

Foundation for a Smoke-Free World

Barriers to Innovation – Final Presentation

14 December, 2018



Our study was designed to start exploring the barriers to greater innovation in smoking cessation, their underlying causes, and identifying potential solutions

Our previous study found a very low level of innovation in smoking cessation

- ▶ In our landscape analysis project we found that the currently available smoking cessation solutions are not sufficiently effective and there is a lack of innovation in developing better smoking cessation solutions
- ▶ This was a surprising finding, given the harm caused by smoking, the large number of active smokers worldwide, and the low efficacy of smoking cessation solutions available today
- ▶ This study was designed to start to explore the barriers to innovation and understand the causes

A wide range of factors are hindering innovation, chiefly a set of unattractive market features, combined with the poorly understood behavioural element in smoking habits and cessation

1. Low perceived commercial attractiveness
 - ▶ Desired pricing scenarios are difficult to achieve as smoking cessation is not a priority public health concern in many markets
 - ▶ Healthcare system differences creates fragmented market environment requiring different business models and approaches for each market
 - ▶ Absence of a successful venture example reinforces investor's lack of interest in smoking cessation
2. Scientific feasibility challenges
 - ▶ Poor understanding of neurophysiology of nicotine addiction and behavioural aspect of smokers
 - ▶ Lack of robust *in vitro* and *in vivo* models for early stage testing
3. Regulatory challenges
 - ▶ High development cost for low expected/predicted returns
 - ▶ Current regulatory requirements for data from pilot and pivot trials are described as stringent and impractical for digital / mHealth solutions

The study pinpoints some actionable areas for improvements

1. Raise awareness and shape healthcare systems to improve access and motivation for smoking cessation
2. Create effective funding opportunities to boost innovation and lower the developmental costs, e.g. VC funds, scientific or social impact funds with focus on either early development or clinical validation of therapies with proof-of-concept data
3. Advocate the need for efficient approval pathways for digital therapies

Table of Content

- ▶ **Primary Research Results**
- ▶ Financial Model Results

The focus on this project was on primary market research capturing the views of academics, industry representatives, providers, payers and financial bodies

Scope and Methodology

Project Scope

- ▶ The aim of the project was to identify the key barriers to greater innovation smoking cessation
- ▶ The focus was on three types of smoking cessation solutions
 - Drugs
 - Medical devices
 - Apps
- ▶ Smoking alternatives as electronic nicotine-delivery system (ENDS, i.e. e-cigarettes) were not in scope of this project
- ▶ The geographic scope of the project was worldwide
- ▶ The interview program focused on experts from the US, Europe and Japan

Primary Market Research Methodology

Objective

- ▶ Walk through the relevant smoking cessation product and service solutions
- ▶ Identify barriers for three types of solutions: Drugs, devices and Apps
- ▶ Map the identified barriers to the innovation pathways for the three different types of solutions

Key Questions

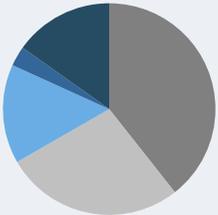
- ▶ How much innovation is taking place in the smoking cessation market?
- ▶ What are the barriers in each step of the innovation/ development/ commercialization process, e.g.
- ▶ What could be done to overcome the barriers to innovation?



Methodology

- ▶ Conducted 33 interviews with smoking cessation experts from a variety of disciplines (behavioural research, financing, drug development, etc.)
- ▶ Use a structured questionnaire containing a mix of qualitative and quantitative questions
- ▶ Set up conversations as 1-on1-telephone interviews

Target Groups



- Industry (13)
- Payers (9)
- Providers (5)
- Academics (1)
- Financial Bodies (5)

The research was focused on products intended for smoking cessation; Products without clinical validation or with evidence limited to harm reduction were omitted

Research Scope

Drugs



Non-nicotine drugs

- ▶ Chantix/Champix (varenicline)
- ▶ Zyban (bupropion)
- ▶ Cytisine

Nicotine replacement therapies (NRTs)

- ▶ Gums
- ▶ Patches
- ▶ Lozenges

Out of scope

Devices



Medical devices

- ▶ Nicotine inhalators
- ▶ Medical ENDS
- ▶ Electronic nicotine patches (e.g. Chronotherapeutics SmartStop)

Consumer devices*

- ▶ Wearables
- ▶ Electronic nicotine delivery systems (ENDS)
 - ▶ E-cigarettes
 - ▶ Heat-not-burn (HnB) devices

Non-clinically validated apps*

Apps



Evidence-based apps

- ▶ Apps with clinical evidence
- ▶ Prescription apps

*Products not intended for smoking cessation (absence of/not pursuing clinical validation for smoking cessation or are intended for harm reduction) were out of scope

Barriers to innovation in smoking cessation



Overview of barriers and root causes preventing greater innovation in smoking cessation market (1/3)

Barriers	Impact on innovation	Description	Root causes
<p>Scientific feasibility challenges</p> 		<ul style="list-style-type: none"> ▶ Nicotine addiction behaviour is not well understood ▶ Efficacy of current solutions is low as there is lack of patient stratification in clinical testing ▶ Absence of robust animal models and testing protocols for drugs and devices 	<ul style="list-style-type: none"> ▶ Although there is a good understanding of the nicotine receptor biology, the pathophysiology of nicotine addiction is poorly understood¹ ▶ A general consensus exists that smokers require a combination approach with behavioural support and pharmacotherapy to increase their likelihood of cessation^{2,3,4,5}, making innovation more complex ▶ Poor availability of animal and in vitro models for proof-of-concept and preclinical testing^{6,7,8,9,10}, specifically developing drugs targeting brain is considered more challenging^{11,12,13,14} ▶ Early stages of innovation are difficult as technology needs to be IP protected and establishing testing systems is often challenging to achieve proof-of-concept
<p>Low perceived market attractiveness</p> 		<ul style="list-style-type: none"> ▶ The behavioural component to addiction is unknown ▶ Past “one-size-fits-all” approach has proved unsuccessful ▶ Cessation infrastructure providing motivation to quit is essential ▶ Local variations in the market environment results in a challenging reimbursement scenarios 	<ul style="list-style-type: none"> ▶ Low to moderate success of the existing OTC and prescription-only drugs¹⁵ despite being on the market for decades propagates a negative perception of smoking cessation market ▶ Strong presence of OTC drugs¹⁶ coupled with low prescription rates^{17,18} requires high investment for marketing and differentiation of new solution ▶ Payers across many markets have misaligned priorities with little interest in funding preventative therapies for smoking cessation, including devices and apps



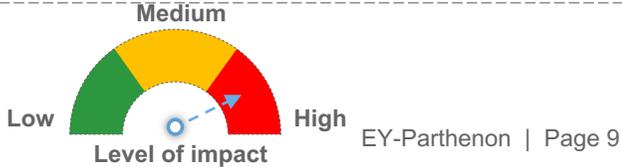
Overview of barriers and root causes preventing greater innovation in smoking cessation market (2/3)

Barriers	Impact on innovation	Description	Root causes
Funding challenges 		<ul style="list-style-type: none"> ▶ Little historical precedence for successful ventures ▶ Unclear unmet need as some consider smoking as a lifestyle choice while others are distracted by an increasing popularity of ENDS as a smarter alternative among smokers 	<ul style="list-style-type: none"> ▶ Pharma and investor funding prioritization skewed towards highly profitable indications and therapeutics (e.g. oncology, gene therapy)^{19,20,21} ▶ Investors are unaware of the high unmet need in smoking cessation and the resulting market gap is overshadowed by debate around ENDS
Regulatory approval 		<ul style="list-style-type: none"> ▶ Standard regulatory timelines and the resulting cost are often incompatible with smoking cessation business models ▶ Lack of standardised procedures for app approvals 	<ul style="list-style-type: none"> ▶ Long approval timelines and clinical trial costs are often incompatible with business plans of most smaller companies and health-tech start-ups ▶ Sourcing talent with regulatory and clinical expertise is challenging for health-tech start-ups ▶ Limited precedence for FDA-approved digital health solutions and resulting uncertainty about success of this business model



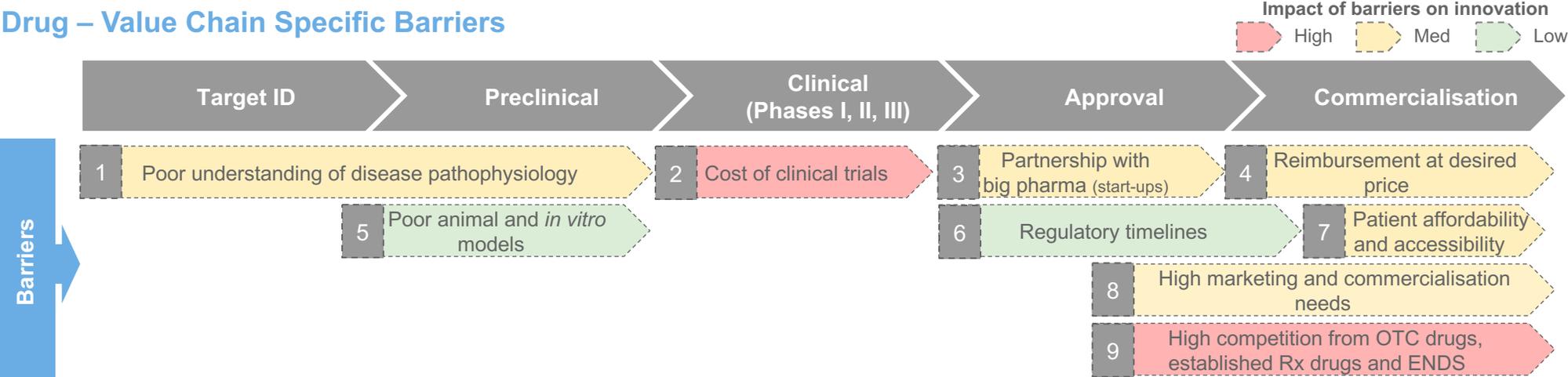
Overview of barriers and root causes preventing greater innovation in smoking cessation market (3/3)

