



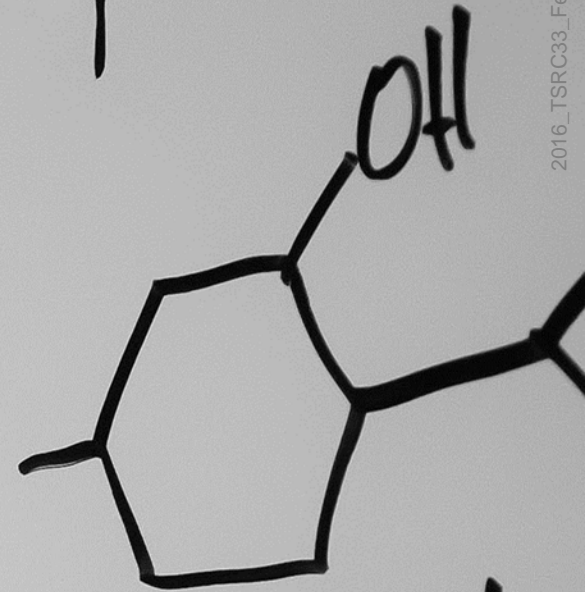
BRITISH AMERICAN  
TOBACCO

LOS ANGELES  
CLINICAL TRIALS

Main Components  
Electronic Cigarette



Nicotine



Menthol

## Nicotine delivery from e-cigarettes part I: study designs for two pharmacokinetic studies.

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PG  
Propylene Glycol

Propylene Glycol

# Content

## Part I

- E-cigarettes and public health
- A brief history of e-cigarettes
- Introduction to nicotine pharmacokinetic (PK) studies
- Study design for two e-cigarette nicotine PK studies
  - Belfast, U.K.
  - Burbank, CA, U.S.A.

## Part II

- Data from U.K. and U.S.A. nicotine PK studies
- Discussion
  - What do our data tell us about nicotine delivery?
  - How can our data inform future study design?
  - Can we do it differently?

# Why might e-cigarettes provide public health benefit?



Professor Michael Russell brought recognition that cigarette smoking is a classic drug dependence behaviour, underpinned by nicotine addiction

People smoke for nicotine but they die from the tar.

*British Medical Journal*, 1976, **1**, 1430-1433

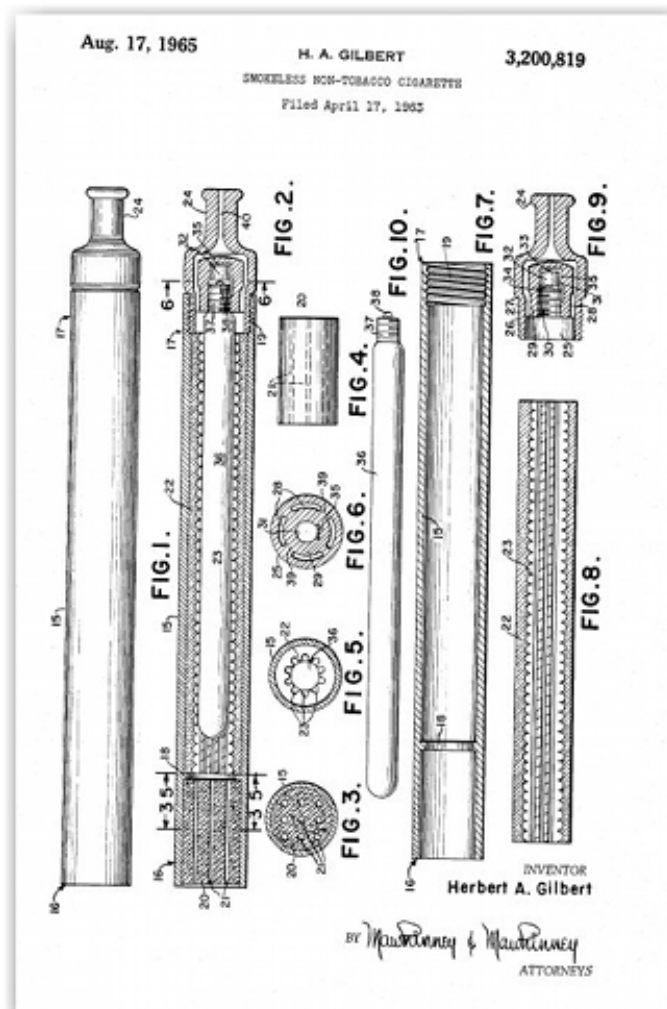


ROYAL COLLEGE  
of PHYSICIANS

“...demonstrate that smokers smoke predominantly for nicotine, that nicotine itself is not especially hazardous, and that if nicotine could be provided in a form that is acceptable and effective as a cigarette substitute, millions of lives could be saved” (2007).

