredited testing facility, and measuring the difference between samples for nicotine levels in blood, expelled breath, saliva, hair, and in urine.

[0093] In some embodiments, components of the subject compliance verification may be performed by a physician, a nurse, a pharmacist, an accredited healthcare provider, or an employee of a convenience or retail store.

[0094] In some embodiments, the subject compliance verification comprises collecting samples and measuring nicotine levels in blood, expelled breath, saliva, hair, and/or urine.

[0095] In some embodiments, the subject compliance verification is performed by a physician, a nurse, a pharmacist, or an accredited healthcare provider.

[0096] In some embodiments, the subject compliance verification is performed by an employee of a convenience or retail store.

[0097] Provided herein is a method for increasing the likelihood that the first subject or a second subject will stop using the tobacco product.

[0098] Provided herein is a method for decreasing the likelihood that a second subject not using the tobacco product will start using the tobacco product.

[0099] Provided herein is a method for verifying the at least one prior failed attempt to stop using tobacco products prior to the modified risk product being provided to a first subject.

[0100] In some embodiments, the verification comprises collecting samples and measuring nicotine levels in blood samples, in expelled breath samples, in saliva samples, in hair samples, and in urine samples to verify that the subject's nicotine or nicotine by-product levels are above or consistent

with levels expected for a tobacco or nicotine user after verification that the subject had previously attempted to stop using tobacco products.

[0101] In some embodiments, the previously failed attempt may have comprised using abstinence, nicotine gum, nicotine oral spray, nicotine inhaler, nicotine nasal spray, nicotine lozenge, nicotine dermal patch, bupropion (which includes 3-chloro-N-tert-butyl-β-ketoamphetamine, a derivative thereof, an analogue thereof, a bupropion metabolite, a pharmaceutically acceptable salts thereof, R,R-hydroxybupropion, S,S-hydroxybupropion, threo-hydroxybupropion, erythro-hydroxybupropion, 1-(3-chlorophenyl)-2-[(1,1dimethyl) amino]-1-propanone hydrochloride, 2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol, 1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-propanol and 1-(3-chlorophenyl)-2-[(1,1-dimethyl ethanol)amino]-1-propanone or combinations thereof), varenicline or 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine or a pharmaceutically acceptable salt thereof, varenicline tartrate or 7,8,9, 10-tetrahydro-6, 10-methano-6H-pyrazino[2,3-h] [3] benzazepine, (2i?,3?)2,3-dihydroxybutanedioate (1:1) or 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine tartrate or a pharmaceutically acceptable salt thereof, or comparable oral nicotine replacement product. Varenicline is sold by Pfizer under the brand name CHANTIX®.

[0102] Provided herein is a method for verifying that a first subject meets at least one eligibility requirement for use of a modified tobacco risk product.

[0103] Provided herein is a method for verifying a subject's eligibility requirement comprising: possession of an eligibility card, meeting qualifications for the eligibility card, possessing a valid verification code, possessing a physician-provided eligibility record, possessing a pharmacist-provided eligibility record, and passing a pharmacist-provided eligibility evaluation.

[0104] In some embodiments of a method having an eligibility requirement, the identity verification step comprises at least one of:

[0105] evidence of meeting a minimum age requirement,  
[0106] evidence of a previously failed nicotine replacement therapy, and

[0107] evidence of at least one failed attempt by the patient to quit using such tobacco product,

[0108] electronic or telephonic verification of a unique subject eligibility card or code identifier,

[0109] software verification of a unique subject eligibility card or code identifier,

[0110] electronic fingerprint verification of an eligible subject,

[0111] an activation code, or

[0112] an electronic dongle, electronic security key fob, or equivalent.

[0113] Provided herein is a method for verifying a subject's eligibility requirement wherein the verifying step is performed by a physician, a nurse, a pharmacist, an accredited healthcare provider an accredited employee of a convenience or retail store, or an employee of an accredited convenience or retail store.

[0114] Provided herein is a method for providing a prescription for a modified risk product, wherein said prescription is provided by a qualified healthcare provider.

[0115] In some embodiments, said modified risk product comprises; an electronic cigarette, an electronic pipe, an elec-

tronic cigar, an electronic water pipe, an electronic vaporizer, and/or a tobacco or nicotine product, used in combination with a risk evaluation and mitigation strategy and may involve subject eligibility verification, subject compliance verification to a risk mitigation strategy and overall validation of the success of said risk evaluation and mitigation strategy.

[0116] Provided herein is a method of verifying eligibility of a first subject addicted to a tobacco product, to be provided with a modified risk product, the method comprising, measuring nicotine levels present in the system of a first subject prior to administration of said modified risk product and confirming that said nicotine levels are above or consistent with those of a tobacco or nicotine product user.

[0117] In some embodiments the method of verifying eligibility comprises; measuring nicotine levels in blood samples, expelled breath samples, saliva samples, hair samples, and urine samples.

[0118] Provided herein is a method of monitoring compliance of a first subject addicted to a tobacco product and participating in a REMS program comprising a modified risk product, the method comprising, measuring nicotine levels of a first subject prior to administration of said modified risk product and measurement of nicotine levels after administration of said modified risk product, and comparing said prior nicotine prior levels to anticipated nicotine levels after administration of said modified risk product.

[0119] In some embodiments, a method of monitoring comprises; using an electronic signature to track the pattern of use of a vaporizer, electronic cigarette, or other modified risk product wherein said product transmits a record of use over a given period of time.

[0120] In some embodiments, a record of use comprises levels of nicotine consumed, times, and dates it was consumed.

[0121] In some embodiments, the record of use is stored to a data storage device and later downloaded for use by a qualified healthcare provider or REMS monitor or administrator.

[0122] In some embodiments, the record of use is transmitted wirelessly to a data storage device and later downloaded for use by a qualified healthcare provider or REMS monitor or administrator.

[0123] In some embodiments, the record of use is stored within the device, and later downloaded for use by a qualified healthcare provider or REMS monitor.

[0124] In some embodiments, the record of use may be wirelessly transmitted from a data storage device or a component of the modified risk product to a remote location for use by a qualified healthcare provider or REMS monitor or administrator.

[0125] Provided herein is a method of monitoring the use of a modified risk product by a first subject addicted to a tobacco product, the method comprising, requiring an identification recognition system be activated before use of a modified risk product can occur.

[0126] In some embodiments, the identification recognition system comprises a fingerprint scanner, a lip print scanner, face recognition, a retinal scan, a combination code, an activation code, security key fob, or dongle.

[0127] In some embodiments, the identification recognition system comprises an electronic application for a smart-phone, laptop, desktop, or tablet computing device, capable of communicating with the modified risk product by a wireless communication system.

[0128] In some embodiments, the identification recognition system must be within a fixed distance of the modified risk product for product to continue to work.

[0129] In some embodiments, the identification recognition system must be within about 5 to 20 feet of the modified risk product.

[0130] In some embodiments, the identification recognition system must be within 10 feet of the modified risk product.

[0131] In some embodiments, the identification recognition system must be within 5 feet of the modified risk product.

[0132] Provided herein is a method of protecting the public health comprising increasing the likelihood that a first subject will stop using a tobacco product by providing a modified risk product for administration to the first subject addicted to the tobacco product wherein the modified risk product provides a faster onset of nicotine delivery, or a higher peak level of nicotine delivery.

[0133] Provided herein is a method of risk mitigation wherein the potential risk of misuse or abuse of a modified risk product is ranked or stratified in comparison to other tobacco products.

[0134] In some embodiments, the relative potential risk of the modified risk product is determined by comparing the pharmacokinetic profile of the modified risk product to nicotine.

[0135] In some embodiments the pharmacokinetic profile of the modified risk product is determined by the maximum plasma concentration (C<sub>max</sub>) of nicotine, compared to a cigarette.

[0136] In some embodiments the pharmacokinetic profile of the modified risk product is determined by the time after administration of the product for nicotine to reach maximum plasma concentration (T<sub>max</sub>), compared to a cigarette.

[0137] In some embodiments the pharmacokinetic profile of the modified risk product is determined by the rate-of-increase of nicotine delivery or concentration in the plasma of a subject compared to a cigarette.

[0138] In some embodiments, the relative potential risk of the modified risk product is determined by comparing the nicotine concentration of the modified risk product other nicotine products in the market.

[0139] In some embodiments, the relative potential risk of the modified risk product is ranked by ease of access associated with the prescriber/administrator.

[0140] In some embodiments, the relative potential risk of the modified risk product is ranked by ease of access through various distribution channels.

[0141] In some embodiments the modified risk product comprises vaporizing tobacco leaves above their pyrolytic temperature.

[0142] In some embodiments the modified risk product comprises heating tobacco leaves below their pyrolytic temperature.

[0143] In some embodiments the modified risk product comprises vaporization of a nicotine salt.

[0144] In some embodiments the modified risk product comprises heating of a nicotine salt below its pyrolytic temperature.

[0145] Provided herein is a method of protecting the public health wherein the provider of a modified risk product is subject to a compliance verification system.

[0146] In some embodiments, the provider verification is performed by an independent auditor.

[0147] Provided herein is a system for verification of subject eligibility, tracking, and reporting use of a modified risk product comprising: an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, or an electronic vaporizer, comprising a battery, an atomizer, electronic circuitry, a memory storage device for tracking components of usage activity, a means of memory transfer, and a charging circuit, a charger base station comprising a memory storage device, a means for receiving data from said modified risk product memory storage device and transmitting said data to a third party, activation software for recognition of a specific device, keyed to said charger base, capable of interfacing with an external device, wherein said external device comprises; a smart phone, computer, electronic fob, electronic dongle, and a wireless communication device, e.g.: Bluetooth device.

[0148] In some embodiments, the system is used in combination with a risk evaluation and mitigation strategy.

[0149] In some embodiments, the system comprises activation means, for recognition and verification of a subject to establish user eligibility prior to use.

[0150] In some embodiments, the system is used to verify subject compliance for use of a modified risk product.

[0151] In some embodiments the system comprises a means for validating overall success of the risk mitigation product when used with the risk evaluation and mitigation strategies.