Barriers	Impact on innovation	Description	Root causes
<p>On-market distractions</p> 		<ul style="list-style-type: none"> ▶ Over reliance on the use of ENDS as a smoking cessation tool by some markets despite the lack of supporting clinical data ▶ Many tobacco companies are actively promoting the use of ENDS as a smarter alternative to combustible cigarettes 	<ul style="list-style-type: none"> ▶ In addition to the established OTC and prescription brands, tobacco companies are also showing an increasing interest in developing alternatives to combustible cigarettes²³ ▶ Smokers and health authorities are distracted by potential application of e-cigarettes in smoking cessation^{24,25} <ul style="list-style-type: none"> ▶ While regulatory authorities in many markets remain ambiguous on the effectiveness and long-term safety of ENDS in smoking cessation, Public Health England has adopted a harm reduction approach by promoting the use of e-cigarettes as one of the cessation tools^{25,26} ▶ ENDS have proved successful among smokers across many markets, for instance a recent study reported a decline in NRT use with an increasing use of ENDS in smoking cessation²⁷
<p>Challenging business model</p> 		<ul style="list-style-type: none"> ▶ Each market has a different cultural perception of smoking and thus impacting the demand for smoking cessation solutions ▶ Difficult to achieve desired reimbursement scenarios ▶ Newer solutions require a tailored go-to-market approach due to varying country specific requirements 	<ul style="list-style-type: none"> ▶ Each market has a different view of smoking cessation and the measures required to achieve optimal cessation rates^{28,29,30,31,32} ▶ The factors contributing to these market-specific views often vary between countries, and thus requiring multiple business models to be successful in more than one market



Industry experts see major challenges of drug development in late development and commercialization

Drug – Value Chain Specific Barriers

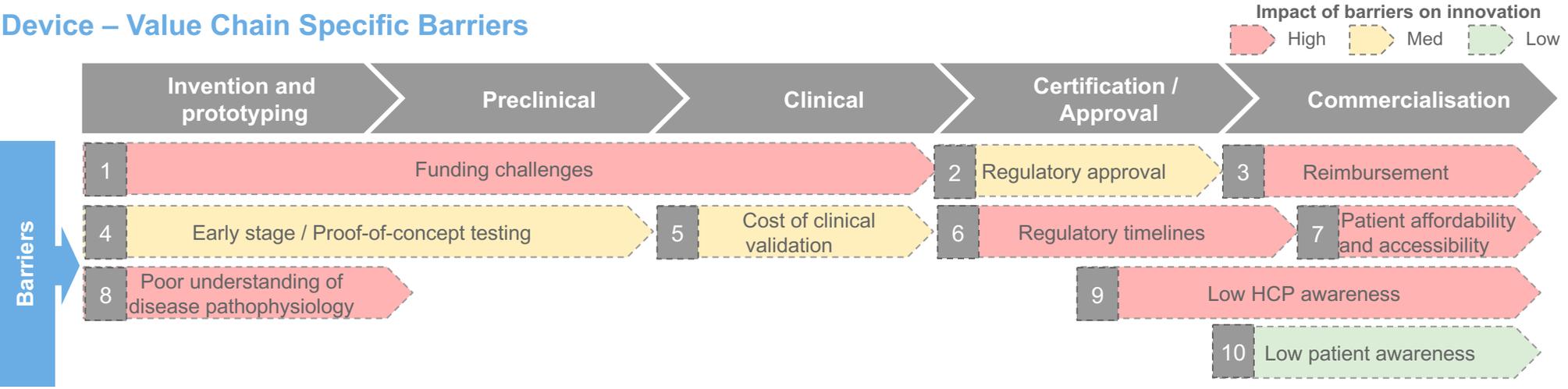


- Causes**
- ▶ Investment decisions within big pharma are prioritized based on NPV calculations, with investments evaluated at each stage of the development for their potential for financial returns and probability of success
 - ▶ Smoking cessation is perceived as a highly competitive market by big pharma in the developed countries, and consequently only essential investments are being made in this area to maintain the status quo
 - ▶ Pharma companies are more interested in updating their existing OTC products which come with high level of consumer awareness and accessibility, than develop prescription drugs requiring high investments and efforts to overcome reimbursement challenges
 - ▶ For big pharma with existing OTC portfolio in this area, developing a prescription drug is sometimes perceived as a conflicting investment
 - ▶ For smaller companies and start-ups, funding availability is challenging due to the perception of low expected success or returns on investment

- Solutions**
- ▶ Increasing awareness of payers and government on the high unmet need in providing efficacious and safer pharmacotherapy and the importance of smoking cessation infrastructure
 - ▶ Funding opportunities for clinical testing of newer technologies with proof-of-concept from government or NGOs or not-for-profit organizations will encourage smaller companies to innovate in this area
 - ▶ Educate HCPs about the importance prescribing pharmacotherapy for smoking cessation and provide incentives for offering proactive guidance to patients
 - ▶ Clinical trials testing the efficacy in a patient subset will reduce the cost and increase the likelihood of success

Most challenges during device development are encountered at early stages or post approval

Device – Value Chain Specific Barriers

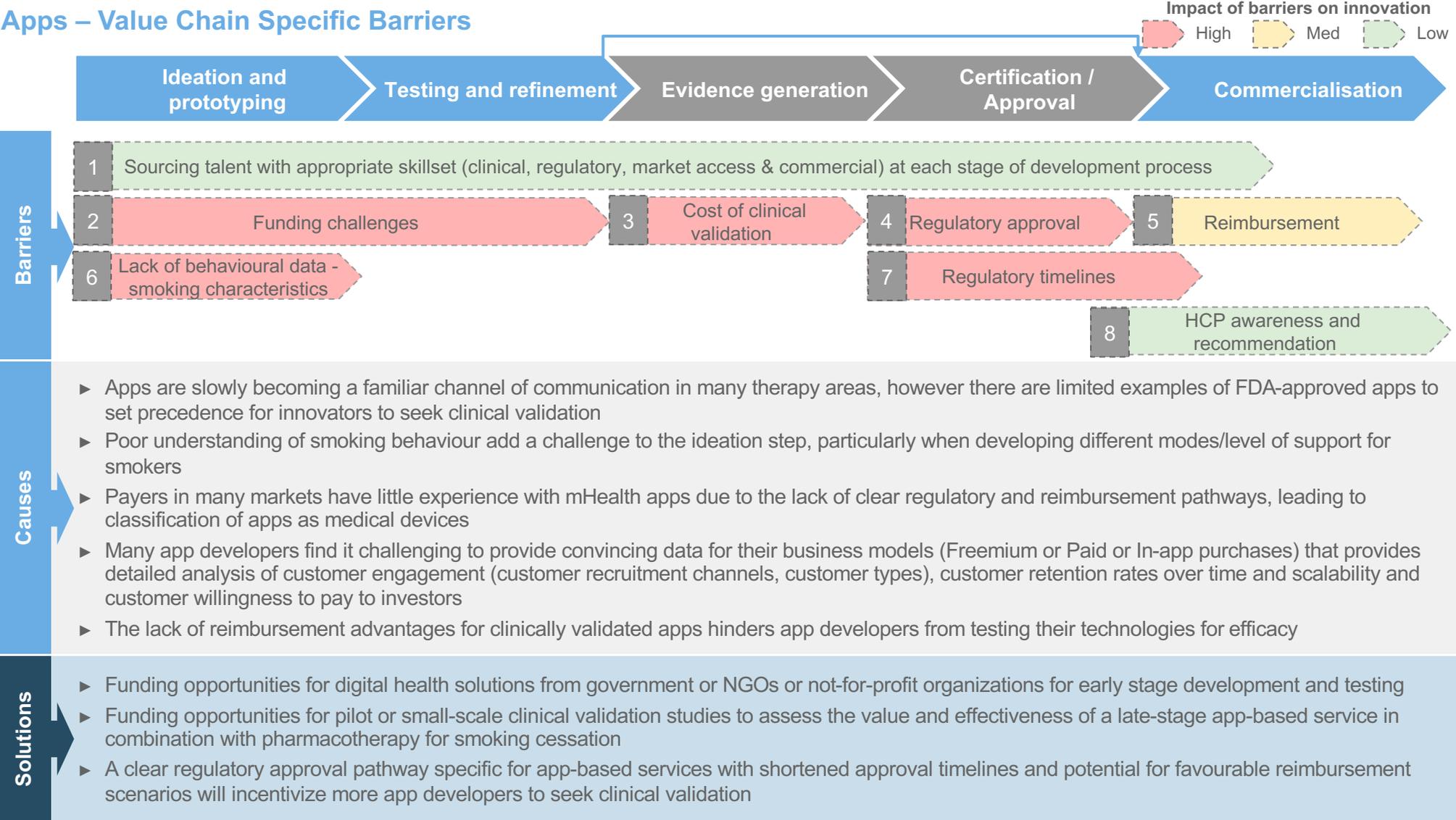


- Causes**
- ▶ Although nicotine receptor biology is a well researched topic, the understanding of the behavioural aspect of nicotine addiction, in particular reward pathways, is inadequate
 - ▶ Medical devices are not a commonplace in smoking cessation market causing a high degree of uncertainty on their utility in helping smokers quit among investors, payers and HCPs on their utility in helping smokers quit
 - ▶ Funding is challenging as many health-tech investors consider smoking cessation as a risky market with huge reimbursement challenges, and often require proof for end user accessibility and affordability at early stages
 - ▶ Investors and innovators expect the commercialization costs to be high due to the limited precedence of successful medical devices in this area

