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Adapting the CDISC Data Models to Support Regulatory Submissions for Modified Risk Tobacco Products

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Tobacco Research

PMI and Tobacco Harm Reduction

Estimated that more than one billion people will continue to smoke in the foreseeable future

- Policy of tobacco harm reduction to complement the other major strategies for reducing smoking-related harm (prevention and cessation).

- PMI's goal is to develop a portfolio of novel products significantly less harmful than cigarette smoke.

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The Science at PMI : Reduced-Risk Products

Reduced-Risk Products ("RRPs") is the term the company uses to refer to products with the potential to reduce individual risk and population harm in comparison to smoking cigarettes. PMI's RRPs are **in various stages of development and commercialization**, and we are conducting **extensive and rigorous scientific studies** to determine whether we can support claims for such products of reduced exposure to harmful and potentially harmful constituents in smoke, and ultimately claims of reduced disease risk, when **compared to smoking cigarettes.**

Before making any such claims, we will **rigorously evaluate the full set of data** from the relevant scientific studies to determine whether they substantiate reduced exposure or risk. Any such claims **may also be subject to government review and** authorization as is the case in the US today.

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The Science at PMI : Reduced-Risk Products

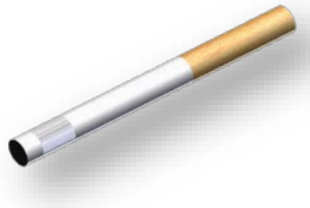
4 product platforms are currently under various stages of development and commercialization :

Heated Tobacco Products

P1

- Heated tobacco
- Main unit & holder
- Specially designed tobacco product

Commercialized



P2

- Heated tobacco
- No device
- Closest to the conventional cigarette

Nicotine Containing Products

P3

- Technology acquired from the Nicorette (NRT patch) inventors
- Chemical reaction of a weak acid with nicotine

P4

- e-Cigarette
- Differentiation through design features, quality and brand building

Commercialized

Product development ongoing

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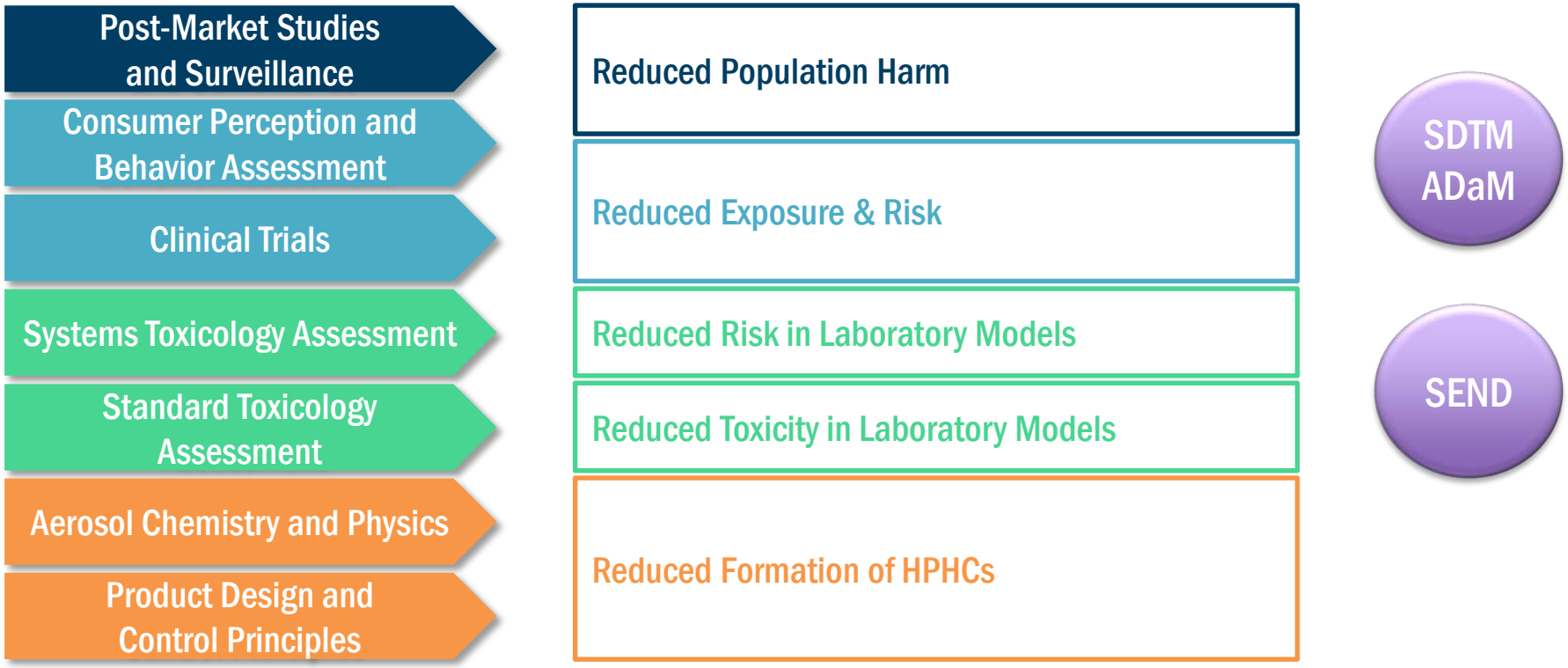
The Science at PMI : Reduced-Risk Products