#### INCORPORATION BY REFERENCE

[0152] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

#### BRIEF DESCRIPTION OF THE DRAWINGS

[0153] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0154] FIG. 1A illustrates a possible configuration of an overall Risk Evaluation and Mitigation Strategy (REMS) where a subject has previously used a nicotine replacement therapy;

[0155] FIG. 1B illustrates another possible configuration of an overall Risk Evaluation and Mitigation Strategy (REMS) where a subject has not used a nicotine replacement therapy;

[0156] FIG. 2 illustrates a possible configuration of a REMS component program for the authorization, verification and program compliance of qualified prescribers and dispensers of modified risk products;

[0157] FIG. 3A illustrates a possible configuration of a REMS component program for the authorization and dispensation of prescriptions for a Modified Risk Product when a subject has previously used a nicotine replacement therapy;

[0158] FIG. 3B illustrates a possible configuration of a REMS component program for the authorization and dispensation of prescriptions for a Modified Risk Product when a subject has previously not used a nicotine replacement therapy;

[0159] FIG. 3C illustrates a representative test strip for verification of nicotine presence in a subject's system;

[0160] FIG. 4 illustrates a possible configuration of a REMS component program for the purchase of Modified Risk Products;

[0161] FIG. 5 illustrates a possible configuration of a REMS component program for User Verification of a Modified Risk Product;

[0162] FIG. 6 illustrates a possible configuration of a REMS component program for User Verification, Tracking, and Automated Reporting Method of a Modified Risk Product and also illustrates a possible system for verification, tracking, and reporting use of, and or subject compliance for the use of a Modified Risk Product;

[0163] FIG. 7A illustrates a possible configuration of a REMS component program for User Eligibility for, or User Compliance of, a Modified Risk Product; and

[0164] FIG. 7B illustrates a representative test strip for verification of nicotine presence in a subject's system which could be adapted for use in a REMS program for User Compliance or testing for misuse or abuse of a Modified Risk Product.

#### DETAILED DESCRIPTION OF THE INVENTION

[0165] Provided herein are methods of protecting the public health by increasing the likelihood that a subject addicted to a tobacco product will stop using a tobacco product wherein the subject has previously failed to stop using a tobacco product by other means.

[0166] It should be understood that at a minimum, terms used throughout this specification have the following meanings.

[0167] Definitions:

[0168] Abstinence: Abstinence has diverse forms and several potential definitions. Commonly it refers to a temporary or partial refrain from food, alcohol, sexual activity, or drugs, such as nicotine in tobacco products. Alternately, it could be used to describe total abstinence where something is completely removed from one's lifestyle for a period of time. As it applies herein, abstinence is generally intended to have the more common meaning of temporary or partial, self-enforced, restraint from indulgence. However, the term may also imply long-term restraint, wherein a subject has maintained a sustained abstinence; i.e.: several years, without necessarily having quit using said products entirely.

[0169] Administer/Administration: Is intended to mean that a product or service has been provided to a subject. Such service may include performing a test, delivering a prescription, or carrying out/providing a verification process.

[0170] Fail/Failed/Failure: is intended to mean that a subject has not succeeded with a previous therapy and returned to previous levels (or greater levels) of tobacco product use. It is commonly understood in therapy programs that early "failure" is a normal part of trying to stop, and more than one attempt at stopping smoking prior to longer-term success is common. Alternatively it could mean inability to refrain from total or sustained abstinence.

[0171] Fail/Failed/Failure: May also mean that a subject continues to use a NRT product longer than indicated by the prescribing method or suggested use, with or without additional use of a tobacco product in addition to the NRT product. For example; a subject may continue using a nicotine patch while continuing to smoke cigarettes, beyond the intended "weaning off" period.

[0172] Initiate: Is intended to mean that a subject has at some point begun using any tobacco cessation therapy or Nicotine Replacement Therapy (NRT) product.

[0173] Modified Risk Product: Is intended to mean a tobacco product that is sold, distributed, or marketed under regulatory authority, with a claim to reduce harm or the risk of tobacco related diseases, or a tobacco product that is shown to substantially reduce the overall exposure to harmful substances.

[0174] Modified Risk Product: May also mean a tobacco or nicotine delivery device or product that is sold, distributed, or marketed under regulatory authority comprising a non-combustion-based, or vaporization-based nicotine delivery mechanism with a lower risk factor for one or more tobacco related diseases or exposure to one or more harmful substances, which may be substituted for any other oral, combustion, or vaporization-based nicotine delivery product having a higher risk factor for one or more tobacco related diseases or exposure to one or more harmful substances.

[0175] Prescribe/Prescription: Is intended to mean that a product has been authorized for distribution to a subject by order of an accredited healthcare provider (a physician); i.e.: by prescription (Rx).

[0176] Prescribe: May also mean a commonly available over-the-counter product that has been recommended by an accredited healthcare provider (a physician, a nurse, a pharmacist); i.e.: by suggestion the use an OTC product, not requiring a Rx, but still requiring verification of a type to meet local, state, or federal regulation by an accredited individual, at the point of distribution. Alternately a person may self-prescribe an available OTC product.

[0177] Quit: is intended to mean that a subject has completely stopped using a (tobacco) product; i.e.: total (i.e.: smoking) cessation.

[0178] Tobacco product: Is generally intended to mean any product produced from any genus of *Nicotiana* plants or nightshade family of plants, or a by-product derived therefrom, comprising nicotine, nicotine salts, or nicotine derivatives, which may produce by-products that can be ingested utilizing oral, combustion, or vaporization delivery.

[0179] Tobacco alternative: May also comprise substitute herbal tobacco products such as corn silk, mint, cinnamon, lemongrass, clover, bugasse, and shisha, among others, comprising nicotine, nicotine salts, or nicotine derivatives, which are often mixed or flavored with various fruit flavors, energy drink flavors, or other appealing flavors and which may produce byproducts that can be ingested utilizing oral, combustion, or vaporization delivery.

[0180] Treat: Is generally intended to mean providing an alternate remediation to a tobacco product to a subject. Providing a remediation to act upon a subject by providing an agent intended to be a substitute for a tobacco product.

[0181] Treat: May also mean substitution of a first tobacco product with a second tobacco product, wherein the second product has a preferable risk profile, i.e.: substitution of a tobacco product which utilizes combustion with a tobacco or nicotine product which does not utilize combustion or which utilizes vaporization.

[0182] Validate/Validation: Is intended to mean a procedure for checking that a product, service, or system has met the needs or requirements of the stakeholder(s), and is typically done in the later phases of product, process, or system development to assure that the development and verification

procedures for a product, service, or system result in a product, service, or system that meets initial requirements, specifications and regulations.

[0183] Vapor/vaporize/vaporization: Is intended to mean converting a normally liquid or solid substance into an aerosol, gaseous or semi-gaseous state, where it is diffused or suspended in the air; i.e.: haze, mist, or steam. Vaporization is also defined as the process for producing a gaseous by-product that is produced from a normally liquid or solid state material, at a temperature which is below the combustion temperature of said material.

[0184] Verify/verification: Is intended to mean a procedure for checking that a product, service, or system complies with a regulation, requirement, specification, or imposed condition; e.g.: has met an initial set of requirements, specifications or regulations and typically performed in the initial or development phases of product, process, or system development.

[0185] Methods:

[0186] Provided herein are methods of protecting the public health by increasing the likelihood that a subject addicted to a tobacco product will stop using a tobacco product wherein the subject has previously failed to stop using a tobacco product by other means. Such methods may include the use of controlled Risk Evaluation and Mitigation Strategies (REMS) such as that illustrated in FIGS. 1A & 1B. These REMS may be applied to drugs, biologics, devices, or combination devices that include any two or more of these things. REMS are intended to answer the question: "Do the benefits of the drug, biologic, (and/or device) outweigh the risks?" Some of the factors taken into consideration include: Seriousness of the disease or condition to be treated

[0187] Size of the patient population;

[0188] Expected benefit of the drug or biologic (and/or device);

[0189] Expected duration of treatment;

[0190] Seriousness of the known or potential adverse events.

[0191] These evaluations are performed not only prior to the approval of a new drug, biologic, (and/or device), in this case, a modified risk product device for delivering nicotine, but also throughout the entire life cycle of the drug, biologic and/or device. This serves as a means to continuously assess the safety and efficacy of existing products based on adverse event reports and results from post-marketing clinical studies.

[0192] For every drug, biologic and/or device approved by the FDA, the risks associated with its use are communicated through the product package insert. In some cases, however, the manufacturer and/or the FDA may determine that expanded REMS are necessary to go beyond product labeling in order to manage risks and thereby ensure that the benefits outweigh the risks.

[0193] As illustrated in FIGS. 1 & 2, elements of a REMS program for Nicotine Replacement Therapy (NRT) may include Elements to Assure Safe Use, (ELASU). A Nicotine REMS program as proposed herein is likely to comprise several algorithms including:

[0194] 1. A Prescriber/Dispenser Authorization Algorithm (FIG. 2); which may include;

[0195] Specific personnel authorized by statute to prescribe or dispense a Modified Risk Product

[0196] A defined Risk Evaluation and Mitigation Strategy for the specific Modified Risk Product

[0197] An auditing and certification program to verify that qualified prescribers/dispensers are appropriately

trained and following the REMS protocols for verification and dispensation of Modified Risk Products

[0198] 2. A Prescription Process and Verification Algorithm (FIGS. 3A & 3B); which may include;

[0199] A method for verifying that only qualified subjects receive a Modified Risk Product, which may include one or more of the following:

[0200] i. evidence of meeting a minimum age requirement;

[0201] ii. evidence of a previously failed nicotine replacement therapy;

[0202] iii. evidence of at least one failed attempt by the patient to quit using such tobacco product;

[0203] iv. collecting samples and measuring nicotine levels in blood, expelled breath, saliva, hair, or urine to verify that the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user; (FIG. 3C)

[0204] v. a prescription from a physician or accredited healthcare provider;

[0205] vi. electronic or telephonic verification of a unique subject eligibility card or code identifier;

[0206] vii. software verification of a unique subject eligibility card or code identifier;

[0207] viii. electronic fingerprint verification of an eligible subject;

[0208] ix. an activation code;

[0209] x. an electronic dongle; and

[0210] xi. an electronic security key fob, or equivalent.