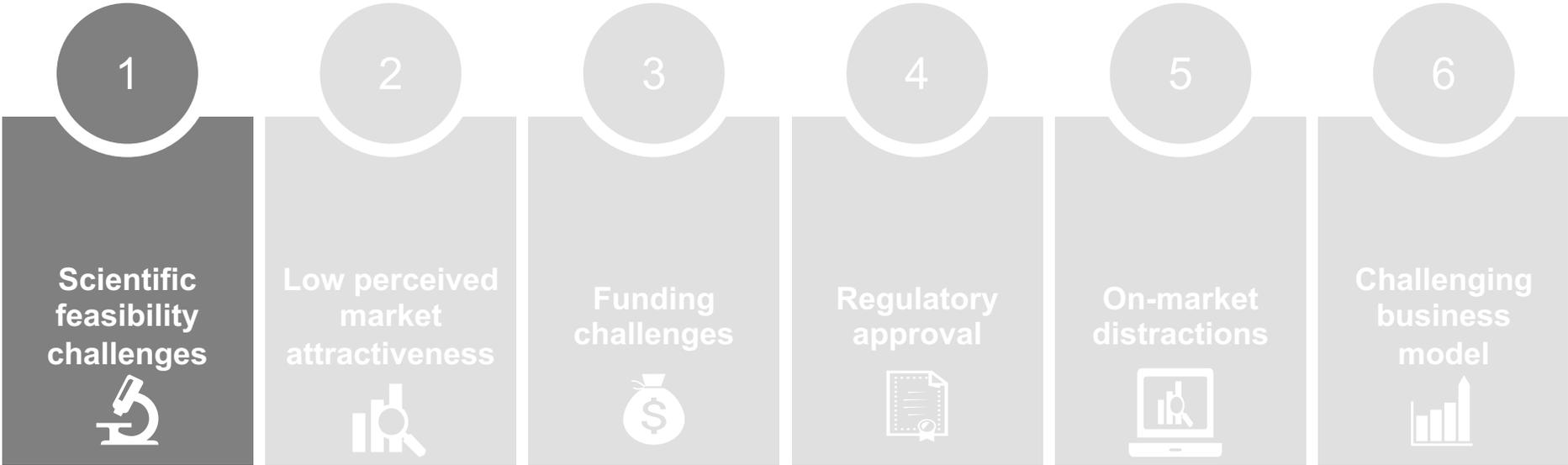
- Solutions**
- ▶ Funding opportunities for high risk technologies with a potential for social impact from government or NGOs or not-for-profit organizations for early stage development and testing
 - ▶ A research study aimed at understanding the unmet need from smoker’s perspective and assessing the usefulness of different types of solutions (drugs, devices and apps) based on the feedback from the following
 - ▶ Current smokers with intention to quit
 - ▶ Current smokers with unsuccessful quit attempts
 - ▶ Smokers who have quit successfully

App developers face most critical challenges during ideation and testing phases

Apps – Value Chain Specific Barriers



Barriers to innovation in smoking cessation



Scientific feasibility challenges

Nicotine addiction behavior is poorly understood which contributes to the lack of development of targeted therapies

*“Pharmacotherapy with appropriate expert behavioural support preferably face to face is the best way to give up smoking”- **Independent consultant***

*“There is a huge amount of misinformation given by medical professionals to the public. The barrier is understanding the levels at which products are used to help people quit smoking”- **General practitioner***

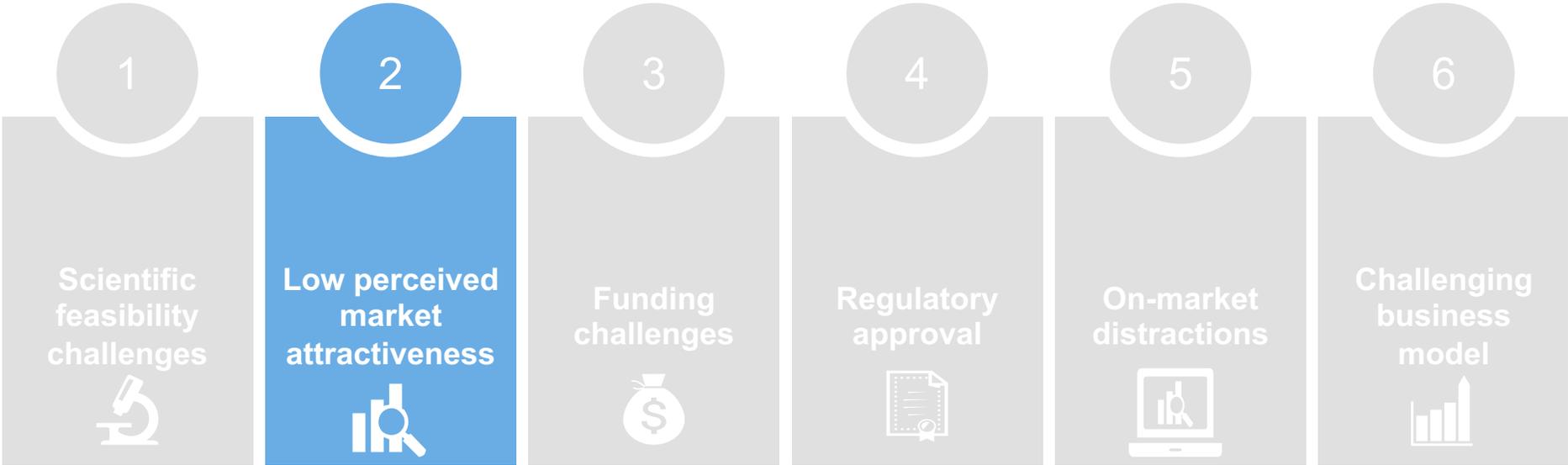
*“There have been lots of different ideas that has not worked out in the past. There are no good animal models for addiction that are viable. There is an unknown behavioural aspect, for e.g. people think that they can quit without any drugs”- **Senior Medical Director***

*“The main reason is there is not much innovation in this because the understanding of the mechanism is still very limited. And when the mechanism of addiction is not well understood then it is really hard to develop a solution. All the pharmacological interventions have failed because these were too general in their MoA and had a complete disregard for the complex reward pathways”- **Research lead***

*“There has to be tracking support in addition to pharmacotherapy. Human beings tend to lose interest if there are no positive reminders of benefits or whatever else that can be used to motivate them”- **Former Director Next Generation Products***

*“There are no good animal models for addiction that are viable”- **Senior Medical Director***

Barriers to innovation in smoking cessation



Low perceived market attractiveness

Investors view smoking cessation market as highly competitive with challenging reimbursement environment

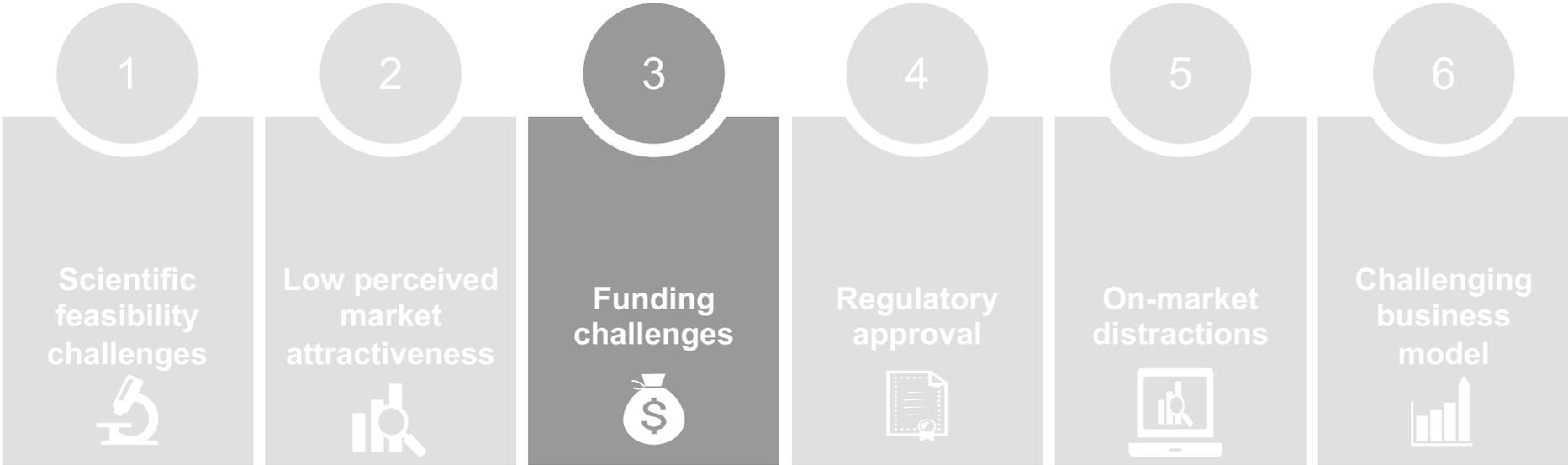
Investors

- ▶ Smoking is regarded as a lifestyle disease and many investors are unaware of the addictive nature of nicotine and therefore the need for medical intervention
- ▶ Investors believe that a strong presence of OTC drugs in this area, creating a highly competitive market for any newer therapies entering this space
- ▶ In addition to OTC presence, many investors consider the increasing use and popularity of e-cigarette amongst smokers as a major competition in the market
- ▶ For many investors, past successes of technology or drugs serve as an indicator for the attractiveness of the market
 - ▶ Although some agree that market presents with a big commercial opportunity, they also suspect the quantification of the opportunity is likely to present with challenges
 - ▶ Some investors believe that market opportunity is unpredictable as there is a heavy reliance on smoker's will to quit
- ▶ Reimbursement structure in many markets is heavily dependent on OOP and this is perceived as a negative feature of the market