Developing robust scientific evidence packages based on state-of-the-art science



Any claims may be subject to government review and authorization.

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Current and Future Tobacco Regulation …

- Currently, only US has regulation on Reduced Risk Products

  ➡ Modified Risk Tobacco Product Application (MRTPA)

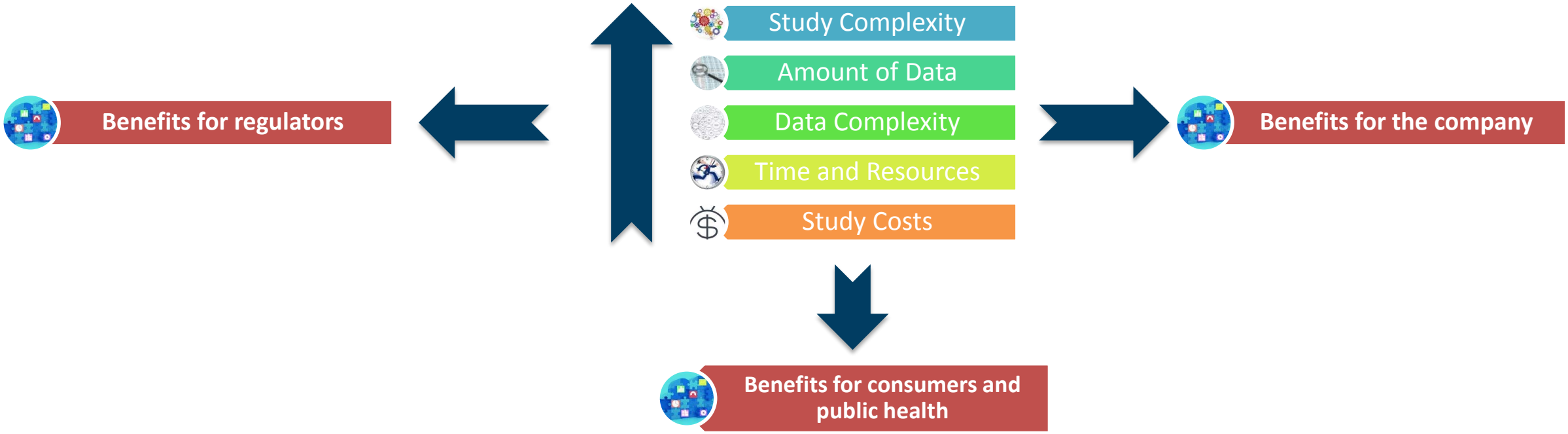
- European Tobacco Product Directive (2014) *
  - Novel tobacco products
    - scientific studies on toxicity, addictiveness and attractiveness of the novel tobacco product
    - studies and market research on the preferences of various consumer groups
  - Electronic cigarette
    - toxicological data regarding the product's ingredients and emissions
    - information on the nicotine doses and uptake when consumed under reasonably conditions

  ➡ Directive to be effective in May 2016

* DIRECTIVE 2014/40/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 3 April 2014 on the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco and related products and repealing Directive 2001/37/EC

Do we need CDISC for tobacco research?

- Required? Not yet
- Benefits?