[0211] A process for dispensing the Modified Risk Product which may include;

[0212] i. Directly providing a dispensing modified risk device and/or a modified risk tobacco/nicotine product

[0213] ii. Registration in a REMS program

[0214] 3. A User Purchasing Verification Algorithm (FIG. 4); which may include;

[0215] A method for verifying that a qualified subject may purchase a modified risk Product from an authorized distributor, which may include one or more of the following:

[0216] i. evidence of meeting a minimum age requirement;

[0217] ii. evidence of a previously failed nicotine replacement therapy;

[0218] iii. evidence of at least one failed attempt by the patient to quit using such tobacco product;

[0219] iv. collecting samples and measuring nicotine levels in blood, expelled breath, saliva, hair, or urine to verify that the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user;

[0220] v. a prescription from a physician or accredited healthcare provider;

[0221] vi. electronic or telephonic verification of a unique subject eligibility card or code identifier;

[0222] vii. software verification of a unique subject eligibility card or code identifier;

[0223] viii. electronic fingerprint verification of an eligible subject;

[0224] ix. an activation code;

[0225] x. an electronic dongle; and

[0226] xi. an electronic security key fob, or equivalent.

[0227] 4. A Product User Verification (FIG. 5): which may include;

[0228] A method or process for verifying a subject is authorized to use a Modified Risk Product before a product will be activated or function; which may include one or more of the following:

[0229] i. software verification;

[0230] ii. card or code identifier;

[0231] iii. electronic fingerprint verification of an eligible subject;

[0232] iv. lip print verification of an eligible subject;

[0233] v. a special article of clothing;

[0234] vi. an activation code;

[0235] vii. an electronic ring;

[0236] viii. an electronic dongle; and

[0237] ix. an electronic security key fob, or equivalent.

[0238] 5. A User Verification and Mitigation Tracking System (FIG. 6): which may include;

[0239] A Modified Risk System (100) comprising: one or more of the following:

[0240] i. an electronic cigarette; (1)

[0241] ii. an electronic pipe;

[0242] iii. an electronic cigar;

[0243] iv. an electronic water pipe; or

[0244] v. an electronic vaporizer (1), and also comprising one or more of the following:

[0245] 1. a battery, an atomizer or cartomizer, electronic circuitry, a memory storage device for tracking component usage activity, a means of memory transfer, and a charging circuit;

[0246] vi. a charger base station (2) comprising one or more of the following:

[0247] 1. a memory storage device; a means for receiving data and transmitting said data from said modified risk product memory storage device to a third party;

[0248] vii. an identification recognition system;

[0249] viii. activation software for recognition of a specific device keyed to said charger base and capable of interfacing with an external device, wherein said external device comprises one or more of the following:

[0250] ix. a smart phone (3); a computer; an electronic fob (4); an electronic dongle; a ring; an article of clothing; and a wireless communication device (5).

[0251] 6. A REMS Compliance Program (FIG. 7A): which may include;

[0252] A method of testing to confirm that a subject is complying with (and not misusing or abusing) the Modified Risk Product.

[0253] i. Testing strips or other methods of compliance verification (FIG. 7B).

[0254] Provided herein is a method of protecting public health comprising: increasing the likelihood that a first subject or a second subject will stop using a tobacco product or tobacco alternative product by providing a modified risk product such as a device for administration of nicotine in a vapor form to a first subject addicted to the tobacco product wherein the first subject has previously failed a nicotine replacement therapy. It is generally understood that there are numerous recognized therapies intended to reduce the use of tobacco and/or bring about the cessation of addiction to tobacco products and in particular, nicotine. These include; abstinence, nicotine gum, nicotine oral spray, nicotine

inhaler, nicotine nasal spray, nicotine lozenge, nicotine dermal patch, bupropion (which includes 3-chloro-N-tert-butyl-β-ketoamphetamine, a derivative thereof, an analogue thereof, a bupropion metabolite, a pharmaceutically acceptable salts thereof, R,R-hydroxybupropion, S,S-hydroxybupropion, threo-hydrobupropion, erythro-hydrobupropion, 1-(3-chlorophenyl)-2-[(1,1-dimethyl) amino]-1-propanone hydrochloride, 2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol, 1-(3-chlorophenyl)-2-[(1,1-dimethyl-ethanol)amino]-1-propanol and 1-(3-chlorophenyl)-2-[(1,1-dimethyl ethanol)amino]-1-propanone or combinations thereof), varenicline or 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine or a pharmaceutically acceptable salt thereof, varenicline tartrate or 7,8,9, 10-tetrahydro-6, 10-methano-6H-pyrazino [2,3-h] [3] benzazepine, (2i?,3?)-2,3-dihydroxybutanedioate (1:1) or 7,8,9, 10-Tetrahydro-6, 10-methano-6H-pyrazino [2,3-h][3] benzazepine tartrate or a pharmaceutically acceptable salt thereof, or comparable oral nicotine replacement product, or similar medications and oral nicotine replacement products. Varenicline is sold by Pfizer under the brand name CHANTIX®. In many cases, these products or methods fail. The applicant believes that by combining a REMS program with their Modified Risk Product, the user will be more likely to switch to a preferred form of nicotine delivery which has a preferable risk profile, while also minimizing the risk that non-tobacco users will initiate use of the modified risk product.

[0255] In some embodiments, the modified risk product comprises; an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, and/or a tobacco or nicotine product, used in combination with a REMS typically involving one or more of the following components; subject eligibility verification, subject compliance verification to a risk mitigation strategy, and overall validation of the success of said risk evaluation and mitigation strategy.

[0256] Among the methods included in the REMS are methods wherein the product is prescribed, provided, or a subject's eligibility is verified by a physician, a nurse, a pharmacist, or an accredited healthcare provider. FIG. 3A illustrates one embodiment of a method wherein the potential subject may request a prescription for a controlled product from a qualified, accredited healthcare provider, who verifies that the subject is qualified to receive said product, prior to issuing a prescription. A subject may be a current tobacco or nicotine user who may have previously tried and failed a nicotine replacement therapy.

[0257] Alternatively, the product may be regulated as an over the counter (OTC) or retail product, wherein the subject may self-subscribe and acquire the product by personally requesting it from a qualified individual, authorized to dispense said product, upon proof or verification of eligibility to acquire said product, such as proof of a minimum age requirement, etc. FIG. 3B illustrates another embodiment of a method wherein the potential subject may request an FDA designated modified risk tobacco product or a tobacco alternative product which may include a non-combustion or vaporization-based delivery of nicotine or tobacco from a qualified, accredited healthcare provider, or employee of a convenience or retail store, who verifies that the subject is qualified to receive said product. A subject may be a current tobacco or nicotine user who may or may not have previously tried and failed a nicotine replacement therapy. A simple

nicotine test strip may be all that is required for this verification. Alternately, verification may require more complex tests comprising: blood, expelled breath, hair, or urine taken for analysis.

[0258] In some embodiments, the devices and methods of using the modified risk product may be provided by, or subject eligibility verified by, an accredited employee of a convenience or retail store or by an employee of an accredited convenience or retail store.

[0259] In still other situations, the product is prescribed, provided, and/or subject eligibility verified by an internet or wireless based application, service or business. While in still other situations the product may be prescribed, provided, or subject eligibility verified by a call center or phone based application service or business. The use of Skype or other real time phone and internet services makes these verification and prescribing services possible.

[0260] In any of the preceding examples, the prescribers or providers of the modified risk product have been qualified to deliver said modified risk product through a REMS compliance verification program as illustrated in FIG. 2, which is typically administered and controlled by a qualified independent party having full authorization to qualify said providers and/or their employees and to audit their internal systems for recordkeeping. Either the facility employing the prescribers or providers or the individual prescribers or providers themselves may be qualified and audited.

[0261] In some embodiments, the subject eligibility verification comprises providing a prescription from an accredited healthcare provider, verifying a subject's identity, a minimum age for eligibility, or verification of a prior nicotine replacement therapy.

[0262] In other embodiments the subject eligibility verification may comprise having the subject provide an electronic or telephonic verification of a unique subject eligibility card or code identifier, software verification of a unique subject eligibility card or code identifier, electronic fingerprint verification, an activation code, or an electronic dongle, electronic security key fob, or the equivalent.

[0263] In some embodiments, the subject eligibility verification comprises collecting samples and measuring nicotine levels in blood samples, expelled breath samples, saliva samples, hair samples, and in urine samples to verify that the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user.

[0264] In some embodiments, the subject compliance verification comprises collecting and sending samples taken before and after being provided a modified risk product, for analysis to an accredited testing facility, and measuring the difference between samples for nicotine levels in blood, expelled breath, saliva, hair, and in urine.

[0265] In some embodiments, components of the subject compliance verification may be performed by a physician, a nurse, a pharmacist, an accredited healthcare provider, or an employee of a convenience or retail store.

[0266] In some embodiments, the risk evaluation and mitigation strategy (REMS) may incorporate a means of subject compliance verification and/or the subject's eligibility to participate in a REMS program and have a modified risk product prescription. Subject compliance is commonly used in clinical drug studies to verify the concentration levels and patient compliance to protocols, among other clinical study outcome measures. FIG. 7 illustrates one possible configuration for such a REMS program wherein a subject's eligibility

to participate in a program is first verified prior to being given a prescription, and the subject may be tested again at a later date to demonstrate program compliance.

[0267] In other embodiments, the compliance verification or the REMS program validation may comprise measuring maximum plasma concentration (Cmax) of nicotine, compared to a cigarette, the pharmacokinetic profile of the modified risk product to determine the time required after administration of the product for nicotine to reach maximum plasma concentration (Tmax), compared to a cigarette, or alternatively, to determine the rate-of-increase of nicotine delivery or concentration in the plasma of a subject compared to a cigarette.

[0268] In still other embodiments, the compliance verification may comprise measuring relative potential risk of the modified risk product by comparing the nicotine concentration of the modified risk product to other nicotine or tobacco products in the market.

[0269] Some aspects of these methods may require physical tests that must be performed to provide accurate and quantifiable data wherein the subject must present themselves to a qualified individual in order for the test to be completed. In some embodiments, the subject compliance verification or the REMS program validation testing is performed by a physician, a nurse, a pharmacist, a phlebotomist, or an accredited healthcare provider and the samples obtained are sent to a qualified lab for analysis.

[0270] In other embodiments, subject compliance verification is performed by an accredited employee of a convenience or retail store, or an employee of an accredited convenience or retail store. Such compliance tests would comprise verification of subject identity and collection of saliva, hair, urine, or breath samples, which could be forwarded to a qualified lab for analysis.