“...the RCP believes that e-cigarettes could lead to significant falls in the prevalence of smoking in the UK, prevent many deaths and episodes of serious illness....” (2014).

# A brief history of e-cigarettes



- First developed in the mid-1960's
- This was a 'smokeless non-tobacco cigarette' which allowed the user to inhale a flavoured vapor
- Proposed to be a useful drug delivery device

# A brief history of e-cigarettes

## Smokeless cigs: 'they satisfy'

**SAN ANTONIO**—Yet another way to help presumed nicotine addicts kick the habit may be a paperless, tobaccoless nicotine "cigarette" that looks just like the usual kind, but doesn't burn. Inhaling through it—a process internist **Norman L. Jacobson** here calls vaping—gives would-be ex-smokers the satisfaction they need without requiring them to breathe carbon monoxide and tar, claims Dr. Jacobson. He's not yet saying how it's made.

Each toke reportedly delivers about 50 µg of nicotine, about half the amount in a conventional puff. Each fake cigarette can be used all day.

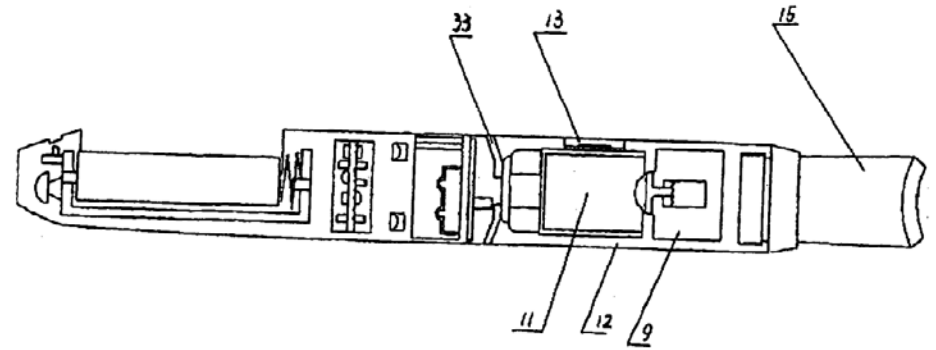
"We have shown—I believe for the first time—that nicotine vapor can be inhaled easily," Dr. Jacobson says. Some patients' nicotine blood levels—and urine levels of the metabolite cotinine—were comparable with smokers'. Others reported satisfaction at levels lower than they were used to.

And with "forced" vaping, faintness, hiccups, and nausea occurred at lower blood levels than with forced smoking, convincing Dr. Jacobson that something in tobacco smoke inhibits nicotine's effects. He doesn't know what the inhibitor might be, but he thinks its existence is implicit in the puzzling lack of dose-effect correlations found in Dr. Russell's nicotine-chewing-gum studies (see story above). Apart from the forced-vaping experiment, Dr. Jacobson says there have been no side effects.

Eight smokers have used the noncombustible cigarette invented by former computer entrepreneur **J. Phillip Ray**. All either cut down or stopped smoking for up to two years. Experienced vapers seem able to titrate their nicotine dosage just as smokers do, Dr. Jacobson says. ■

- Nicotine-containing non-combustible 'Favor' cigarette developed in the late-1970's
- First use of the term 'vaping'