Industry Experts

- ▶ Many decision makers view smoking cessation market as a saturated space with branded OTC NRTs
 - ▶ Industry innovation has mostly been limited to the modification of existing OTC NRTs to leverage smoker familiarity of the brands while requiring low investments
- ▶ Industry experts also consider tobacco companies and their ongoing attempts at developing innovative non-combustible forms of cigarettes as a massive competition
- ▶ Reimbursement at a desired price can prove challenging due to conflicting priorities of payers across many markets and less focus on long term cost savings from preventative therapies

Barriers to innovation in smoking cessation



Funding challenges

Smoking cessation market is deprioritized by investors as many external factors require efforts beyond funding to ensure a desirable return on investment

Investors

- ▶ Investors often identify investment opportunities based on the level of unmet needs and innovation
 - ▶ Investors remain unclear on the level of unmet need in the smoking cessation market, due to a large number of OTC products and rising popularity of ENDS
- ▶ Investors acknowledge the benefits of digital solutions for smoking cessation, however struggle to envisage adoption and reimbursement scenarios due to the lack of past successful ventures
- ▶ Investors only have access to a finite pool of investment, and there are multiple promising technologies with application in multiple diseases
- ▶ Investors favour projects with greater predictability of success and favourable reimbursement scenarios
- ▶ There is little evidence of interest in newer smoking cessation solutions by payers in major markets, as there are no 'soft pathways' or 'expedited approvals' for smoking cessation products
- ▶ Many investors find the long regulatory approval timelines as a barrier for a treatment expected to face reimbursement challenges

Industry Experts

- ▶ Investment decisions in big pharma companies are mostly driven by the level of investment required at each stage of development and NPV estimates
 - ▶ Smoking cessation market is often deprioritized over more trendy and economically promising indications
- ▶ Industry experts acknowledge the high level of unmet need, however the fact that smoking rates are declining in many developed markets is a contributing factor towards their lack of interest
- ▶ Smoking cessation market is not perceived as a growing market despite the unmet need by pharma companies with existing portfolio
 - ▶ Consequently, resource allocation is implemented with an aim of maintaining the status quo
- ▶ The general consensus is that "one solution fits all" is not a suitable approach as smokers have varying levels of nicotine addiction and dependence and different behavioural aspects
 - ▶ This realization further shrinks the target market size and commercial interest

Barriers to innovation in smoking cessation



Regulatory approval

Funding challenges coupled with stringent regulatory requirements have forced some start-ups and smaller companies to avoid gaining approval despite superior pricing scenarios

Existing App-Based Business Models

- | | | |
|----------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  Fast and cost-effective development |  Price in range with OTC cessation drugs, but lower development cost |  Similar price as Rx cessation drugs, but significantly lower development cost |
|  Low price, need high volume |  Reimbursement challenging for non FDA-approved products |  Regulatory path complex, little precedence |
|  Crowded market | |  Reimbursement policies only emerging |
|  No reimbursement | | |

Legend  Upside  Neutral  Downside

Validated Apps

- ▶ Price for App/device tandem products in range with OTC drug-based products e.g. 5\$ / day
- ▶ Medical evidence available, but not validated by regulatory authorities
- ▶ In tandem with a device the development timeline is 6-8 years on average, and cost depends on device, typically in ~\$200mn range



FDA approved Apps

- ▶ Price ~10\$ / day, in range with Rx cessation drug product Champix
- ▶ For an App, the development timeline is about 3-4 years and cost is significantly lower than drug²²



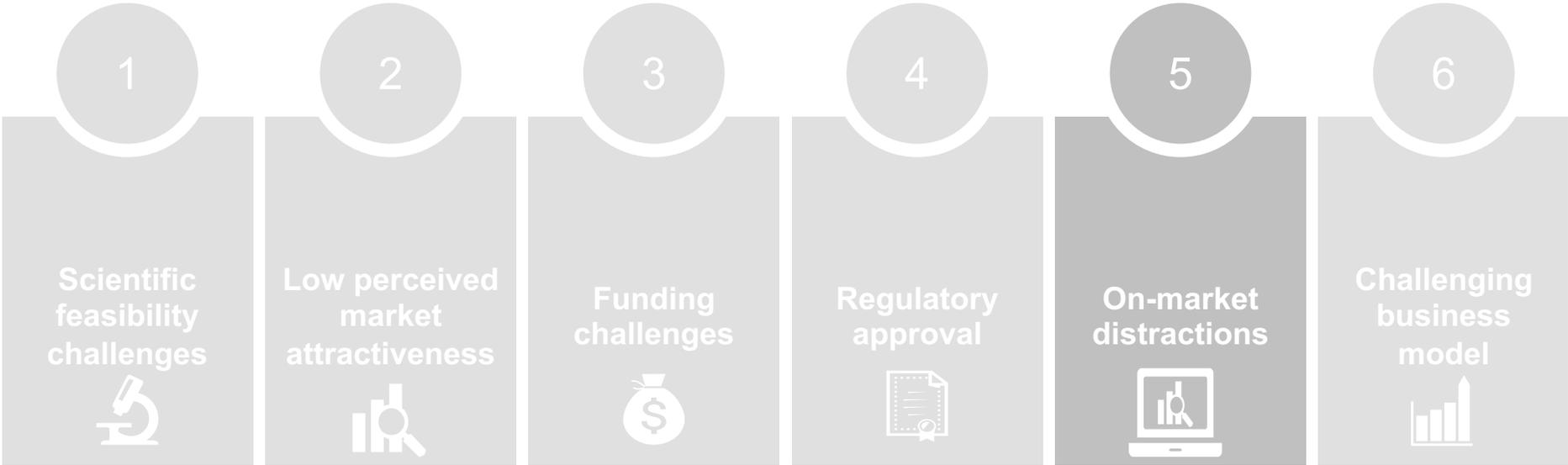
Non-validated Apps

- ▶ Low price or free of charge
- ▶ Typically contain advertisement
- ▶ Evidence based on user feedback
- ▶ Development time < 2 years

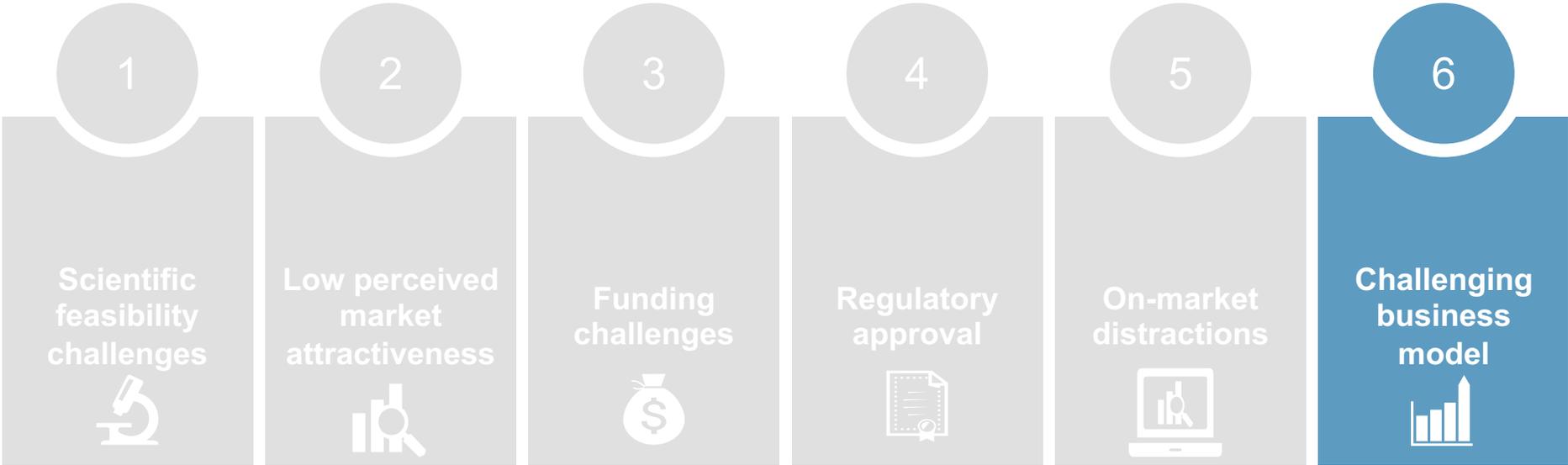
QUITNOW!



