The Role of Biomarkers in Assessing Individual Health Risks of Tobacco Products

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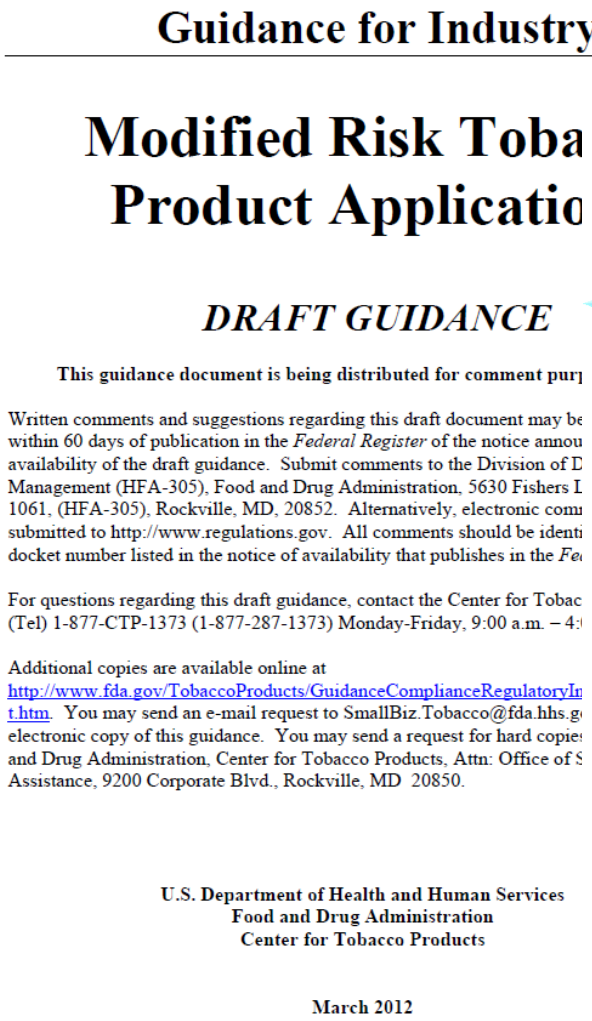
WHO Perspective on Biomarkers

"The WHO Study Group on Tobacco Product Regulation recognizes that effective regulation of tobacco products, particularly products offered as reduced exposure or reduced risk products, can be greatly facilitated by development of validated biomarkers…."

"Measuring changes early in the mechanistic pathway of disease occurrence offers the promise of more rapid characterization of the risks that can result from use of different tobacco products"

Biomarkers in Regulatory Submissions



Guidance for Industry

Modified Risk Toba
Product Applicatio

DRAFT GUIDANCE

This guidance document is being distributed for comment pur

Written comments and suggestions regarding this draft document may be
within 60 days of publication in the *Federal Register* of the notice annou
availability of the draft guidance. Submit comments to the Division of D
Management (HFA-305), Food and Drug Administration, 5630 Fishers L
1061, (HFA-305), Rockville, MD, 20852. Alternatively, electronic com
submitted to http://www.regulations.gov. All comments should be identi
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For questions regarding this draft guidance, contact the Center for Tobac
(Tel) 1-877-CTP-1373 (1-877-287-1373) Monday-Friday, 9:00 a.m. – 4:

Additional copies are available online at
http://www.fda.gov/TobaccoProducts/GuidanceComplianceRegulatoryIn
t.htm. You may send an e-mail request to SmallBiz.Tobacco@fda.hhs.g
electronic copy of this guidance. You may send a request for hard copie
and Drug Administration, Center for Tobacco Products, Attn: Office of S
Assistance, 9200 Corporate Blvd., Rockville, MD 20850.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Tobacco Products

March 2012

"FDA recommends that applicants conduct human studies to assess the full range of the human health risks related to the use of the tobacco product, including exposure to tobacco-related compounds (e.g., biomarkers of exposure) and health outcomes (e.g., disease incidence or mortality)"