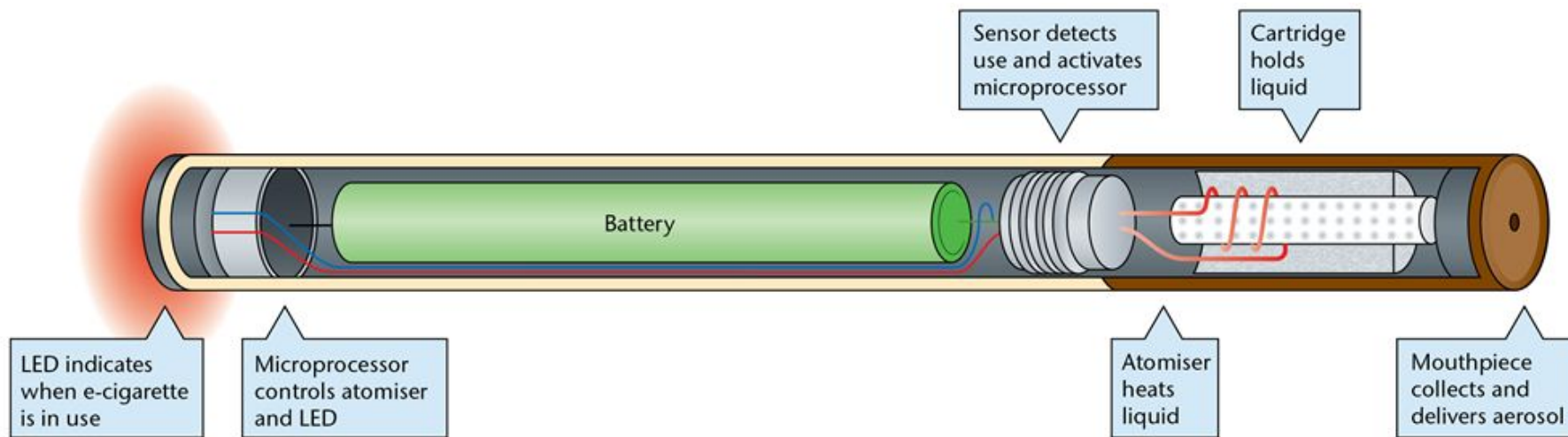
# A brief history of e-cigarettes



- Hon Lik attributed as the inventor of the ‘modern’ e-cigarette in 2003
- Large device which resembled the early ‘cig-a-like’ e-cigarettes we are now familiar with