Barriers to innovation in smoking cessation



Barriers to innovation in smoking cessation



Challenging business model

Reimbursement for smoking cessation therapies is often challenging in many markets, and this is described as one of the biggest barriers to innovation in this area

1 Misconceptions – Smoking is viewed as a lifestyle disease in some markets, and not considered as a public health concern



7 Unfavourable pricing environment – Payers in some markets are unwilling to offer premium prices for newer drugs, particularly if the MoA is similar to the existing class of drugs



6 Harm reduction approach – Payers in the UK have adopted a harm-reduction approach towards smoking cessation by promoting the use of e-cigarette as one of the smoking cessation solutions



5 Lack of focus on preventative therapies – Payers in some markets are often unaware of both short-term and long-term pharmacoeconomics of smoking-related diseases and complications



Payers have described multiple factors that contribute to a challenging reimbursement environment

2 Short-term focus on cost savings – Payers in most markets face budget constraints and strict saving targets, causing them to deprioritise prevention therapies



3 Lack of government focus on smoking cessation – Government in many countries believes that high taxes on tobacco products is sufficient to motivate smokers to quit

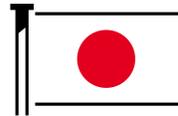


4 Legacy of OTC NRTs – Payers have historically not been responsible for reimbursing NRTs in many markets and thus consider smoking cessation as an individual burden

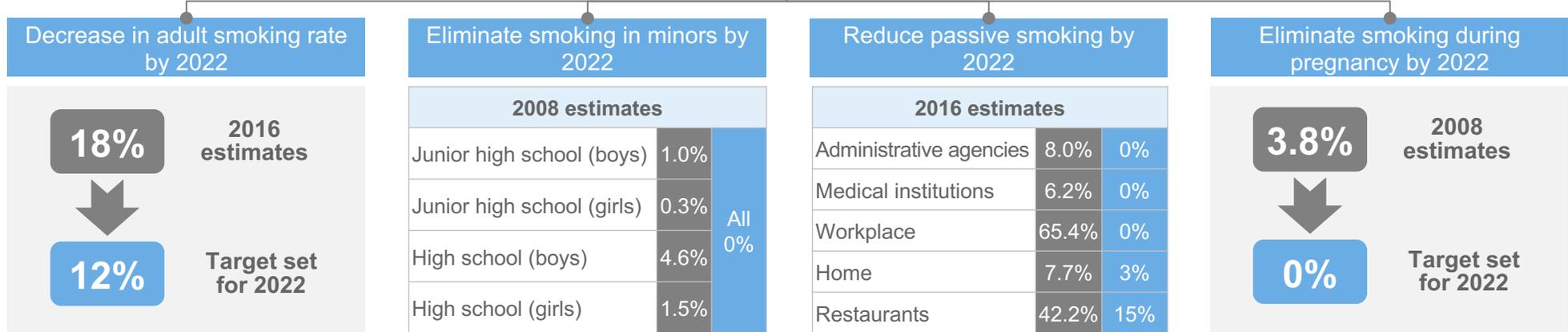


Challenging business model

Certain environmental factors are also essential for creating a demand for innovation – Japan is a case in point

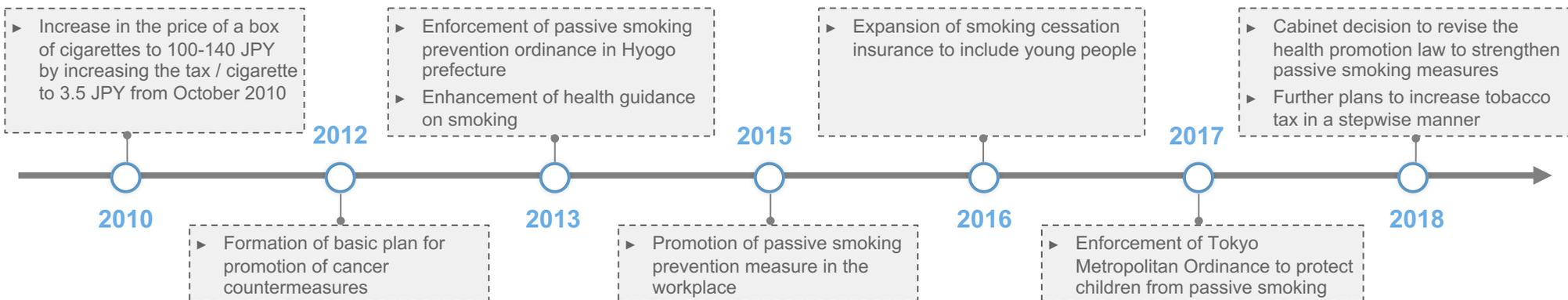


Goals set by Japan for tobacco control as part of its Healthy Japan 21 Project (Second version)²⁸



- ▶ Japan adopted a systematic approach to tackling rising smoking rates by first setting up targets and goals
- ▶ Secondly, Japan implemented various measures ranging from tax increase on tobacco products to reimbursement of smoking cessation drugs under public health insurance to achieve these targets

Implementation timeline of initiatives²⁸

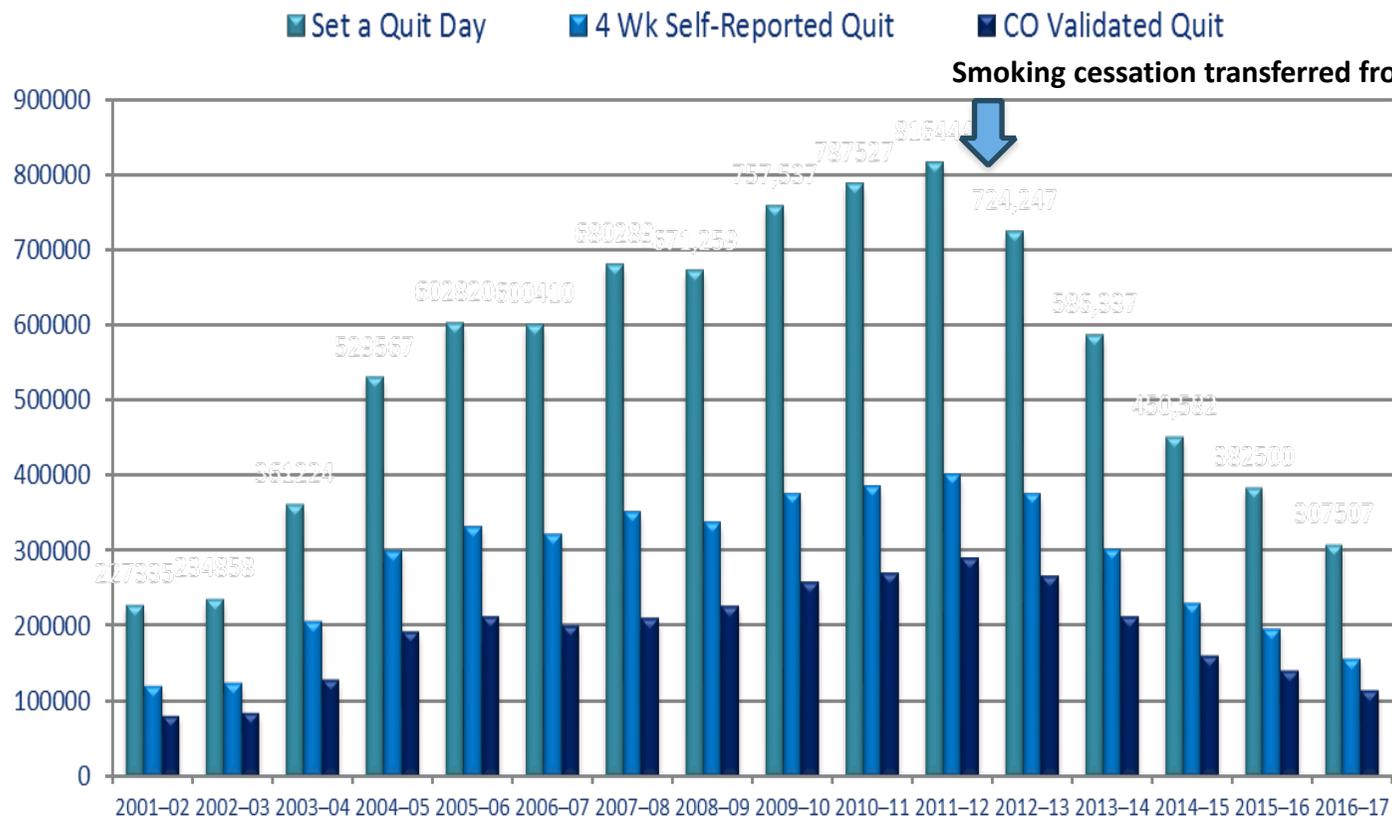


Challenging business model

Successful cessation requires a supportive healthcare infrastructure, which is often deprioritized by many health authorities



- ▶ In a move to empower local authorities with their budget allocation, funding for smoking cessation services transferred from the NHS to local authorities in 2012
- ▶ Consequently, budgets for stop smoking services were cut in 50% of local authorities in England in 2017 and this follows cuts in 59% and 39% of local authorities in 2016 and 2015, respectively²⁹
- ▶ According to data from the NHS Digital, statistics on NHS Stop Smoking Services show a reduction in proportion of smokers setting a quit day as the number of smokers successfully quitting (validated by CO measurements)³⁰



Number of smokers setting a quit day²⁹

816,444

in 2011-12

307,507

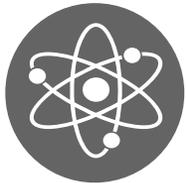
in 2016-17

Our initial exploration suggests solutions to overcome commercial, scientific and regulatory challenges