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FDA's perspective on Biomarkers in MRTPs

"FDA will always promote science based decision making"
Statement by FDA Commissioner, Scott Gottlieb, M.D. 6/9/2018

"Currently, there is no single biomarker that predicts the risk of disease in people who use tobacco products "

Challenges and Issues with Biomarkers for Smoking Related Diseases

- Smoking related diseases are complex and multi-factorial

Smoking related disease: relative risk and risk factors

Disease	RR *	Estimated Number of Risk Factors**	Estimated % of Cases Due to Smoking**
Lung Cancer	Men – 23.3 Women – 12.7	<5	~90+
COPD	Men – 10.6 Women – 13.1	<5	~80-90
CVD	Men – 2.8 Women – 3.1	>100	~20+

* From CPS-2 as listed in U.S. Department of Health and Human Services. 2004. *The health consequences of smoking. A report of the Surgeon General*. Atlanta, GA, Center for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health

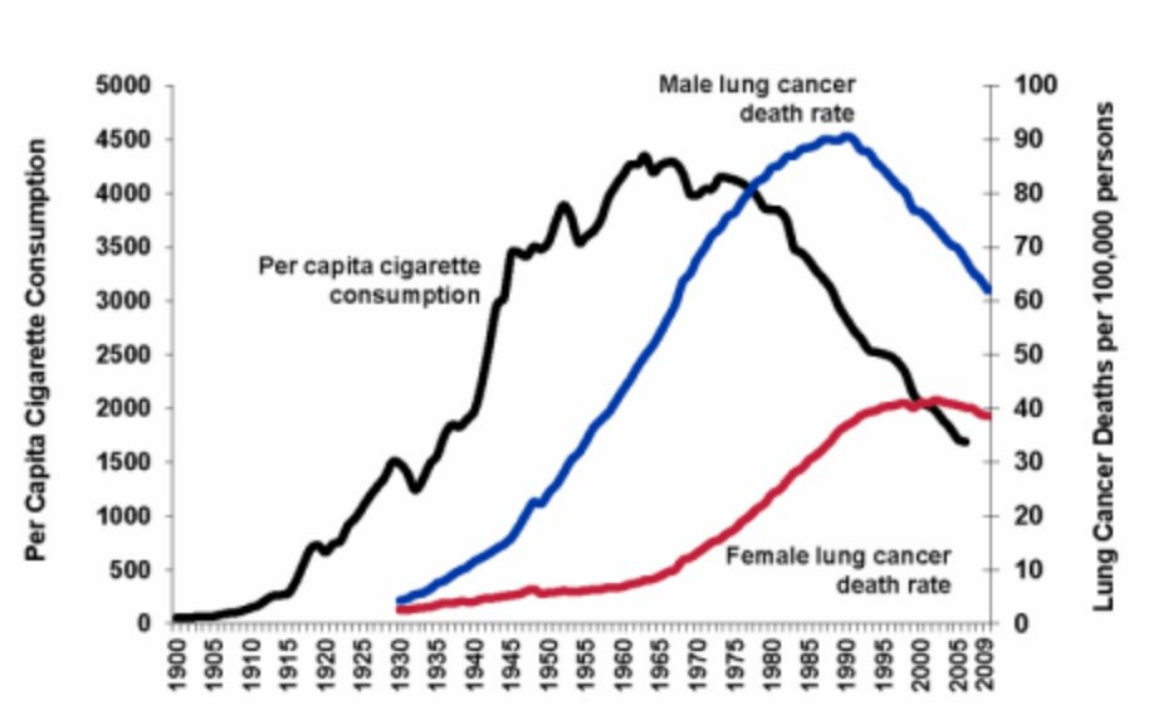
** Approximations from the scientific literature