# What's inside an e-cigarette?

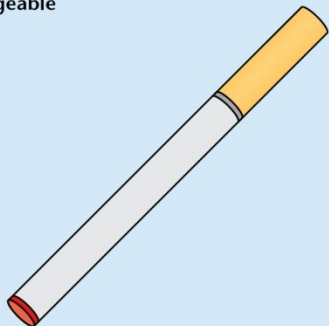


# E-cigarette evolution in the last half-decade

## Cig-a-like (sticks)

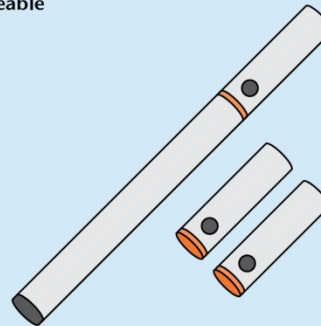
### Disposable

Not rechargeable



### Cartomisers

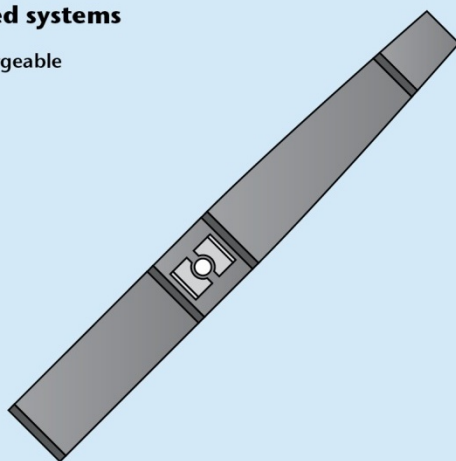
Rechargeable



## Modular (tank systems)

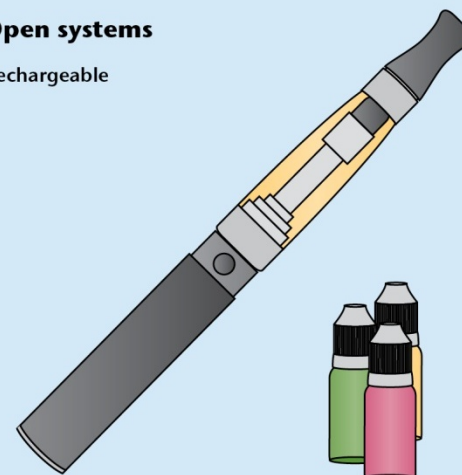
### Closed systems

Rechargeable



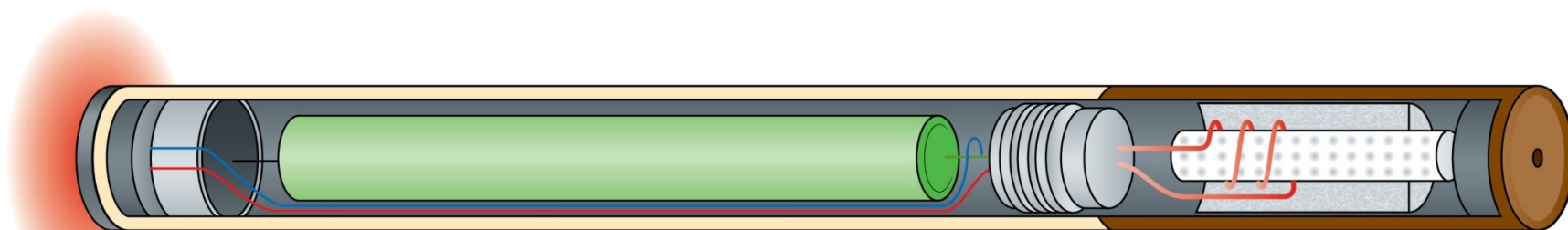
### Open systems

Rechargeable





# What does an e-cigarette contain?



**Typical constituent levels in e-liquid:**

- Nicotine 2-5%
- Glycerol 20%
- Propylene glycol 70%
- Water 5%
- Flavourings <0.5%

# Introduction to nicotine PK studies

Why should we do them?



**Royal College  
of Physicians**

**Nicotine without smoke**  
Tobacco harm reduction

- > Nicotine regulatory approaches should therefore be designed to encourage as many smokers as possible to either quit all nicotine use, or switch completely from smoking to an alternative source of nicotine.
- > Products are regulated to ensure that they are safe and fit for purpose. Regulation of e-cigarettes and other similar products should therefore aim to minimise potential exposure to harmful vapour constituents, ensure that those that deliver nicotine do so in doses that smokers find satisfying, and encourage substitution for smoked tobacco.

# Introduction to nicotine PK studies

Why should we do them?

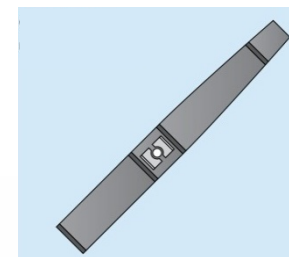
- Understanding our products
  - Product development
  - Efficacy measurement
- Understanding consumer behaviour
- Regulatory engagement/submissions

# BAT nicotine PK studies – study #1

- “A study in healthy smokers to determine the delivery of nicotine and satisfaction/craving relief gained from an e-cigarette containing different solutions (e-liquids)”
- ISRCTN74070762; REC-approved



- Study designed to understand nicotine delivery in smokers using rechargeable e-cigarettes



# BAT PK study #1 - design



- Randomised, controlled clinical study in 24 healthy (high tar) smokers
- Subjects smoked a cigarette, and then used Vype vPro ePens with 2% nicotine solutions after a 2-day familiarisation period
- Measured blood nicotine, heart rate, subjective effects (urge to smoke, satisfaction, MPSS)
- 22 subjects completed all study visits

## BAT PK study #2

- “Pharmacokinetic Study Comparing Nicotine Delivery From E-cigarettes and a Conventional Cigarette in Healthy Subjects”
- ClinicalTrials.gov Identifier NCT02474849; IRB approved



LOS ANGELES CLINICAL TRIALS

- Study designed to understand nicotine delivery in **vapers** using rechargeable e-cigarettes and in more real-world conditions

# BAT PK study #2 - design



Study #1	Study #2
24 smokers of high-tar cigarettes	18 vapers who smoke occasionally
Northern Ireland	USA
Defined (30 second puff intervals for 5 minutes)	<i>Ad libitum</i> puffing over 5 minutes
10 puffs each	Number of puffs decided by subjects
90 minute monitoring period (includes 60min <i>ad libitum</i> use)	60 minute monitoring period (no further product use)
Cigarette comparator (typical market brand)	Cigarette and e-cigarette comparators

# Study Products



Study	Form	Product	Liquid nicotine content	Nicotine yield	Other ingredients
1	Cigarette	JPS Blue	NA	1.0 mg/cig	NA
	Closed modular e-cig	Vype vPro ePen	1.86% w/w	0.6 mg/puff	Glycerol, PG, water, 0.3MEq organic acid, tobacco flavour
2	Cigarette	Marlboro UL	NA	0.5 mg/cig	NA
	Closed modular e-cig	Vype vPro ePen	1.86% w/w	0.6 mg/puff	Glycerol, PG, water, 0.3MEq organic acid, tobacco flavour
	First-generation e-cig	Nicolites;	1.33% w/w	ND	Glycerol, PG, water, flavourings



# BAT PK studies – common concepts

- Pharma standard studies in healthy adult subjects
  - Proven smokers/vapers
  - ICH-GCP
  - REC/IRB approved; subjects' informed consent obtained
  - Fully monitored and audited
  - Registered on public databases
- Overnight abstinence from nicotine/tobacco products (exCO)
- Product familiarisation period (2-7 days)
- Exclusion - drugs of abuse, pregnancy, serology

SCIENCE

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