1 Commercial challenges

- ▶ Influence health authorities and payers to adapt their reimbursement strategies by offering favorable pricing to novel smoking cessation solutions
- ▶ Funding opportunities to enable innovators to lower developmental costs for drugs, devices and digital solutions



2 Scientific challenges

- ▶ Funding opportunities for research projects aimed at better understanding the neurophysiology of nicotine addiction
- ▶ Funding opportunities for studies aimed at characterizing smoker behavior to enable patient stratification



3 Regulatory challenges

- ▶ Engage key regulatory authorities in modifying current framework to include efficient approval pathways for digital therapeutics

Table of Content

- ▶ Primary Research Results
- ▶ **Financial Model Results**

EY-Parthenon developed global forecast and valuation models in Excel for 3 hypothetical product types for smoking cessation

Model Overview

Product types



Drug
Prescription drug with novel mechanism



Device
Portable home-use neurostimulation device



App
FDA-approved prescription app

Model summary outputs



Peak net sales



Net present value (NPV)
Risk-adjusted NPV (rNPV)



Net sales forecast

Geographic scope: Global (20 independent country forecasts plus ROW)

Higher-income countries



Australia



Japan



Canada



South Korea



France



Spain



Germany



UK



Italy



US

Lower-income countries



Brazil



China



Egypt



India



Indonesia



Mexico



Philippines



Russia



South Africa



Turkey

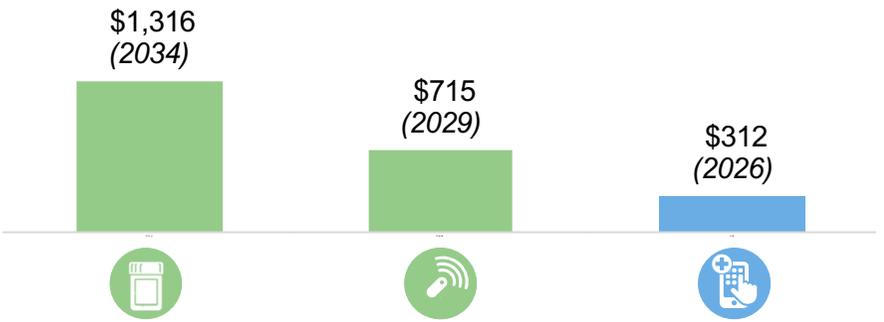
Rest of World (RoW)



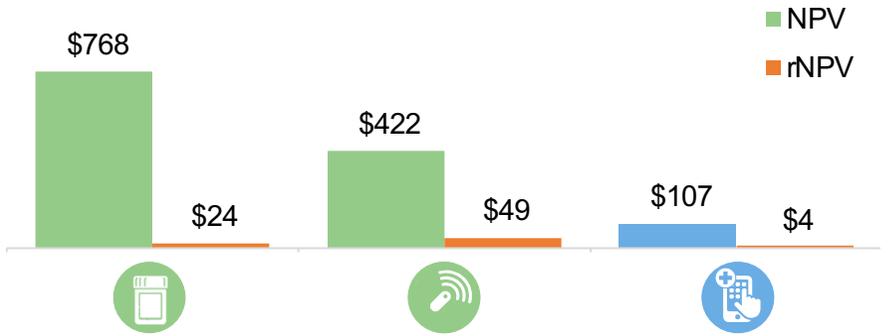
Our valuation models yield positive NPVs for all 3 product types, but attractiveness may be limited when evaluated against other opportunities

Model Summary Outputs (Base Case)

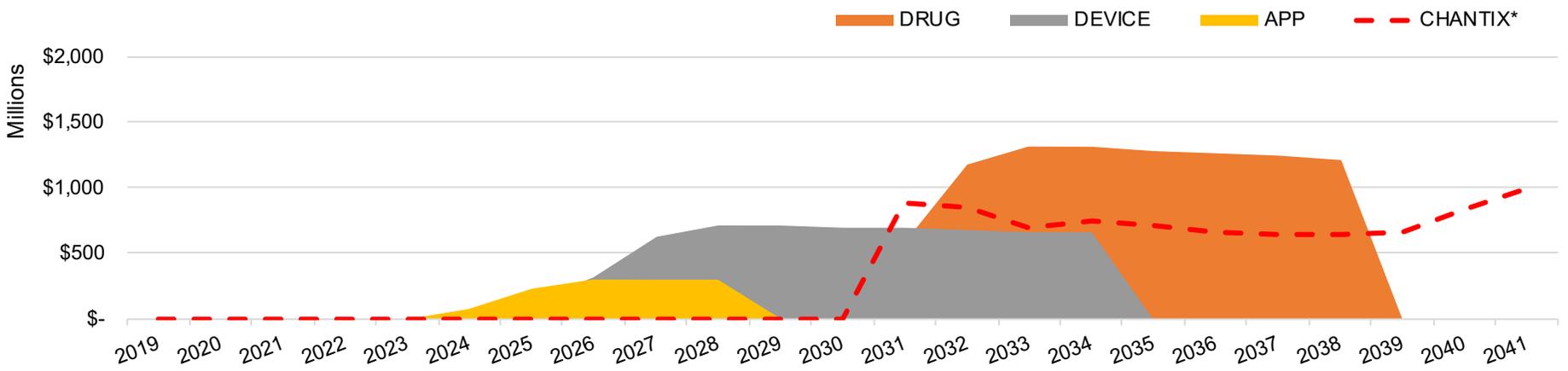
Peak net sales, \$ USD Million (year)



NPV and rNPV, \$ USD Million



Net sales forecast, \$ USD Million



*Top-down validation: Chantix sales (EvaluatePharma) adjusted to launch in the same year as the Drug product for reference



The cockpit tab outlines the model structure and serves as the navigation page among the summary, input and output content

Model Structure & Navigation



Hyperlinks to:

Summary tabs

<i>Overview</i>	<i>Methodology</i>	<i>Summary Outputs</i>
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Input tabs

<i>Epidemiology</i>	<i>Target Product Profiles (TPPs)</i>	<i>Assumptions</i>	<i>Adoption Curves</i>
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Output tabs

<i>Gross Sales</i>	<i>Development Time & Costs</i>	<i>P&L & NPV</i>
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Gross Sales	Scenario Selection <input type="text" value="Base"/>
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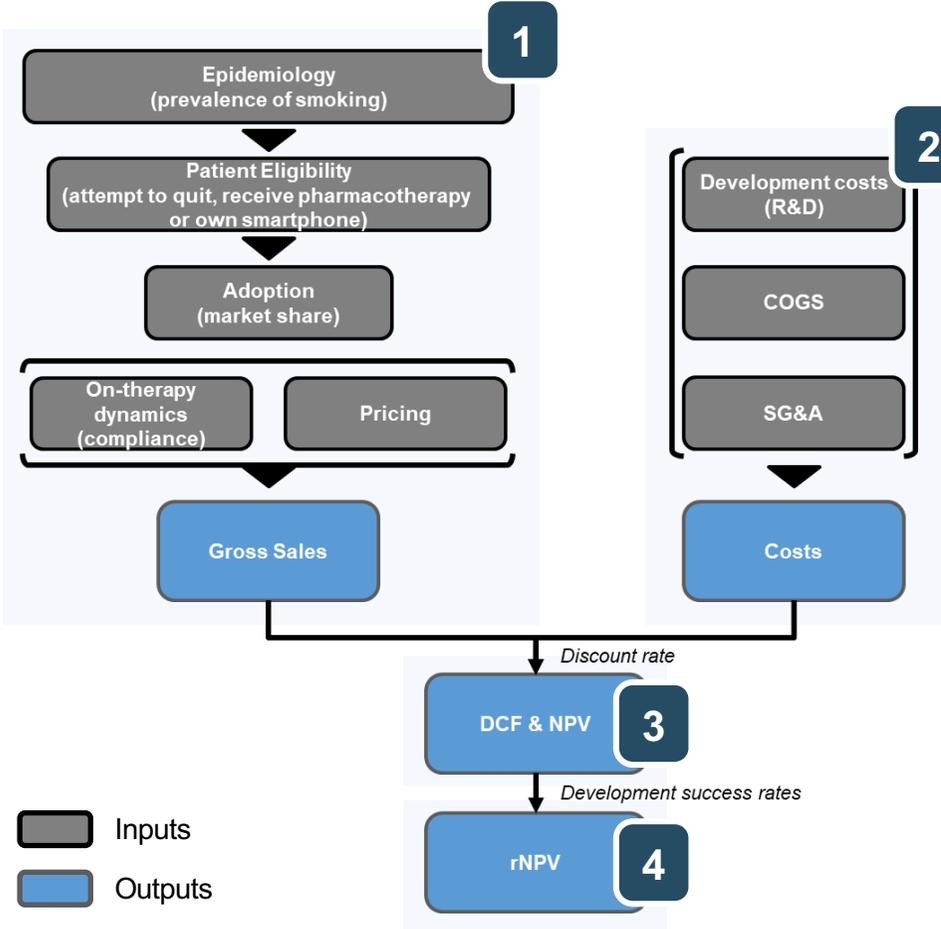
Hyperlink to model cockpit

Tab title

Tool used to define the current scenario (downside, base upside) and assumptions for the entire workbook

All models employ bottom-up gross sales forecasts by country, product development and commercialization costs, discounting, and probability of success