Challenges and Issues with Biomarkers for Smoking Related Diseases

- Smoking related diseases are complex and multi-factorial
- Significant lag time exists before smokers manifest disease symptoms

Lag Time Between Exposure and Disease

Trends in Cigarette Consumption and Lung Cancer Death Rates* in the US



*Age-adjusted to US population in 2000

Death rates: US Mortality Data, 1960-2009, US Mortality Volumes, 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention. Cigarette Consumption: US Department of Agriculture 1900-2007

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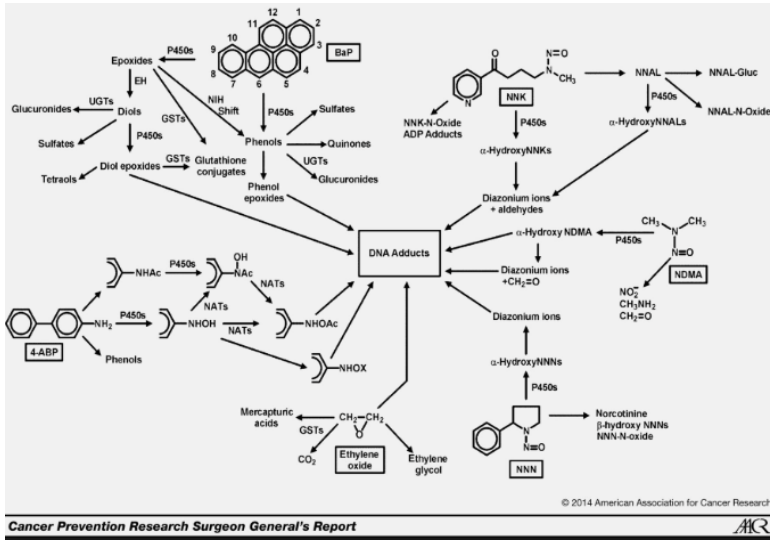
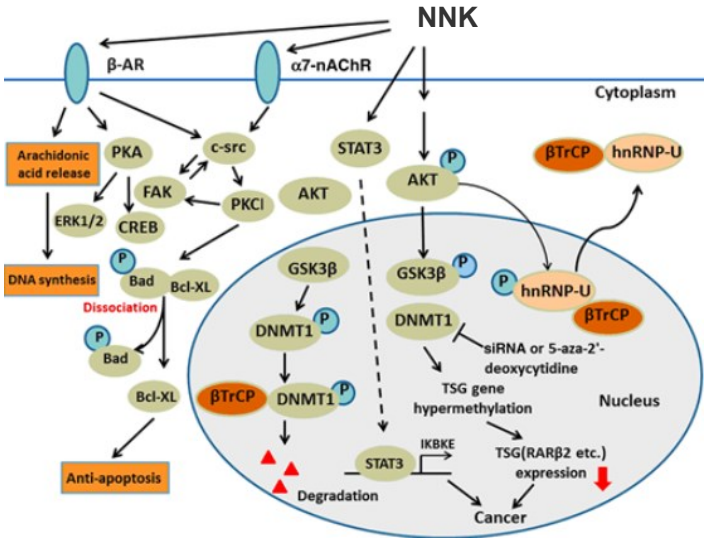
Challenges and Issues with Biomarkers for Smoking Related Diseases