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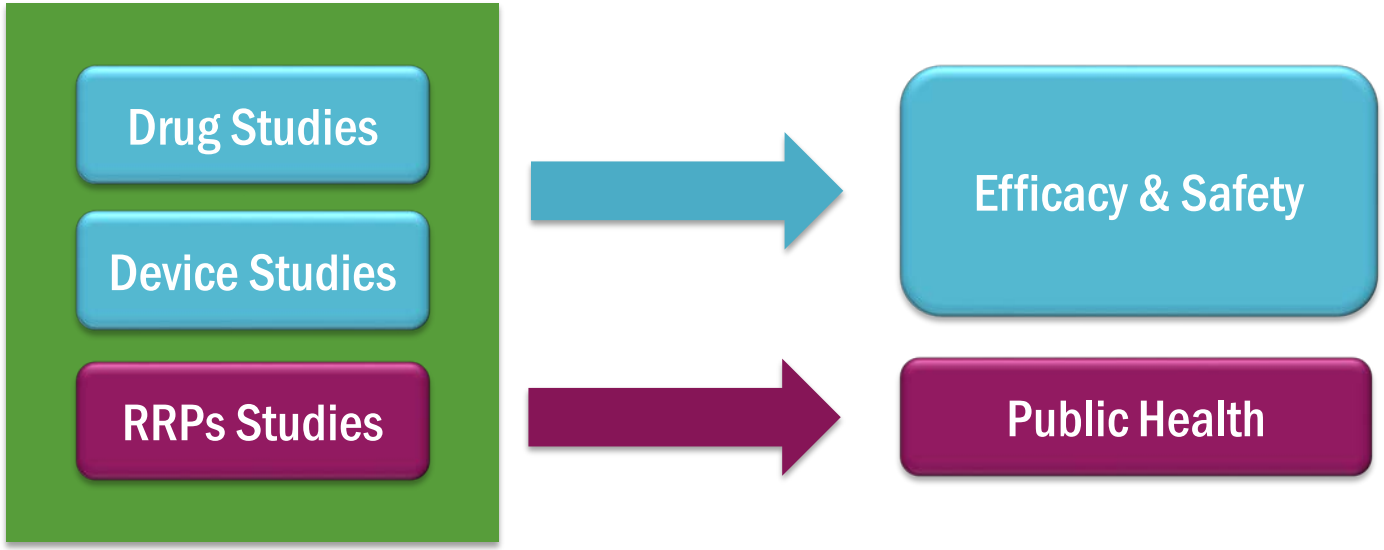
CDISC Standards Adaptation

Can CDISC be applied for tobacco studies?



- Many similarities
- CDISC Data Models are adaptable and expandable for observational studies
- Therapeutic Area Standards

➡ Approach to developing Therapeutic Area Standards could be leveraged to develop Tobacco-Specific Standards

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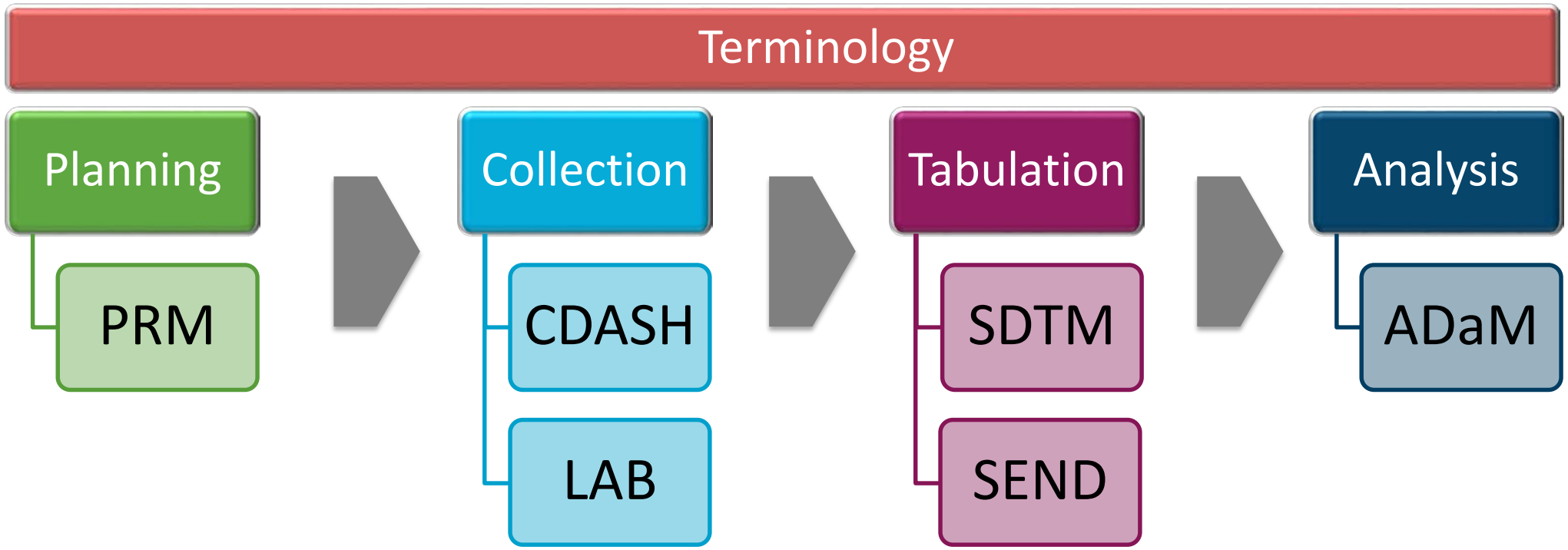
CDISC Standards