[0271] Alternatively, subject compliance or the REMS program validation may be measured passively through the use of electronic technology. One such example of this is illustrated in FIG. 6. In this example, a device that is a component of modified risk system, may comprise an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, or an electronic vaporizer for delivering a nicotine-containing vapor, comprising a battery, an atomizer, electronic circuitry, a memory storage device for tracking components of usage activity, a means of memory transfer, and a charging circuit, along with a charger base station comprising a memory storage device, a means for receiving data from said component device memory storage device and then having the ability to transmit said data to a third party which passively monitors the device and indirectly, the subject for compliance based on the transmitted data.

[0272] The component device and the charging base would be configured such that activation software would be required for recognition of the specific device, keyed to said charger base. This software could be embedded and matched to each component set in a modified risk product, and be capable of interfacing with an external device, wherein said external device comprises; a smart phone, computer, electronic fob, electronic dongle and a Bluetooth or wireless communication device, which would need to be within a fixed range for activation and continued use.

[0273] Alternatively, the components could be configured with a programmable code which must be entered periodically for activation. Still further the components could be hard

wired with a timing circuit that requires periodic physical contact between the components for activation.

[0274] In addition, the transmission of collected data could occur over the internet via a hardwired or wireless connection through a base computer device for analysis and validation by an accredited healthcare professional or REMS monitor or administrator.

[0275] Provided herein is a method of protecting public health comprising: increasing the likelihood that a first subject or a second subject will stop using a tobacco product by providing a modified risk product for administration to the first subject addicted to the tobacco product only after at least one failed attempt by the first subject to quit using such tobacco product. These modified risk products comprise an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, and/or a tobacco or nicotine product, used in combination with a risk evaluation and mitigation strategy and may involve subject eligibility verification, subject compliance verification to a risk mitigation strategy and overall validation of the success of said risk evaluation and mitigation strategy.

[0276] The previously failed attempt to quit using a tobacco product commonly comprises abstinence, nicotine gum, nicotine oral spray, nicotine inhaler, nicotine nasal spray, nicotine lozenge, nicotine dermal patch, bupropion (which includes 3-chloro-N-tert-butyl-β-ketoamphetamine, a derivative thereof, an analogue thereof, a bupropion metabolite, a pharmaceutically acceptable salts thereof, R,R-hydroxybupropion, S,S-hydroxybupropion, threo-hydrobupropion, erythro-hydrobupropion, 1-(3-chlorophenyl)-2-[(1,1dimethyl) amino]-1-propanone hydrochloride, 2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol, 1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-propanol and 1-(3-chlorophenyl)-2-[(1,1-dimethyl ethanol) amino]-1-propanone or combinations thereof), varenicline or 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino [2,3-h][3]benzazepine or a pharmaceutically acceptable salt thereof, varenicline tartrate or 7,8,9, 10-tetrahydro-6, 10-methano-6H-pyrazino[2,3-h] [3]benzazepine, (2i?,3?)-2,3-dihydroxybutanedioate (1:1) or 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine tartrate or a pharmaceutically acceptable salt thereof, or comparable oral nicotine replacement product. Varenicline is sold by Pfizer under the brand name CHANTIX®.

[0277] In some embodiments of the method, the product is prescribed, provided, administered, or a subject's eligibility is verified by a physician, a nurse, a pharmacist, or an accredited healthcare provider, as illustrated in FIG. 3.

[0278] In other embodiments, the product, which may be an OTC product, is provided, administered, or subject eligibility verified by an accredited employee of a convenience or retail store. In still other embodiments, the product is provided, administered, or a subject's eligibility is verified by an employee of an accredited convenience or retail store.

[0279] In still other embodiments, the product which may be either a prescription or OTC product, is provided, administered, or a subject's eligibility is verified by an internet or wireless based application, service or business. In still other embodiments of the method the product is provided, administered, or a subject's eligibility is verified by a call center or phone based application service or business, using Skype or other real time phone and internet services.

[0280] In some embodiments, the subject eligibility verification comprises providing a prescription from an accredited

healthcare provider, verifying a subject's identity, a minimum age for eligibility, or verification of a prior nicotine replacement therapy.

[0281] In other embodiments the subject eligibility verification may comprise having the subject provide an electronic or telephonic verification of a unique subject eligibility card or code identifier, software verification of a unique subject eligibility card or code identifier, electronic fingerprint verification, an activation code, or an electronic dongle, electronic security key fob, or the equivalent.

[0282] In some embodiments, the subject eligibility verification comprises collecting samples and measuring nicotine levels in blood samples, expelled breath samples, saliva samples, hair samples, and in urine samples to verify that the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user.

[0283] In some embodiments, the risk evaluation and mitigation strategy incorporates a means of subject compliance verification.

[0284] In some embodiments, the subject compliance verification comprises collecting and sending samples taken before and after being provided a modified risk product, for analysis to an accredited testing facility, and measuring the difference between samples for nicotine levels in blood, expelled breath, saliva, hair, and in urine.

[0285] In some embodiments, components of the subject compliance verification may be performed by a physician, a nurse, a pharmacist, an accredited healthcare provider, or an employee of a convenience or retail store.

[0286] In other embodiments, the compliance verification may comprise measuring maximum plasma concentration (Cmax) of nicotine, compared to a cigarette, the pharmacokinetic profile of the modified risk product to determine the time required after administration of the product for nicotine to reach maximum plasma concentration (Tmax), compared to a cigarette, or alternatively, to determine the rate-of-increase of nicotine delivery or concentration in the plasma of a subject compared to a cigarette.

[0287] In still other embodiments, the compliance verification may comprise measuring relative potential risk of the modified risk product by comparing the nicotine concentration of the modified risk product to other nicotine products in the market. Analysis of lab results and statistical analysis of subject outcomes would be performed to provide regular reports to the manufacture(s) and the FDA so that periodic evaluation of reports of patient responses to treatment, medication/devices, and revisions to medication guides, may be reassessed.

[0288] As mentioned previously, some aspects of these methods may require physical tests that must be performed to verify subject compliance or REMS validation wherein the subject must present themselves to a qualified individual in order for the test to be completed. In some embodiments, the subject compliance verification or REMS validation testing is performed by a physician, a nurse, a pharmacist, a phlebotomist, or an accredited healthcare provider.

[0289] In other embodiments, subject compliance verification is performed by an accredited employee of a convenience or retail store, or an employee of an accredited convenience or retail store.

[0290] Provided herein is a method of protecting public health comprising increasing the likelihood that a first subject or a second subject will stop using a tobacco product by providing a modified risk product for administration to the

first subject addicted to the tobacco product, only after the modified risk product is prescribed to the first subject.

[0291] In some embodiments, the modified risk product comprises; an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, and/or a tobacco or nicotine product, used in combination with a risk evaluation and mitigation strategy and may involve subject eligibility verification, subject compliance verification to a risk mitigation strategy and overall validation of the success of said risk evaluation and mitigation strategy.

[0292] In some embodiments, the product is prescribed by a physician, a nurse, a pharmacist, or an accredited healthcare provider.

[0293] In some embodiments, the subject eligibility verification comprises providing a prescription from an accredited healthcare provider, verifying a subject's identity, a minimum age for eligibility, or verification of a prior nicotine replacement therapy.

[0294] In other embodiments the subject eligibility verification may comprise having the subject provide an electronic or telephonic verification of a unique subject eligibility card or code identifier, software verification of a unique subject eligibility card or code identifier, electronic fingerprint verification, an activation code, or an electronic dongle, electronic security key fob, or the equivalent.

[0295] In some embodiments, the subject eligibility verification comprises collecting samples and measuring nicotine levels in blood samples, expelled breath samples, saliva samples, hair samples, and in urine samples to verify that the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user.

[0296] In some embodiments, the risk evaluation and mitigation strategy incorporates a means of subject compliance verification.

[0297] In some embodiments, the subject compliance verification comprises collecting and sending samples taken before and after being provided a modified risk product, for analysis to an accredited testing facility, and measuring the difference between samples for nicotine levels in blood, expelled breath, saliva, hair, and in urine.

[0298] In some embodiments, components of the subject compliance verification may be performed by a physician, a nurse, a pharmacist, an accredited healthcare provider, or an employee of a convenience or retail store.

[0299] In other embodiments, the compliance verification may comprise measuring maximum plasma concentration (C<sub>max</sub>) of nicotine, compared to a cigarette, the pharmacokinetic profile of the modified risk product to determine the time required after administration of the product for nicotine to reach maximum plasma concentration (T<sub>max</sub>), compared to a cigarette, or alternatively, to determine the rate-of-increase of nicotine delivery or concentration in the plasma of a subject compared to a cigarette.

[0300] In still other embodiments, the compliance verification may comprise measuring relative potential risk of the modified risk product by comparing the nicotine concentration of the modified risk product to other nicotine products in the market. Analysis of lab results and statistical analysis of subject outcomes would be performed to provide regular reports to the manufacture(s) and the FDA so that periodic evaluation of reports of patient responses to treatment, medication/devices, and revisions to medication guides, may be reassessed.

[0301] As mentioned previously, some aspects of these methods may require physical tests that must be performed to verify subject compliance or REMS validation wherein the subject must present themself to a qualified individual in order for the test to be completed. In some embodiments, the subject compliance verification or REMS validation testing is performed by a physician, a nurse, a pharmacist, a phlebotomist, or an accredited healthcare provider.

[0302] In other embodiments, subject compliance verification is performed by an employee of a convenience or retail store.

[0303] Provided herein is a method of protecting public health comprising decreasing the likelihood that a second subject not using a tobacco product will start using the tobacco product by providing a modified risk product for administration to the first subject addicted to the tobacco product wherein the first subject has previously failed nicotine replacement therapy.