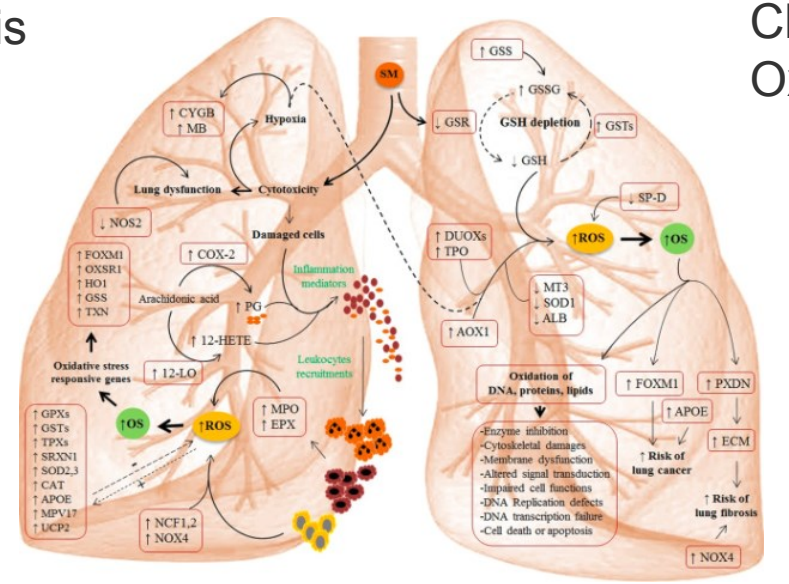
- Smoking related diseases are complex and multi-factorial
- Significant lag time exists before smokers manifest disease symptoms
- Some of the disease mechanisms are yet to be definitively established e.g. although smoking causes lung cancer, various mechanisms are proposed

Proposed mechanisms for lung cancer





Chemical Carcinogenesis



Chronic Inflammation & Oxidative Stress

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Challenges and Issues with Biomarkers for Smoking Related Diseases

- Smoking related diseases are complex and multi-factorial
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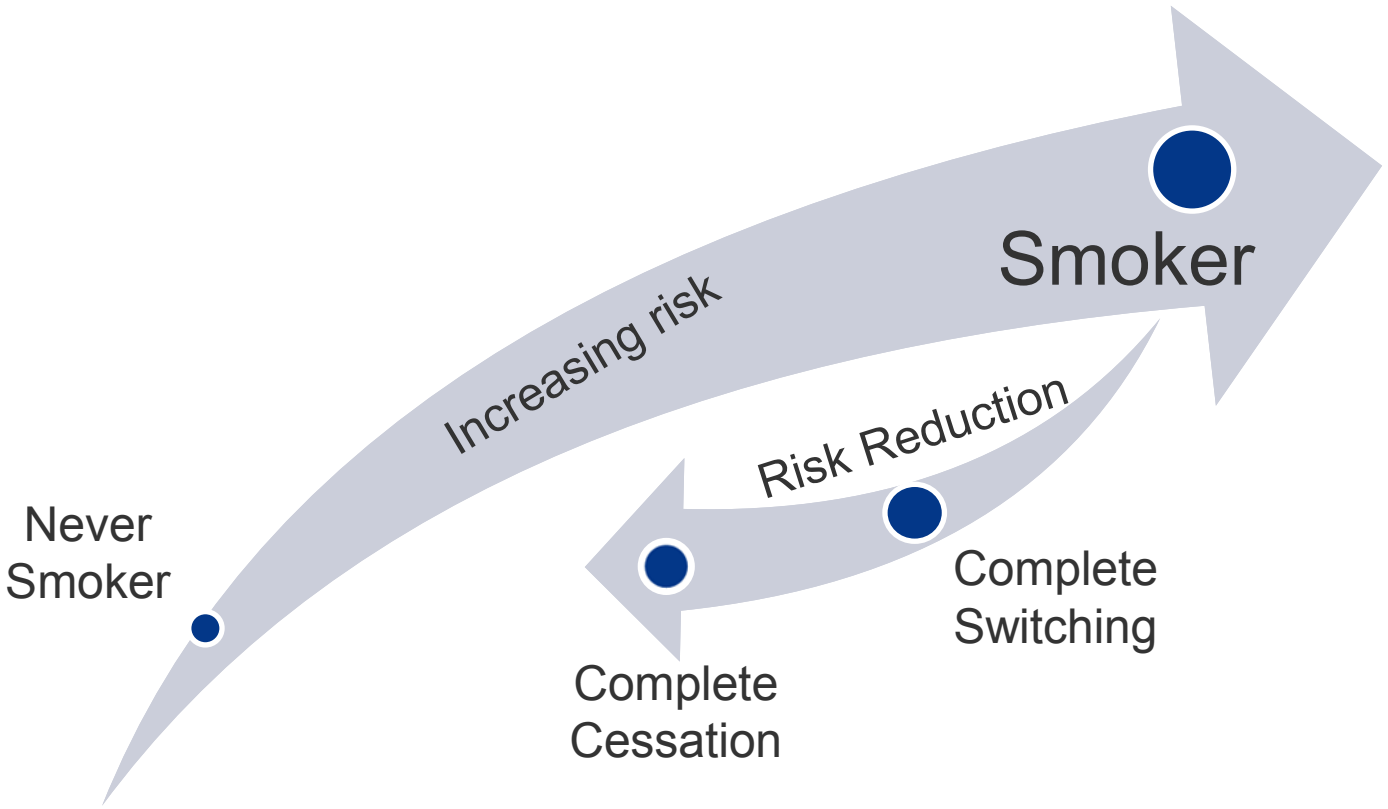
- Some of the disease mechanisms are yet to be definitively established e.g. although smoking causes lung cancer varied mechanisms are proposed
- Relatively small changes in biomarkers of potential harm in studies where “healthy smokers” completely switch to a new product