Protocol Representation Model (PRM)

Clinical Data Acquisition Standards Harmonization (CDASH)

Laboratory Data Model (LAB)

Study Data Tabulation Model (SDTM)

Standard for Exchange of Nonclinical Data (SEND)

Analysis Data Model (ADaM)

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CDISC Terminology

Terminology

- Origins of the Current CDISC Terminology
  - National Cancer Institute's Enterprise Vocabulary Services (EVS),
  - Extensive disease and device based language

Adapting and Expanding to support tobacco products

- Drug Related Terms → adapted
- Product Use → adapted and expanded
- Measurement Units → expanded
- Questionnaires → standardized (for common ques

DATESTCD : Drug Accountability Test Code

CDISC Terminology	PMI Terminology
Action Taken with Study Treatment	Action Taken with Study Product
ACN	ACP
DRUG WITHDRAWN	PRODUCT USE STOPPED
NOT APPLICABLE	NOT APPLICABLE
UNKNOWN	NONE

CDISC Terminology	PMI Terminology	PMI Lab Test
Unit	Unit	Laboratory Test Code
UNIT	LBSTRESU	LBTESTCD
pg/L	fg/mL	B[a]P
ng/L	pg/mL	NNAL

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SDTM Domains

SDTM

Trial Design
- Trial Arms (TA)
- Trial Disease Assessment (TD)
- Trial Elements (TE)
- Trial Inclusion / Exclusion Criteria (TI)
- Trial Summary (TS)
- Trial Visits (TV)

Relationship Data
- Supplemental Qualifiers (SUPP)
- Related Records (RELREC)

Special Purpose
- Comments (CO)
- Demographics (DM)
- Device Identifiers (DI)
- Device-Subject Relationship (DR)
- Subject Elements (SE)
- Subject Visits (SV)

Findings
- Drug Accountability (DA)
- Death Details (DD)
- ECG Test Results (EG)
- Inclusion / Exclusion Criterion Not Met (IE)
- Immunogenicity Specimen (IS)
- Laboratory Test Results (LB)
- Microbiology Specimen (MB)
- Microscopic Findings (MI)
- Morphology (MO)
- Microbiology Susceptibility Test (MS)
- PK Concentrations (PC)
- PK Parameters (PP)
- Physical Examination (PE)
- Questionnaires (QS)
- Reproductive Findings (RP)
- Disease Response (RS)
- Subject Characteristics (SC)
- Subject Status (SS)
- Tumor Identification (TU)
- Tumor Results (TR)
- Vital Signs (VS)

Events
- Adverse Events (AE)
- Clinical Events (CE)
- Device Event (DE)
- Disposition (DS)
- Device Tracking (DT)
- Protocol Deviations (DV)
- Healthcare Encounters (HO)
- Medical History (MH)

Interventions
- Concomitant Meds (CM)
- Device Exposure (DX)
- Exposure (EX)
- Exposure as Collected (EC)
- Substance Use (SU)
- Procedures (PR)

Findings About
- Findings About (FA)
- Skin Response (SR)

Adaptation – example of EX, DX and SU

SDTM

Study Drug Exposure (EX)

The amount of study drug to which the subject is exposed

Includes study drug delivered via a device

Device Exposure (DX)

The interaction between the subject and the device

Substance Use (SU)

Self-administered substance like tobacco, drugs, alcohol

- Where do we collect tobacco exposure? EX or SU?
- Where do we collect Heated Tobacco and E-cigarette ? EX or DX?
  - Room for interpretation and un-standardization
- Common agreement between all parties involved

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Tobacco-Specific Domains

SDTM

SDTM allows for Sponsor Specific Domains

- Topography (consumption behavior)
  - Puffing topography
- Tobacco Filter Analysis
- Lung Function
  - Lung capacity
  - Gas transfer
  - Lung volume
- Others --

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Conclusions

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- Regulation on Modified Risk Tobacco Product exists in US
- Standardization is beneficial for companies, regulators and consumers
- CDISC provides a solid starting point for tobacco research data standards
- Therapeutic Area Standard process could be used to develop Tobacco Standards
- All stackholders should be involved in the development of Tobacco Standards

Ultimate beneficiary is the consumer and public health

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Thank you for your attention