[0304] In some embodiments, the modified risk product comprises; an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, and/or a tobacco or nicotine product, used in combination with a risk evaluation and mitigation strategy and may involve subject eligibility verification, subject compliance verification to a risk mitigation strategy and overall validation of the success of said risk evaluation and mitigation strategy. In some embodiments, the previously failed attempt to quit using said tobacco product comprises abstinence, nicotine gum, nicotine oral spray, nicotine inhaler, nicotine nasal spray, nicotine lozenge, nicotine dermal patch, bupropion (which includes 3-chloro-N-tert-butyl-β-ketoamphetamine, a derivative thereof, an analogue thereof, a bupropion metabolite, a pharmaceutically acceptable salts thereof, R,R-hydroxybupropion, S,S-hydroxybupropion, threo-hydrobupropion, erythro-hydrobupropion, 1-(3-chlorophenyl)-2-[(1,1dimethyl) amino]-1-propanone hydrochloride, 2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol, 1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-propanol and 1-(3-chlorophenyl)-2-[(1,1-dimethyl ethanol)amino]-1-propanone or combinations thereof), varenicline or 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine or a pharmaceutically acceptable salt thereof, varenicline tartrate or 7,8,9, 10-tetrahydro-6,10-methano-6H-pyrazino [2,3-h] [3] benzazepine, (2i?,3?)2,3-dihydroxybutanedioate (1:1) or 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino [2,3-h][3]benzazepine tartrate or a pharmaceutically acceptable salt thereof, or comparable oral nicotine replacement product. Varenicline is sold by Pfizer under the brand name CHANTIX®.

[0305] In some embodiments, the product is prescribed by a physician, a nurse, a pharmacist, or an accredited healthcare provider.

[0306] In some embodiments, the subject eligibility verification comprises providing a prescription from an accredited healthcare provider, verifying a subject's identity, a minimum age for eligibility, and/or verification of a previously failed prior nicotine replacement therapy.

[0307] In other embodiments the subject eligibility verification may comprise having the subject provide an electronic or telephonic verification of a unique subject eligibility card or code identifier, software verification of a unique subject eligibility card or code identifier, electronic fingerprint verification, an activation code, or an electronic dongle, electronic security key fob, or the equivalent.

[0308] In some embodiments, the subject eligibility verification comprises collecting samples and measuring nicotine levels in blood samples, expelled breath samples, saliva samples, hair samples, and in urine samples to verify that the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user.

[0309] One such mitigation strategy is illustrated in FIG. 4. As illustrated herein, the subject attempting to purchase or acquire a controlled modified risk product would provide some form of qualified proof that verifies they are qualified to obtain said Modified Risk product and participate in the REMS. This purchase verification requirement would typically comprises, a prescription for a controlled substance in addition to a formal verification of subject identity which may comprise a fingerprint, facial recognition, retinal scan, or other biometric identification. Alternatively the identification and verification may comprise having the subject providing a code, a dongle, an electronic FOB, or web registration, to name but a few methods.

[0310] In some embodiments, the product is provided or a subject's eligibility is verified by a physician, a nurse, a pharmacist, an accredited healthcare provider, an accredited employee of a convenience or retail store, or an employee of an accredited convenience or retail store.

[0311] In some embodiments, the product is prescribed, provided, or subject eligibility verified by an internet or wireless based application, service or business, or by a call center or phone based application service or business. The use of Skype or other real time phone and internet services makes these verification and prescribing services possible.

[0312] In some embodiments, the subject compliance verification comprises collecting and sending samples for analysis, taken before and after being provided a modified risk product, and measuring the difference between samples for nicotine levels in blood, expelled breath, saliva, hair, and in urine.

[0313] In some embodiments, components of the subject compliance verification may be performed by a physician, a nurse, a pharmacist, an accredited healthcare provider, or an employee of a convenience or retail store.

[0314] In other embodiments, the compliance verification may comprise measuring maximum plasma concentration (C<sub>max</sub>) of nicotine, compared to a cigarette, the pharmacokinetic profile of the modified risk product to determine the time required after administration of the product for nicotine to reach maximum plasma concentration (T<sub>max</sub>), compared to a cigarette, or alternatively, to determine the rate-of-increase of nicotine delivery or concentration in the plasma of a subject compared to a cigarette.

[0315] In still other embodiments, the compliance verification may comprise measuring relative potential risk of the modified risk product by comparing the nicotine concentration of the modified risk product to other nicotine products in the market. Analysis of lab results and statistical analysis of subject outcomes would be performed to provide regular reports to the manufacture(s) and the FDA so that periodic evaluation of reports of patient responses to treatment, medication/devices, and revisions to medication guides, may be reassessed.

[0316] As mentioned previously, some aspects of these methods may require physical tests that must be performed to verify subject compliance or REMS validation wherein the subject must present themselves to a qualified individual in order for the test to be completed. In some embodiments, the

subject compliance verification or REMS validation testing is performed by a physician, a nurse, a pharmacist, a phlebotomist, or an accredited healthcare provider.

[0317] In other embodiments, subject compliance verification is performed by an accredited employee of a convenience or retail store, or an employee of an accredited convenience or retail store.

[0318] Provided herein is a method of protecting public health comprising decreasing the likelihood that a second subject not using a tobacco product will start using the tobacco product by providing a modified risk product for administration to the first subject addicted to the tobacco product only after at least one failed attempt by the first subject to quit using such tobacco product.

[0319] In some embodiments, the modified risk product comprises; an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, and/or a tobacco or nicotine product, used in combination with a risk evaluation and mitigation strategy and may involve subject eligibility verification, and overall validation of the success of said risk evaluation and mitigation strategy.

[0320] In some embodiments, the previously failed attempt to quit using said tobacco product comprises abstinence, nicotine gum, nicotine oral spray, nicotine inhaler, nicotine nasal spray, nicotine lozenge, nicotine dermal patch, buproprion (which includes 3-chloro-N-tert-butyl- $\beta$ -ketoamphetamine, a derivative thereof, an analogue thereof, a buproprion metabolite, a pharmaceutically acceptable salts thereof, R,R-hydroxybuproprion, S,S-hydroxybuproprion, threo-hydrobuproprion, erythro-hydrobuproprion, 1-(3-chlorophenyl)-2-[(1,1dimethyl) amino]-1-propanone hydrochloride, 2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol, 1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-propanol and 1-(3-chlorophenyl)-2-[(1,1-dimethyl ethanol) amino]-1-propanone or combinations thereof), varenicline or 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino [2,3-h][3] benzazepine or a pharmaceutically acceptable salt thereof, varenicline tartrate or 7,8,9, 10-tetrahydro-6, 10-methano-6H-pyrazino[2,3-h] [3] benzazepine, (2i?3?)-2,3-dihydroxybutanedioate (1:1) or 7,8,9,10-Tetrahydro-6,10-methano-6H<sup>-</sup>-pyrazino[2,3-h][3]benzazepine tartrate or a pharmaceutically acceptable salt thereof, or comparable oral nicotine replacement product. Varenicline is sold by Pfizer under the brand name CHANTIX®.

[0321] In some embodiments, the product is prescribed, provided, or subject eligibility verified by a physician, a nurse, a pharmacist, an accredited healthcare provider, an accredited employee of a convenience or retail store, or by an employee of an accredited convenience or retail store.

[0322] In some embodiments, the product is prescribed, provided, or subject eligibility verified by an internet or wireless based application, service or business, or by a call center or phone based application service or business. The use of Skype or other real time phone and internet services makes these verification and prescribing services possible.

[0323] In other embodiments, the product, which may be an OTC product, is provided, administered, or a subject's eligibility is verified by an accredited employee of a convenience or retail store, or by an employee of an accredited convenience or retail store.

[0324] In still other embodiments, the product which may be either a prescription or OTC product, is provided, administered, or a subject's eligibility is verified by an internet or wireless based application, service or business, or by a call

center or phone based application service or business, using Skype or other real time phone and internet services.

[0325] In some embodiments, the subject eligibility verification comprises providing a prescription from an accredited healthcare provider, verifying a subject's identity, a minimum age for eligibility, or verification of a prior nicotine replacement therapy.

[0326] In other embodiments the subject eligibility verification may comprise having the subject provide an electronic or telephonic verification of a unique subject eligibility card or code identifier, software verification of a unique subject eligibility card or code identifier, electronic fingerprint verification, an activation code, or an electronic dongle, electronic security key fob, or the equivalent.

[0327] In some embodiments, the subject eligibility verification comprises collecting samples and measuring nicotine levels in blood samples, expelled breath samples, saliva samples, hair samples, and in urine samples to verify that the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user. If a second subject has not been using a tobacco product or alternative tobacco product comprising nicotine, such samples would be negative and disqualify said second subject from obtaining a modified risk under this criteria.

[0328] As previously described, another method of decreasing the likelihood that a second subject not using a tobacco product, will start using the tobacco product after a first addicted subject is prescribed a modified use product after a previously failed attempt to quit, could comprise the passive use of electronic technology. One such example of this is illustrated in FIG. 5. In this example, a device that is a component of a modified risk system, may comprise an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, and/or a tobacco or nicotine product, for delivering a nicotine-containing vapor, comprising a battery, an atomizer, electronic circuitry, a memory storage device for tracking various aspects of component usage activity, a means of memory transfer, and a charging circuit, along with a charger base station comprising a memory storage device, a means for receiving data from said component device memory storage device and comprising the means to transmit said data to a third party which passively monitors the device and indirectly, the subject, for compliance to the REMS based on the transmitted data.

[0329] The component device would be configured such that activation software acting as a user identification system would be required for recognition of the specific device, keyed to said charger base. This software could be embedded and matched to each component set in a modified risk product, and be capable of interfacing with an external device, wherein said external device comprises; a smart phone, computer, electronic fob, electronic dongle, a special ring, and/or a Bluetooth or wireless device, which would need to be within a fixed range for activation and continued use.

[0330] Alternatively, the device could be configured to have a fingerprint or lip print reader on the body or mouth-piece that is matched to the first subject.

[0331] Alternatively a special ring or wrist band worn on the hand of the first subject or other article of jewelry could provide a user identification system and be configured to mate with the device, wherein the device will only activate if it is in the immediate proximity of the subject's hand.

[0332] In any of the prior examples, the devices could be configured with proximity sensors requiring the subject to be

within a fixed distance such as 20 feet, or ten feet, or more preferably within five feet or less.

[0333] Alternatively, the components could be configured with a programmable code which must be entered periodically for activation. Still further the components could be hard wired with a timing circuit that requires a minimal period of time between uses for activation.

[0334] In addition, the device could be configured as shown in FIG. 6 with a base having hardware and software for the transmission of collected data as previously described. In this example, the modified risk product configuration could be used for user verification, user compliance, or even validation of a REMS for a modified risk product.

[0335] Provided herein is a method of protecting public health comprising increasing the likelihood that a first subject or a second subject will stop using a tobacco product by providing a modified risk product for administration to the first subject addicted to the tobacco product, only after the modified risk product is prescribed to the first subject.