Risk Reduction Continuum



Risk reduction depends on smoking history and time since quitting

Challenges and Issues with Biomarkers for Smoking Related Diseases

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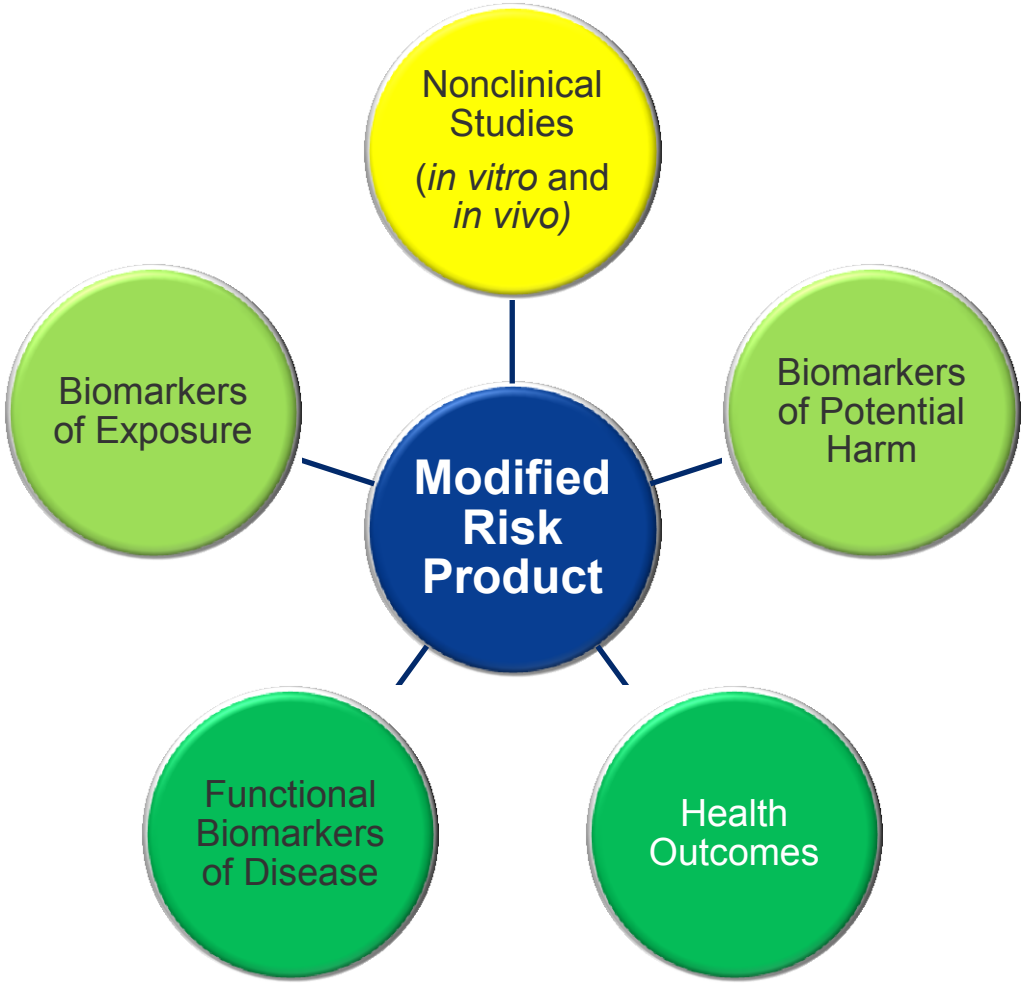