Model Methodology



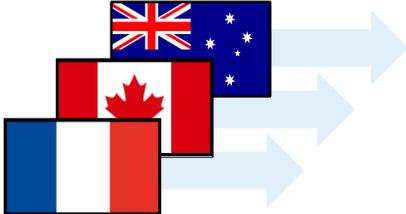
- 1** Gross Sales forecast for each market are estimated bottom-up using market-specific assumptions
- 2** Total costs are calculated, including COGS, out-of-pocket development costs (R&D) and SG&A from industry analogues
- 3** Net sales (after discounts etc.) and annualized costs incorporated into a P&L to derive net income, discounted cash flows (DCF) and net present value (NPV)
- 4** Development-stage probability of success rates applied to calculate risk-adjusted net present value (rNPV)

Model inputs are displayed in 4 tabs: Epidemiology, Target Product Profiles (TPPs), Assumptions and Adoption Curves

Model Inputs

Epidemiology

- Forecasted tobacco smoking prevalence (N) for each country and RoW (2019-2050)
- Utilizes forecasted population data (WorldBank) and extrapolated tobacco smoking prevalence (%) (WHO) for both sexes



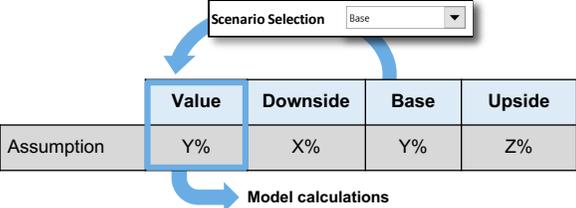
Target Product Profiles (TPPs)

- Target product profiles (TPPs) were prepared for all 3 product types and are available in the model
- TPPs inform the model assumptions, including Adoption, On-Therapy Dynamics, and Pricing



Assumptions

- Detailed assumptions tab defines the inputs that drive the model for each of the 3 product types and scenarios
- Assumptions are fully editable, and the Scenario Selection tool determines the current “Value” used in the models



Adoption Curves

- Adoption curves define the adoption dynamics for each product
 - Drug: Adoption defined by uptake analysis of analogues (Chantix, Vivitrol and Campral) and immediate decrease to 0 at loss of exclusivity (20 years after development start)
 - Device: Longer time-on-market due to sustained R&D efforts
 - App: Accelerated uptake and obsolescence

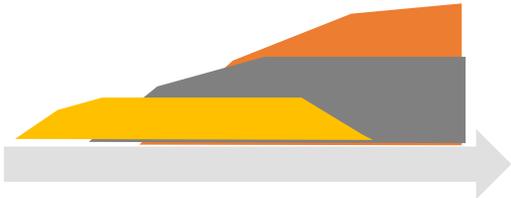


Model output calculations are detailed in 3 tabs: Gross Sales, Development Time & Costs, and P&L & NPV

Model Inputs

Gross Sales

- Bottom-up forecasts of Gross Sales for all 3 products
- Utilizes forecasted epidemiology, patient eligibility (quit attempts, pharmacotherapy use), product adoption, compliance and price



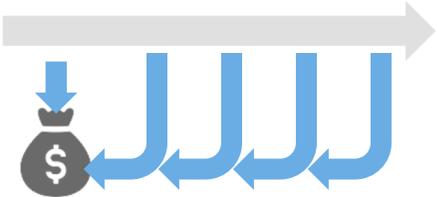
Development Time & Costs

- Simple (annual) and detailed (monthly) depictions of development timelines automatically generated for each product type
- Annualized development costs for each stage for P&L



P&L & NPV

- Sales and Costs are integrated into a P&L to calculate:
 - Discounted cash flow (DCF): Discount rate applied to free cash flows to account for time-value-of-money
 - Net present value (NPV) – Sum of DCFs indicates present value of future cash flows
 - Risk-adjusted NPV (rNPV) – Probability of success at each stage of development applied to risk-adjust NPV





Appendix



Drug – Value Chain Specific Barriers (Supporting evidence) (1/2)

Barriers	Supporting evidence
1. Poor understanding of disease pathophysiology	<ul style="list-style-type: none"> ▶ “The main reason is the limited understanding of mechanism. And when the mechanism of addiction is not well understood then it is really hard to develop a solution”- Research lead ▶ “There is a huge amount of misinformation given by medical professionals to the public. The barrier is understanding the levels at which products are used to help people quit smoking”- General Practitioner
2. Cost of clinical trials	<ul style="list-style-type: none"> ▶ “Clinical trials are too expensive to be conducted”- Director, Healthcare company ▶ “The cost of running clinical trials is too high for smaller tech or start-ups, making it incredibly challenging for these companies to get clinical validation for their products- President, Healthcare company
3. Partnership with pharma (start-ups)	<ul style="list-style-type: none"> ▶ “FDA at this point is providing lot of requirement for the approval process. Regulatory requirement in the US makes it very difficult for the product (combination of pharmacological and motivational tools) like these to come into the market”- Head R&D, Pharmaceutical company
4. Reimbursement at desired price	<ul style="list-style-type: none"> ▶ “Use of sick funds completely depends upon their availability. If the funds are available then it can even be used for a long period. For example, HPV vaccination is reimbursable for girls till the age group of 12 in most of the countries whereas in Germany it is reimbursable till 16. Lately they have decided to extend this option till the age group of 24 and even introduce reimbursements for boys”- Head, Drug Reimbursement ▶ “Reimbursement structure is heavily dependent on out-of-pocket (OOP) and this is not a preferred characteristic as it limits the price of the drug”- Associate, VC
5. Poor animal and in vitro models	<ul style="list-style-type: none"> ▶ “There are no good animal models for addiction that are viable”- Senior Medical Director
6. Regulatory timelines	<ul style="list-style-type: none"> ▶ “Stability studies take 2-3 years”- VP & Commercial Lead, Pharmaceutical company
7. Patient affordability and accessibility (1/2)	<ul style="list-style-type: none"> ▶ “Smoking Cessation products are expensive . It costs 60 euros to buy Champix in Italy. It is more expensive than buying a pack of cigarette and in the initial months if needed 3-4 boxes it would cost a lot of money. Affordability is a major problem”- MD, Cessation product ▶ “India, China, Brazil and Africa are incredibly big markets for both smoking and smoking cessation markets, however there are challenges there in terms of affordability and access”- SVP R&D ▶ “Clinical benefits of the existing solutions needs to be improved and the most unmet need is in the affordability of these treatments”- Associate, VC

Drug – Value Chain Specific Barriers (Supporting evidence) (2/2)

Barriers	Supporting evidence
<p>7. Patient affordability and accessibility (2/2)</p>	<ul style="list-style-type: none"> ▶ “Government involvement is needed to make the product much more accessible to the consumers”. “The OTC space is much more easier to access” – Head R&D, Pharmaceutical company ▶ “A combination of all the factors, something easy to use and adhere to in the long run, let it be the combination of drug component or behavioural support, having more access to it and making sure that the potential user know such kind of product exists has a greater chance of working”- Sr. R&D Manager
<p>8. High marketing and commercialisation needs</p>	<ul style="list-style-type: none"> ▶ “Proper marketing message with a tagline will be helpful. The key motive is to educate people, to make them aware why they are doing and how they are doing and why they are into (smoking) this”- President, Healthcare company ▶ “There is a direct co-relation between advertisement and promotion vs your sales“- Head R&D, Pharmaceutical company
<p>9. High competition from OTC drugs, established Rx drugs and ENDS</p>	<ul style="list-style-type: none"> ▶ “It is estimated to somewhere between 9%-12% people who use these products (OTC) eventually succeed quitting”- Managing Director ▶ “Health Authorities in UK and other countries promote the use of e-cigarettes. NHS says that e-cigarettes are 95% safer in certain aspects than smoking a combustible cigarettes”- Managing Director ▶ “A lot of smokers are interested in electronic cigarettes. E-cigarettes, more than just looking sleek, comes in different flavours and also deliver more nicotine, quickly”- Senior Medical Director

Device – Value Chain Specific Barriers (Supporting evidence) (1/2)

Barriers	Supporting evidence
1. Funding Challenges	<ul style="list-style-type: none"> ▶ “The problem with this market is lack of funding. Innovation requires strong funding. Innovation which will solve this problem won't come easy and it won't be a single product solution”- SVP R&D ▶ “Funding is the biggest challenge. Government, Investors or Venture Capitalist just doesn't see smoking as a concern because they think that nicotine addiction is not a disease, it is a lifestyle choice. Also they believe that smoking is not a current problem and that it is well under control”- President, healthcare company
2. Regulatory Approval	<ul style="list-style-type: none"> ▶ “Many smaller companies or start-up's don't have the expertise or knowledge or resources to navigate through regulatory complexities of getting a product approved in the US or Europe.”- SVP R&D ▶ “Regulatory requirement in the US makes it very difficult for the product (combination of pharmacological and motivational tools) like these to come into the market”- Head R&D, Pharmaceutical company ▶ “Approvals in Japan are based on efficacies and effectiveness of therapy”- Senio Researcher, MA, Reg, P&R Expert
3. Reimbursement	<ul style="list-style-type: none"> ▶ “The reimbursement outside US is quite tricky for smoking cessation products”- Former Head of Research and Development of a Pharmaceutical company ▶ “If you are looking from the reimbursement perspective of the government, combination therapies are challenging. There is a lot of interest in devices now and then in apps. Payers generally don't pay for it.”- Independent consultant
4. Early stage/ Proof of concept testing	<ul style="list-style-type: none"> ▶ “When it comes to initial stages, expenses are very low. Things get expensive when you go from exploring the development side. At every stage there is a huge amount of financial evaluation done, but NPV is one of the major thing that is looked into”- Head R&D, Pharmaceutical company
5. Cost of Clinical validation	<ul style="list-style-type: none"> ▶ “The cost of running clinical trials is too high for smaller tech or start-ups, making it incredibly challenging for these companies to get clinical validation for their products”- President, Healthcare company
6. Regulatory timelines	<ul style="list-style-type: none"> ▶ “Stability studies take 2-3 years”- VP & Commercial Lead, Pharmaceutical company ▶ “FDA at this point is providing lot of requirement for the approval process”- Head R&D, Pharmaceutical company
7. Patient affordability and accessibility (1/2)	<ul style="list-style-type: none"> ▶ “Smoking Cessation products are expensive . It costs 60 euros to buy Champix in Italy. It is more expensive than buying a pack of cigarette and in the initial months if needed 3-4 boxes it would cost a lot of money. Affordability is a major problem”- Managing Director ▶ “India, China, Brazil and Africa are incredibly big markets for both smoking and smoking cessation markets, however there are challenges there in terms of affordability and access”- SVP R&D ▶ “Clinical benefits of the existing solutions needs to be improved and the most unmet need is in the affordability of these treatments”- Associate, VC