[0336] In some embodiments, the modified risk product comprises; an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, and/or a tobacco or nicotine product, used in combination with a risk evaluation and mitigation strategy and may involve subject eligibility verification, subject compliance verification to a risk mitigation strategy and overall validation of the success of said risk evaluation and mitigation strategy.

[0337] In some embodiments, the product is prescribed by a physician, a nurse, a pharmacist, or an accredited healthcare provider.

[0338] In some embodiments, the subject eligibility verification comprises providing a prescription from an accredited healthcare provider, verifying a subject's identity, a minimum age for eligibility, or verification of a prior nicotine replacement therapy.

[0339] In other embodiments the subject eligibility verification may comprise having the subject provide an electronic or telephonic verification of a unique subject eligibility card or code identifier, software verification of a unique subject eligibility card or code identifier, electronic fingerprint verification, an activation code, or an electronic dongle, electronic security key fob, or the equivalent.

[0340] In some embodiments, the subject eligibility verification comprises collecting samples and measuring nicotine levels in blood samples, expelled breath samples, saliva samples, hair samples, and in urine samples to verify that the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user.

[0341] In some embodiments, the product is administered by physician, a nurse, a pharmacist, an accredited healthcare provider, or an employee of a convenience or retail store.

[0342] In some embodiments, the product is administered by an internet or wireless based application, service or business, or by a call center or phone based application service or business. The use of Skype or other real time phone and internet services makes these verification and prescribing services possible.

[0343] In some embodiments, the risk evaluation and mitigation strategy incorporates a means of subject compliance verification.

[0344] In some embodiments, the subject compliance verification comprises collecting and sending samples for analysis, taken before and after being provided a modified risk

product, and measuring the difference between samples for nicotine levels in blood, expelled breath, saliva, hair, and in urine.

[0345] In some embodiments, components of the subject compliance verification may be performed by a physician, a nurse, a pharmacist, an accredited healthcare provider, or an employee of a convenience or retail store.

[0346] In other embodiments, the compliance verification may comprise measuring maximum plasma concentration (C<sub>max</sub>) of nicotine, compared to a cigarette, the pharmacokinetic profile of the modified risk product to determine the time required after administration of the product for nicotine to reach maximum plasma concentration (T<sub>max</sub>), compared to a cigarette, or alternatively, to determine the rate-of-increase of nicotine delivery or concentration in the plasma of a subject compared to a cigarette.

[0347] In still other embodiments, the compliance verification may comprise measuring relative potential risk of the modified risk product by comparing the nicotine concentration of the modified risk product to other nicotine products in the market. Analysis of lab results and statistical analysis of subject outcomes would be performed to provide regular reports to the manufacture(s) and the FDA so that periodic evaluation of reports of patient responses to treatment, medication/devices, and revisions to medication guides, may be reassessed.

[0348] As mentioned previously, some aspects of these methods may require physical tests that must be performed to verify subject compliance or REMS validation wherein the subject must present themselves to a qualified individual in order for the test to be completed. In some embodiments, the subject compliance verification or REMS validation testing is performed by a physician, a nurse, a pharmacist, a phlebotomist, or an accredited healthcare provider.

[0349] In other embodiments, subject compliance verification is performed by an accredited employee of a convenience or retail store, or an employee of an accredited convenience or retail store.

[0350] In some embodiments, the risk evaluation and mitigation strategy incorporates a passive means of subject compliance verification.

[0351] As previously described, a device that is a component of a modified risk system, may comprise an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, and/or a tobacco or nicotine product, for delivering a nicotine-containing vapor, comprising a battery, an atomizer, electronic circuitry, a memory storage device for tracking various aspects of component usage activity, a means of memory transfer, and a charging circuit, along with a charger base station comprising a memory storage device, a means for receiving data from said component device memory storage device and comprising the means to transmit said data to a third party which monitors the device and indirectly, the subject, for compliance to the REMS based on the transmitted data.

[0352] The component device would be configured such that activation software acting as a user identification system would be required for recognition of the specific device, keyed to said charger base. This software could be embedded and matched to each component set in a modified risk product, and be capable of interfacing with an external device, wherein said external device comprises; a smart phone, computer, electronic fob, electronic dongle, and a Bluetooth or

wireless device, which would need to be within a fixed range for activation and continued use.

[0353] Alternatively, the device could be configured to have a fingerprint or lip print reader on the body or mouthpiece that is matched to the first subject.

[0354] Alternatively a special ring or wrist band worn on the hand of the first subject or other article of jewelry or clothing could provide a user identification system and be configured to mate with the device, wherein the device will only activate if it is in the immediate proximity of the subject's hand or the subject.

[0355] In any of the prior examples, the devices could be configured with proximity sensors requiring the subject to be within a fixed distance such as 20 feet, or ten feet, or more preferably within five feet or less.

[0356] Alternatively, the components could be configured with a programmable code which must be entered periodically for activation. Still further the components could be hard wired with a timing circuit that requires a minimal period of time between uses for activation.

[0357] In addition, the device could be configured as shown in FIG. 6 with a base having hardware and software for the transmission of collected data as previously described.

[0358] Provided herein is a method of treating a first subject addicted to a tobacco product, the method comprising administering to the first subject who has previously failed nicotine replacement therapy, a modified risk product.

[0359] In some embodiments the modified risk product comprises; an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, and/or a tobacco or nicotine product, used in combination with a risk evaluation and mitigation strategy and may involve subject eligibility verification, subject compliance verification to a risk mitigation strategy and overall validation of the success of said risk evaluation and mitigation strategy.

[0360] In some embodiments the previously failed nicotine replacement therapy comprises abstinence, nicotine gum, nicotine oral spray, nicotine inhaler, nicotine nasal spray, nicotine lozenge, nicotine dermal patch, bupropion (which includes 3-chloro-N-tert-butyl-β-ketoamphetamine, a derivative thereof, an analogue thereof, a bupropion metabolite, a pharmaceutically acceptable salts thereof, R,R-hydroxybupropion, S,S-hydroxybupropion, threo-hydrobupropion, erythro-hydrobupropion, 1-(3-chlorophenyl)-2-[(1,1dimethyl) amino]-1-propanone hydrochloride, 2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol, 1-(3-chlorophenyl)-2-[(1,1-dimethyllethanol)amino]-1-propanol and 1-(3-chlorophenyl)-2-[(1,1-dimethyl ethanol)amino]-1-propanone or combinations thereof), varenicline or 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino [2,3-h][3] benzazepine or a pharmaceutically acceptable salt thereof, varenicline tartrate or 7,8,9, 10-tetrahydro-6, 10-methano-6H-pyrazino[2,3-h] [3] benzazepine, (2i?3/?)2,3-dihydroxybutanediol (1:1) or 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine tartrate or a pharmaceutically acceptable salt thereof, or comparable oral nicotine replacement product. Varenicline is sold by Pfizer under the brand name CHANTIX®.

[0361] In some embodiments, the product is administered by a physician, a nurse, a pharmacist, or an accredited healthcare provider.

[0362] In some embodiments, the product is administered by or an employee of a convenience or retail store.

[0363] In some embodiments, the subject eligibility verification comprises collecting samples and measuring nicotine levels in blood samples, in expelled breath samples, in saliva samples, in hair samples, and in urine samples to verify that the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user.

[0364] In some embodiments, the subject compliance verification comprises collecting and sending samples for analysis, taken before and after being provided a modified risk product, and measuring the difference between samples for nicotine levels in blood, expelled breath, saliva, hair, and in urine.

[0365] In some embodiments, components of the subject compliance verification may be performed by a physician, a nurse, a pharmacist, an accredited healthcare provider, or an employee of a convenience or retail store.

[0366] In some embodiments, the subject compliance verification comprises collecting samples and measuring nicotine levels in blood samples, measuring nicotine levels in expelled breath samples, measuring nicotine levels in saliva samples, measuring nicotine levels in hair samples, and measuring nicotine levels in urine samples.

[0367] In some embodiments, the subject compliance verification is performed by a physician, a nurse, a pharmacist, or an accredited healthcare provider.

[0368] In some embodiments, the subject compliance verification is performed by or an employee of a convenience or retail store.

[0369] Provided herein is a method of treating a first subject addicted to a tobacco product, the method comprising administering to the first subject a modified risk product only after at least one failed attempt by the first subject to quit using such tobacco product.

[0370] In some embodiments the modified risk product comprises; an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, and/or a tobacco or nicotine product, used in combination with a risk evaluation and mitigation strategy and may involve subject eligibility verification, subject compliance verification to a risk mitigation strategy and overall validation of the success of said risk evaluation and mitigation strategy.

[0371] In some embodiments the previously failed nicotine replacement therapy comprises abstinence, nicotine gum, nicotine oral spray, nicotine inhaler, nicotine nasal spray, nicotine lozenge, nicotine dermal patch, bupropion (which includes 3-chloro-N-tert-butyl- $\beta$ -ketoamphetamine, a derivative thereof, an analogue thereof, a bupropion metabolite, a pharmaceutically acceptable salts thereof, R,R-hydroxybupropion, S,S-hydroxybupropion, threo-hydrobupropion, erythro-hydrobupropion, 1-(3-chlorophenyl)-2-[(1,1dimethyl) amino]-1-propanone hydrochloride, 2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol, 1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-propanol and 1-(3-chlorophenyl)-2-[(1,1-dimethyl ethanol)amino]-1-propanone or combinations thereof), varenicline or 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine or a pharmaceutically acceptable salt thereof, varenicline tartrate or 7,8,9, 10-tetrahydro-6, 10-methano-6H-pyrazino[2,3-h][3]benzazepine, (2i?,3?)2,3-dihydroxybutanedioate (1:1) or 7,8,9,10-Tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazepine tartrate or a pharmaceutically acceptable salt thereof, or comparable oral

nicotine replacement product. Varenicline is sold by Pfizer under the brand name CHANTIX®.

[0372] In some embodiments, the product is administered by a physician, a nurse, a pharmacist, or an accredited healthcare provider.

[0373] In some embodiments, the product is administered by an employee of a convenience or retail store.

[0374] In some embodiments, the subject eligibility verification comprises collecting samples and measuring nicotine levels in blood samples, in expelled breath samples, in saliva samples, in hair samples, and in urine samples to verify that the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user.

[0375] In some embodiments, the subject compliance verification comprises collecting and sending samples for analysis, taken before and after being provided a modified risk product, and measuring the difference between samples for nicotine levels in blood, expelled breath, saliva, hair, and in urine.