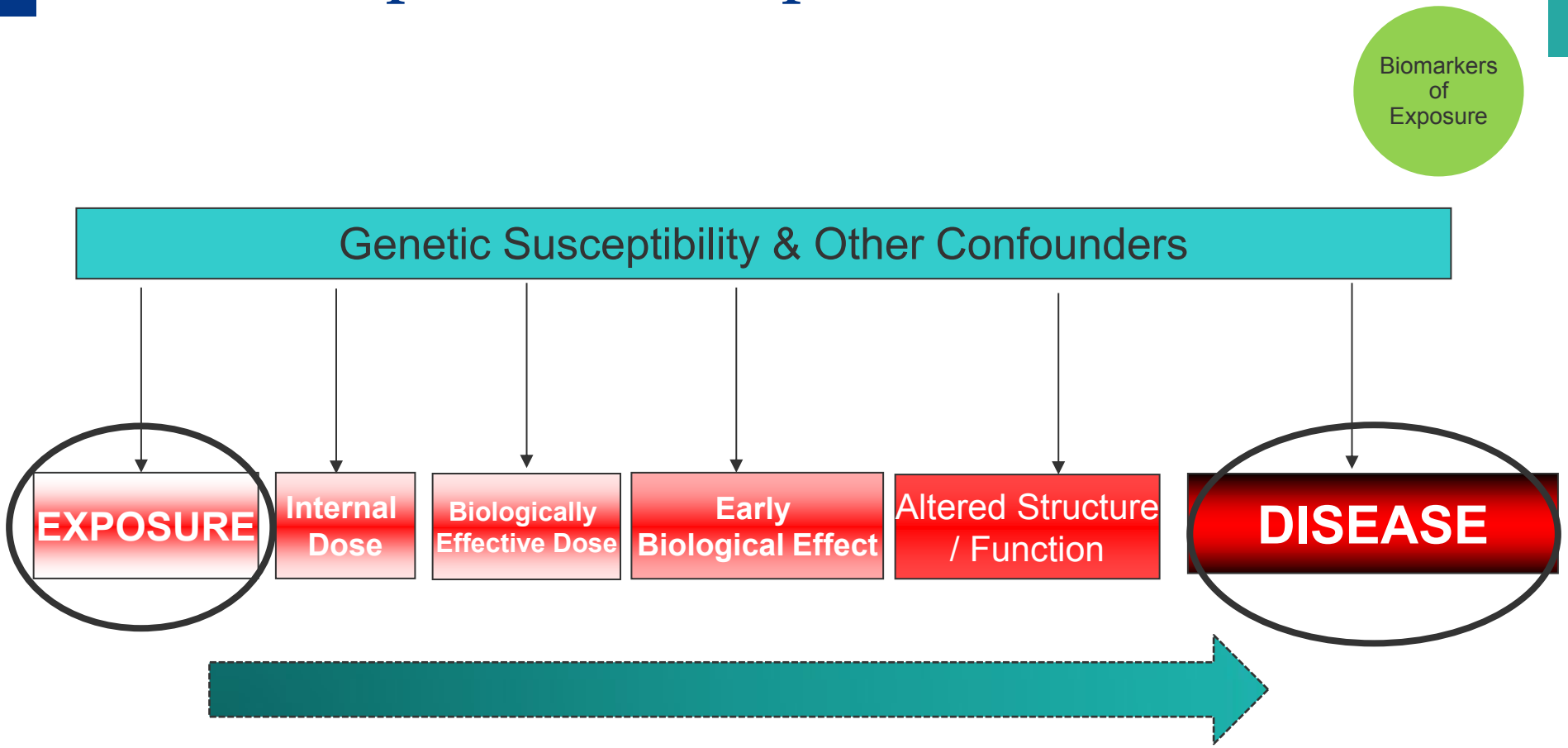
- Relatively small changes in biomarkers of potential harm in studies where “healthy smokers” completely switch to a new product
- Potential confounders – e.g. Compliance to test product, BMI, genetic susceptibility