Device – Value Chain Specific Barriers (Supporting evidence) (2/2)

Barriers	Supporting evidence
<p>7. Patient affordability and accessibility (2/2)</p>	<ul style="list-style-type: none"> ▶ “Government involvement is needed to make the product much more accessible to the consumers”. “The OTC space is much more easier to access” - Head R&D, Pharmaceutical company ▶ “A combination of all the factors, something easy to use and adhere to in the long run, let it be the combination of drug component or behavioural support, having more access to it and making sure that the potential user know such kind of product exists has a greater chance of working”- Sr. R&D Manager
<p>8. Poor understanding of disease pathophysiology</p>	<ul style="list-style-type: none"> ▶ “The main reason is the limited understanding of mechanism. And when the mechanism of addiction is not well understood then it is really hard to develop a solution”- Research lead ▶ “There is a huge amount of misinformation given by medical professionals to the public. The barrier is understanding the levels at which products are used to help people quit smoking”- General Practitioner
<p>9. Low HCP awareness</p>	<ul style="list-style-type: none"> ▶ “They don't see it as a medical problem”- General Practitioner
<p>10. Low patient awareness</p>	<ul style="list-style-type: none"> ▶ “Everything needs to be defined, the problem, the way to mitigate, the solutions which can cause deflection of that particular disease. People don't just consider smoking a risky behaviour”- Vice President ▶ Proper marketing message with a tagline will be helpful. The key motive is to educate people, to make them aware why they are doing and how they are doing and why they are into (smoking) this- President

Apps – Value Chain Specific Barriers (Supporting evidence)

Barriers	Supporting evidence
1. Sourcing talent with appropriate skillset (clinical, regulatory, market access and commercial) at each stage of development process	<ul style="list-style-type: none"> ▶ “One can really have a good app in less than half a million dollar, if there is right skill and the right talent. With companies having knowledge in that field one can really develop a decent app”- Head R&D, Pharmaceutical company
2. Funding challenges	<ul style="list-style-type: none"> ▶ “The problem with this market is lack of funding. Innovation requires strong funding. Innovation which will solve this problem won't come easy and it won't be a single product solution”- SVP R&D ▶ “Funding with the right innovation. Organization majorly look at the product which has good return on innovation and has low risk profile and if consumers are also interested in that product, appropriate funding would be provided”- Head R&D, Pharmaceutical company
3. Cost of clinical validation	<ul style="list-style-type: none"> ▶ “The cost of running clinical trials is too high for smaller tech or start-ups, making it incredibly challenging for these companies to get clinical validation for their products”- President, Healthcare company
4. Regulatory approval	<ul style="list-style-type: none"> ▶ “Many smaller companies or start-up's don't have the expertise or knowledge or resources to navigate through regulatory complexities of getting a product approved in the US or Europe”- SVP R&D ▶ “Regulatory requirement in the US makes it very difficult for the product (combination of pharmacological and motivational tools) like these to come into the market”- Head R&D, Pharmaceutical company ▶ “Approvals in Japan are based on efficacies and effectiveness of therapy”- Senior Researcher, P&R Expert
5. Reimbursement	<ul style="list-style-type: none"> ▶ “For apps, reimbursement can be done on regional basis rather than national reimbursement”- Professor of Health Economics
6. Lack of behavioural data – smoking characteristics	<ul style="list-style-type: none"> ▶ “Addiction is as little as a chronic disease and can be treated as an acute disease”. “There is no one stop solution to make people quit smoking. People quit smoking for different reasons. There should be a behavioural program to help people quit smoking”- Senior Medical Director ▶ “There are breakthrough therapies in development, Chronos is developing a behavioural platform which looks very promising at this stage”- SVP R&D
7. Regulatory timelines	<ul style="list-style-type: none"> ▶ “Stability studies take 2-3 years”- VP& Commercial Lead, Pharmaceutical company ▶ “FDA at this point is providing lot of requirement for the approval process”- Head R&D
8. HCP awareness and recommendation	<ul style="list-style-type: none"> ▶ “They don't see it as a medical problem”- General Practitioner

Barriers in smoking cessation market (Supporting evidence)

Barriers	Supporting evidence		
	Industry Experts	Investors	Payers
 <p>Low perceived market attractiveness</p>	<ul style="list-style-type: none"> ▶ “Tobacco companies are 100% considered as competitor of pharma companies. Any tobacco company would be familiar with the smoking cessation and even though they are not specific, they are pretty much aware that many smokers are using them in order to give up or reduce smoking. So yes they are not just the competitor but arguably the most important and the growing competitor for pharma companies that are offering smoking cessation solutions”. “In many countries the market is dominated by OTC medicines rather than prescribed ones. Most smokers don’t see themselves as patient and they are not, it’s much more of lifestyle. Most smokers don’t think about going to the doctor when they are quitting smoking, they might not be even aware of what support is available to them”- Scientific and Medical Affairs Consultant ▶ “Industry innovation has been limited to different flavours. No new players are coming out there”- VP & Commercial Lead 	<ul style="list-style-type: none"> ▶ “Smoking is considered as a lifestyle disease and over-time it certainly becomes nicotine addiction, which could be a disease. This not very clear to investors”. “There is lack of funding, as investors don’t consider cessation market as attractive, due to high reliance on people’s will to quit”- Associate, VC ▶ “US market is primarily dominated by OTC channel. The OTC opportunity makes it very difficult to get shelf-space in the drug stores and compete with large franchises”. “The OTC market is quite substantial & significant but it has fallen significantly in the past 4-5 years due to e-cigarettes”- General Partner, Finance company 	<ul style="list-style-type: none"> ▶ “There is also a consensus amongst payers or investors or decision makers that smoking is a lifestyle choice and doesn’t require any intervention if the person really wants to quit” ▶ “In Italy, cigarettes are one of the highest taxed item in the world. This generates a lot of tax for the government. So, there is a conflict of interest for the government - encouraging smoking cessation and losing high tax income on it ▶ “For payers to be interested in any new drug especially a prevention therapy, there needs to be strong and convincing pharmacoeconomics data. Such data is not easily generated and efforts need to be made to make sure market specific nuances are also met when applying for reimbursement” <p>- Professor of Health Economics</p>

Barriers in smoking cessation market (Supporting evidence)

Barriers	Supporting evidence	
	Industry Experts	Investors
 Funding challenges	<ul style="list-style-type: none"> ▶ ““There are lot of different stages and in every stage there is a return on investment and NPV. Different things are considered in different stages. When it comes to initial stages, when you are more into the concept phase, you try to test proof- of- concept principle. Expenses are very low at that point. Things get expensive when you go from exploring to the development side. So at every stage there is a huge amount of financial evaluation done, but NPV is one of the major thing that is looked into”- Head R&D, Pharmaceutical company ▶ “There is a high commercial opportunity owing to the high unmet need in this area. Despite having some products in the market currently, there is still a need for efficacious and safer therapies, as the existing therapies have safety and/or efficacy concerns”- Senior Medical Director ▶ “One solution isn't going to work for all, there is need for multiple strategies/solutions to have a measurable impact on the smoking population as a whole”- Managing Director ▶ “As one solution is not possible for all, there has to be some sought of combination therapy considering the behavioural aspect of the people”- President 	<ul style="list-style-type: none"> ▶ “Investors look markets for which there is a larger unmet need, limited innovation and also previous success in terms of ideas acquisitions and IPOs. Smoking cessation is a hard market to diagnose or to really quantify the numbers for comparing”- Venture Capitalist ▶ “A lot of venture capitalist don't want to play in this area, for a lot of people this could be marketed as a social impact investment. VCs don't want to invest in this area, even how great the opportunity is. If you look anything which is sort of digital device, self-help wellness, Fitbit, etc. they haven't exactly been that successful”- Co-Founder & Partner, Finance company ▶ “Pressure is need to be put on the payers in the US healthcare system. They are not motivated to long term preventative care because in smoking cessation in particular the return on investment is quite short”. “Getting the FDA license is a tough process”- General Partner, Finance company ▶ “From a investor point of view, the behavioural aspect of smoking cessation is the riskiest aspect of this market. Investors are not keen for relying on the ability of the smoker to avoid the urge to smoke. The other parameter is the reimbursement of any new drug. Investors like markets where reimbursement is usually either by national insurance or private insurance”- Associate, VC

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