[0376] In some embodiments, components of the subject compliance verification may be performed by a physician, a nurse, a pharmacist, an accredited healthcare provider, or an employee of a convenience or retail store.

[0377] In some embodiments, the subject compliance verification comprises collecting samples and measuring nicotine levels in blood samples, measuring nicotine levels in expelled breath samples, measuring nicotine levels in saliva samples, measuring nicotine levels in hair samples, and measuring nicotine levels in urine samples.

[0378] In some embodiments, the subject compliance verification is performed by a physician, a nurse, a pharmacist, or an accredited healthcare provider.

[0379] In some embodiments, the subject compliance verification is performed by an employee of a convenience or retail store.

[0380] Provided herein is a method of treating a first subject addicted to a tobacco product, the method comprising administering a modified risk product to the first subject only after the modified risk product is prescribed to the first subject.

[0381] In some embodiments, said modified risk product comprises; an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, and/or a tobacco or nicotine product, used in combination with a risk evaluation and mitigation strategy and may involve subject eligibility verification, subject compliance verification to a risk mitigation strategy and overall validation of the success of said risk evaluation and mitigation strategy.

[0382] In some embodiments, the modified risk product is prescribed and administered by a physician, a nurse, a pharmacist, or an accredited healthcare provider.

[0383] In some embodiments, the product is administered by an accredited employee of a convenience or retail store, or an employee of an accredited convenience or retail store.

[0384] In some embodiments, the product is administered by an internet or wireless based application, service or business.

[0385] In some embodiments, the product is administered by a call center or phone based application service or business.

[0386] In some embodiments, the subject eligibility verification comprises collecting samples and measuring nicotine levels in blood samples, in expelled breath samples, in saliva samples, in hair samples, and in urine samples to verify that

the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user.

[0387] In some embodiments, the subject compliance verification comprises collecting and sending samples for analysis, taken before and after being provided a modified risk product, and measuring the difference between samples for nicotine levels in blood, expelled breath, saliva, hair, and in urine.

[0388] In some embodiments, components of the subject compliance verification may be performed by a physician, a nurse, a pharmacist, an accredited healthcare provider, or an employee of a convenience or retail store.

[0389] In some embodiments, the subject compliance verification comprises collecting samples and measuring nicotine levels in blood samples, measuring nicotine levels in expelled breath samples, measuring nicotine levels in saliva samples, measuring nicotine levels in hair samples, and measuring nicotine levels in urine samples.

[0390] In some embodiments, the subject compliance verification is performed by a physician, a nurse, a pharmacist, or an accredited healthcare provider.

[0391] In some embodiments, the subject compliance verification is performed by an employee of a convenience or retail store.

[0392] Provided herein is a method for increasing the likelihood that the first subject or a second subject will stop using the tobacco product.

[0393] In some embodiments, the subject compliance verification comprises collecting and sending samples for analysis, taken before and after being provided a modified risk product, and measuring the difference between samples for nicotine levels in blood, expelled breath, saliva, hair, and in urine.

[0394] In some embodiments, components of the subject compliance verification may be performed by a physician, a nurse, a pharmacist, an accredited healthcare provider, or an employee of a convenience or retail store.

[0395] In other embodiments, the compliance verification may comprise measuring maximum plasma concentration (C<sub>max</sub>) of nicotine, compared to a cigarette, the pharmacokinetic profile of the modified risk product to determine the time required after administration of the product for nicotine to reach maximum plasma concentration (T<sub>max</sub>), compared to a cigarette, or alternatively, to determine the rate-of-increase of nicotine delivery or concentration in the plasma of a subject compared to a cigarette.

[0396] In still other embodiments, the compliance verification may comprise measuring relative potential risk of the modified risk product by comparing the nicotine concentration of the modified risk product to other nicotine products in the market. Analysis of lab results and statistical analysis of subject outcomes would be performed to provide regular reports to the manufacture(s) and the FDA so that periodic evaluation of reports of patient responses to treatment, medication/devices, and revisions to medication guides, may be reassessed.

[0397] As a result of having performed the compliance verification testing, subjects are more likely to be interested in the outcomes and act on those results, including increasing the likelihood that the first subject or a second subject will stop using the tobacco product.

[0398] Provided herein is a method for decreasing the likelihood that a second subject not using the tobacco product will

start using the tobacco product. FIGS. 4 and 5 are both illustrations of how a second user would be prevented from acquiring and using a modified risk tobacco product, hence, reducing the likelihood of starting to use the tobacco product.

[0399] Provided herein is a method for verifying the at least one prior failed attempt to stop using tobacco products prior to the modified risk product being provided to a first subject.

[0400] Provided herein is a method for verifying that a first subject meets at least one eligibility requirement for use of a modified tobacco risk product, as illustrated by FIGS. 3A & 3B.

[0401] Provided herein is a method for verifying a subject's eligibility requirement comprising: possession of an eligibility card, meeting qualifications for the eligibility card, possessing a valid verification code, possessing a physician-provided eligibility record, possessing a pharmacist-provided eligibility record, passing a pharmacist-provided eligibility evaluation, as illustrated by FIG. 4.

[0402] In some embodiments of a method having an eligibility requirement, the identity verification step comprises at least one of:

[0403] evidence of a minimum age requirement,

[0404] evidence of a previously failed nicotine replacement therapy, and

[0405] evidence of a at least one failed attempt by the patient to quit using such tobacco product,

[0406] electronic or telephonic verification of a unique subject eligibility card or code identifier,

[0407] software verification of a unique subject eligibility card or code identifier,

[0408] electronic fingerprint verification of an eligible subject,

[0409] an activation code, or

[0410] an electronic dongle, electronic security key fob, or equivalent.

[0411] Provided herein is a method for verifying a subject's eligibility requirement wherein the verifying step is performed by a physician, a nurse, a pharmacist, or an accredited healthcare provider.

[0412] In some embodiments, the verifying a subject's eligibility requirement is performed by an accredited employee of a convenience or retail store, or by an employee of an accredited convenience or retail store.

[0413] In some embodiments, the verifying a subject's eligibility requirement is performed by an internet or wireless based application, service or business.

[0414] In some embodiments, the verifying a subject's eligibility requirement is performed by an internet or wireless based application, service or business.

[0415] Provided herein is a method for providing a prescription for a modified risk product, wherein said prescription is provided by a qualified healthcare provider.

[0416] Provided herein is a method of monitoring compliance of a first subject addicted to a tobacco product, and provided with a modified risk product, the method comprising, measuring nicotine levels of a first subject prior to administration of said modified risk product and routine measurement after administration of said modified risk product, and comparing said prior nicotine levels to anticipated nicotine levels of the first subject after administration of said modified risk product.

[0417] In some embodiments the method of monitoring compliance comprises; measuring nicotine levels in blood samples, measuring nicotine levels in expelled breath

samples, measuring nicotine levels in saliva or urine samples, as illustrated in FIG. 7, or measuring nicotine levels in hair samples.

[0418] Provided herein is a method of monitoring compliance of a first subject addicted to a tobacco product, and provided with a modified risk product, the method comprising, measuring nicotine levels consumed by a first subject prior to administration of said modified risk product and routine measurement of nicotine levels consumed after administration of said modified risk product, and comparing said prior nicotine levels to anticipated nicotine levels of the first subject after administration of said modified risk product. Numerous methods can be devised as evidence herein, and further illustrated by one example as shown in FIG. 6.

[0419] In some embodiments, a method of monitoring comprises; using an electronic signature to track the pattern of use of a vaporizer, electronic cigarette, or other modified risk product wherein said product transmits a record of use over a given period of time.

[0420] In some embodiments, a record of use comprises levels of nicotine consumed, times, and dates it was consumed.

[0421] In some embodiments, the record of use is stored to a data storage device and later downloaded for use by a qualified healthcare provider.

[0422] In some embodiments, the record of use is transmitted wirelessly to a data storage device and later downloaded for use by a qualified healthcare provider.

[0423] In some embodiments, the record of use is stored within the device, and later downloaded for use by a qualified healthcare provider.

[0424] Provided herein is a method of monitoring the use of a modified risk product by a first subject addicted to a tobacco product, the method comprising, requiring an identification recognition system be activated before use of a modified risk product can take place.

[0425] In some embodiments, the identification recognition system comprises, a fingerprint scanner, a lip print scanner, face recognition, a retinal scan, a combination code, an activation code, security key fob, or dongle.

[0426] In some embodiments, the identification recognition system comprises an electronic application for a smartphone, laptop, desktop, or tablet computing device, capable of communicating with the modified risk product by a Bluetooth or wireless communication system.

[0427] In some embodiments, the identification recognition system must be within a fixed distance of the modified risk product for product to continue to work.

[0428] In some embodiments, the identification recognition system must be within 20 feet of the modified risk product.

[0429] In some embodiments, the identification recognition system must be within 10 feet of the modified risk product.

[0430] In some embodiments, the identification recognition system must be within 5 feet of the modified risk product.

[0431] Provided herein is a method of risk mitigation wherein the potential risk of misuse or abuse of a modified risk product may be present and require a distinct form of compliance monitoring.

[0432] For example, an addicted subject may continue to use the first tobacco product after being provided the modified

risk product, thus increasing the potential risk for one or more tobacco related diseases or exposure to one or more harmful substances.

[0433] In some embodiments, monitoring for misuse or abuse of a modified risk product comprises measuring nicotine levels consumed by a first subject prior to administration of said modified risk product and routine measurement of nicotine levels consumed after administration of said modified risk product, and comparing said prior nicotine levels to anticipated nicotine levels of the first subject after administration of said modified risk product.

[0434] For example, if an investigator suspected that the subject was continuing to use cigarettes after receiving a modified risk product, the results of additional nicotine in the subject's system would be a relatively simple calculation. An example of this calculation could be: [Nicotine or cotinine from cigarettes]=[amount measured in blood or saliva]−[amount reported as dispensed by modified risk device]. It is understood that a similar calculation could be derived from any comparable nicotine/cotinine test regardless of the testing method, provided testing methods were consistent and/or interchangeable.

[0435] In some embodiments, multiple compliance verification and tracking systems could be combined and randomly or non-randomly applied as part of a REMS program. For example, results of a subject's nicotine level testing could be compared to prior results (FIG. 7), in addition to remotely monitoring transmitted usage patterns of the modified risk product (FIG. 6). Upon comparison, a skilled health professional could determine if abuse or misuse is potentially occurring.

[0436] Provided herein is a method of protecting the public health comprising increasing the likelihood that a first subject or a second subject will stop using a tobacco product by providing a modified risk product for administration to the first subject addicted to the tobacco product wherein the modified risk product provides a faster onset of nicotine delivery, or a higher peak level of nicotine delivery.

[0437] Provided herein is a method of risk mitigation wherein the potential risk of misuse or abuse of a modified risk product is ranked or stratified in comparison to other tobacco products.

[0438] In some embodiments, the relative potential risk of the modified risk product is determined by comparing the pharmacokinetic profile of the modified risk product to nicotine.

[0439] In some embodiments the pharmacokinetic profile of the modified risk product is determined by the maximum plasma concentration (Cmax) of nicotine, compared to a cigarette.

[0440] In some embodiments the pharmacokinetic profile of the modified risk product is determined by the time after administration of the product for nicotine to reach maximum plasma concentration (Tmax), compared to a cigarette.

[0441] In some embodiments the pharmacokinetic profile of the modified risk product is determined by the rate-of-increase of nicotine delivery or concentration in the plasma of a subject compared to a cigarette.

[0442] In some embodiments, the relative potential risk of the modified risk product is determined by comparing the nicotine concentration of the modified risk product other nicotine products in the market.

[0443] In some embodiments, the relative potential risk of the modified risk product is ranked by ease of access associated with the prescriber/administrator.

[0444] In some embodiments, the relative potential risk of the modified risk product is ranked by ease of access through various distribution channels.

[0445] In some embodiments the modified risk product comprises vaporizing tobacco leaves or finely chopped tobacco below their pyrolytic temperature.

[0446] In some embodiments the modified risk product comprises heating tobacco leaves or finely chopped tobacco below their pyrolytic temperature.

[0447] In some embodiments the modified risk product comprises vaporization of a nicotine salt.

[0448] In some embodiments the modified risk product comprises heating of a nicotine salt below its pyrolytic temperature.

[0449] Provided herein is a method of validating the effectiveness of a modified risk product used with a Risk Evaluation and Mitigation Strategy comprising: collecting and sending a subject's samples taken before and after being provided a modified risk product, for analysis to an accredited testing facility, measuring the difference between samples for nicotine levels in blood, expelled breath, saliva, hair, and/or urine, and performing an appropriate analysis to determine if the modified risk product met the goals of the Risk Evaluation and Mitigation Strategy.

[0450] In some embodiments, components of the validation process may be performed by a physician, a nurse, a pharmacist, an accredited healthcare provider, or an employee of a convenience or retail store or an accredited testing facility.

[0451] Provided herein is a method of protecting the public health wherein the provider of a modified risk product is subject to a compliance verification system.

[0452] In some embodiments, the provider verification is performed by an independent auditor.

[0453] Provided herein is a system for verification, tracking, and reporting use of a modified risk product comprising: an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, and a tobacco or nicotine product, comprising a battery, an atomizer, electronic circuitry, a memory storage device for tracking components of usage activity, a means of memory transfer, and a charging circuit, a charger base station comprising a memory storage device, a means for receiving data from said modified risk product memory storage device and transmitting said data to a third party, activation software for recognition of a specific device, keyed to said charger base, capable of interfacing with an external device, wherein said external device comprises; a smart phone, computer, electronic fob, electronic dongle, and a Bluetooth or wireless device.

[0454] In some embodiments, the system is used in combination with a risk evaluation and mitigation strategy.

[0455] In some embodiments, the system comprises activation means, for recognition and verification of a subject to establish user eligibility prior to use.

[0456] In some embodiments, the system comprises activation means, for recognition and verification of a subject to establish user eligibility prior to use.

[0457] In some embodiments, the system is used to verify subject compliance for use of a modified risk product. In some embodiments the system comprises a means for vali-

dating overall success of the risk mitigation product when used with the risk evaluation and mitigation strategies

[0458] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

1-10. (canceled)

11. A method of protecting public health comprising increasing the likelihood that a first subject or a second subject will stop using a first tobacco or tobacco alternative product by providing a modified risk product for administration to the first subject addicted to the first tobacco product only after at least one failed attempt by the first subject to quit using said first tobacco product.

12. The method of claim 11, wherein said modified risk product comprises:

an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, or other vaporization device, and  
a second tobacco or nicotine product,  
used in combination with a risk evaluation and mitigation strategy.

13. The method of claim 11, wherein said previously failed at least one attempt to quit using said first tobacco product comprises, abstinence, nicotine gum, nicotine oral spray, nicotine inhaler, nicotine nasal spray, nicotine lozenge, nicotine dermal patch, bupropion, varenicline, or a comparable oral nicotine replacement product.

14. The method of claim 12, wherein said risk evaluation and mitigation strategy comprises subject identification and eligibility verification wherein the first subject or second subject meets at least one eligibility verification requirement for receiving said modified risk product.

15. The method of claim 14, wherein the at least one eligibility verification requirement comprises one or more of the following:

evidence of meeting a minimum age requirement;  
evidence of a previously failed nicotine replacement therapy;  
evidence of at least one failed attempt by the patient to quit using such tobacco product;  
collecting samples and measuring nicotine levels in blood, expelled breath, saliva, hair, or urine to verify that the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user;  
measuring saliva or blood levels with a test strip for nicotine or cotinine presence in a subject's system;  
a prescription from a physician or accredited healthcare provider;  
electronic or telephonic verification of a unique subject eligibility card or code identifier;  
software verification of a unique subject eligibility card or code identifier;  
electronic fingerprint verification of an eligible subject;  
an activation code;

an electronic dongle; and  
an electronic security key fob, or equivalent.

**16.** The method of claim **14**, comprising a method wherein the first subject's or second subject's eligibility is verified by a physician, a nurse, a pharmacist, an accredited healthcare provider, an employee of a convenience or retail store, an internet or wireless based application, service or business, or a call center or phone based application, service or business.

**17.** The method of claim **11**, wherein said modified risk product is provided to said first subject or second subject by a physician, a nurse, a pharmacist, an accredited healthcare provider, an accredited employee of a convenience or retail store, an employee of a convenience or retail store, an internet or wireless based application, service or business, or a call center or phone based application, service or business.

**18-20.** (canceled)

**21.** A method of protecting public health comprising increasing the likelihood that a first subject or a second subject will stop using a first tobacco or tobacco alternative product by providing a modified risk product for administration to the first subject addicted to the first tobacco product only after the modified risk product is prescribed to the first subject.

**22.** The method of claim **21**, wherein said modified risk product comprises:

an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, or other vaporization device, and  
a second tobacco or nicotine product,  
used in combination with a risk evaluation and mitigation strategy.

**23.** The method of claim **22**, wherein said risk evaluation and mitigation strategy comprises subject identification and eligibility verification wherein said first subject meets at least one eligibility verification requirement for receiving said modified risk product.

**24.** The method of claim **23**, wherein said at least one eligibility verification requirement comprises one or more of the following:

evidence of meeting a minimum age requirement;  
evidence of a previously failed nicotine replacement therapy;  
evidence of a at least one failed attempt by the patient to quit using such tobacco product;  
collecting samples and measuring nicotine levels in blood, expelled breath, saliva, hair, or urine to verify that the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user;  
measuring saliva or blood levels with a test strip for nicotine or cotinine presence in a subject's system;  
a prescription from a physician or accredited healthcare provider;  
electronic or telephonic verification of a unique subject eligibility card or code identifier;  
software verification of a unique subject eligibility card or code identifier;  
electronic fingerprint verification of an eligible subject;  
an activation code;  
an electronic dongle; and  
an electronic security key fob, or equivalent.

**25.** The method of claim **23**, comprising a method wherein the first subject's eligibility is verified by a physician, a nurse, a pharmacist, an accredited healthcare provider, an employee

of a convenience or retail store, an internet or wireless based application, service or business, or a call center or phone based application, service or business.

**26.** The method of claim **21**, wherein said modified risk product is prescribed by a physician, a nurse, a pharmacist, or an accredited healthcare provider.

**27.** The method of claim **22**, wherein said risk evaluation and mitigation strategy incorporates subject compliance verification.

**28-39.** (canceled)

**40.** A method of protecting public health comprising decreasing the likelihood that a second subject not using any tobacco or tobacco alternative product will start using a first tobacco product by providing a modified risk product for administration to the first subject addicted to the first tobacco product only after at least one failed attempt by the first subject to quit using said first tobacco product.

**41.** The method of claim **40**, wherein said modified risk product comprises:

an electronic cigarette, an electronic pipe, an electronic cigar, an electronic water pipe, an electronic vaporizer, or other vaporization device, and  
a second tobacco or nicotine product,  
used in combination with a risk evaluation and mitigation strategy.

**42.** The method of claim **40** wherein said at least one previously failed attempt to quit using said tobacco product comprises: abstinence, nicotine gum, nicotine oral spray, nicotine inhaler, nicotine nasal spray, nicotine lozenge, nicotine dermal patch, bupropion, varenicline, or comparable oral nicotine replacement product.

**43.** The method of claim **41**, wherein said risk evaluation and mitigation strategy comprises subject identification and eligibility verification wherein said first subject meets at least one eligibility verification requirement for receiving said modified risk product.

**44.** The method of claim **43**, wherein said at least one eligibility verification requirement comprises one or more of the following:

evidence of meeting a minimum age requirement;  
evidence of a previously failed nicotine replacement therapy;  
evidence of a at least one failed attempt by the patient to quit using such tobacco product;  
collecting samples and measuring nicotine levels in blood, expelled breath, saliva, hair, or urine to verify that the subject's nicotine or nicotine by-product levels are above or consistent with levels expected for a tobacco or nicotine user;  
measuring saliva or blood levels with a test strip for nicotine or cotinine presence in a subject's system;  
a prescription from a physician or accredited healthcare provider;  
electronic or telephonic verification of a unique subject eligibility card or code identifier;  
software verification of a unique subject eligibility card or code identifier;  
electronic fingerprint verification of an eligible subject;  
an activation code;  
an electronic dongle; and  
an electronic security key fob, or equivalent.

**45-46.** (canceled)

**47.** The method of claim **41**, wherein said risk evaluation and mitigation strategy incorporates subject compliance verification.

**48-122.** (canceled)

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