Potential Solutions – Utilize multiple lines of evidence in absence of epi data



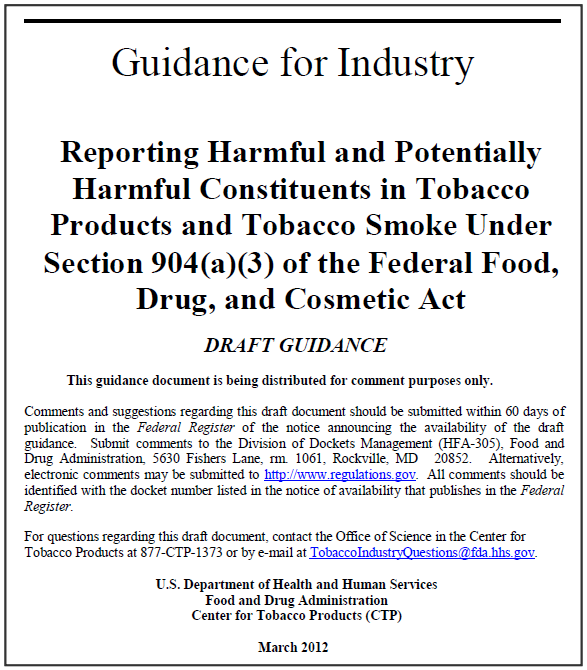
Relationship Between Exposure and Disease



Adapted from: National Research Council. 1987. Biological markers in environmental health research. Environmental Health Perspectives 74:1-191.

Association of HPHC to Smoking Related Diseases

Biomarkers of Exposure



Guidance for Industry

Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Alternatively, electronic comments may be submitted to http://www.regulations.gov. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact the Office of Science in the Center for Tobacco Products at 877-CTP-1373 or by e-mail at TobaccoIndustryQuestions@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Tobacco Products (CTP)

March 2012

CA=Carcinogen
RT=Respiratory Toxicant
CT=Cardiovascular Toxicant
RDT=Reproductive or Developmental Toxicant
AD=Addictive

Abbreviated HPHC List for Cigarette Smoke	Disease Association Stated by FDA
Acetaldehyde	**CA, RT, AD**
Acrolein	**RT, CT**
Acrylonitrile	**CA, RT**
4-Aminobiphenyl	**CA**
1-Aminobiphenyl	**CA**
Ammonia	**RT**
Benzene	**CA, RT, RDT**
Benzo[a]pyrene	**CA**
1,3-Butadiene	**CA, RT, RDT**
Carbon monoxide	**RDT**
Crotonaldehyde	**CA**
Formaldehyde	**CA, RT**
Isoprene	**CA**
Nicotine (total)	**RDT, AD**
NNK	**CA**
NNN	**CA**
Toluene	**RT, RDT**

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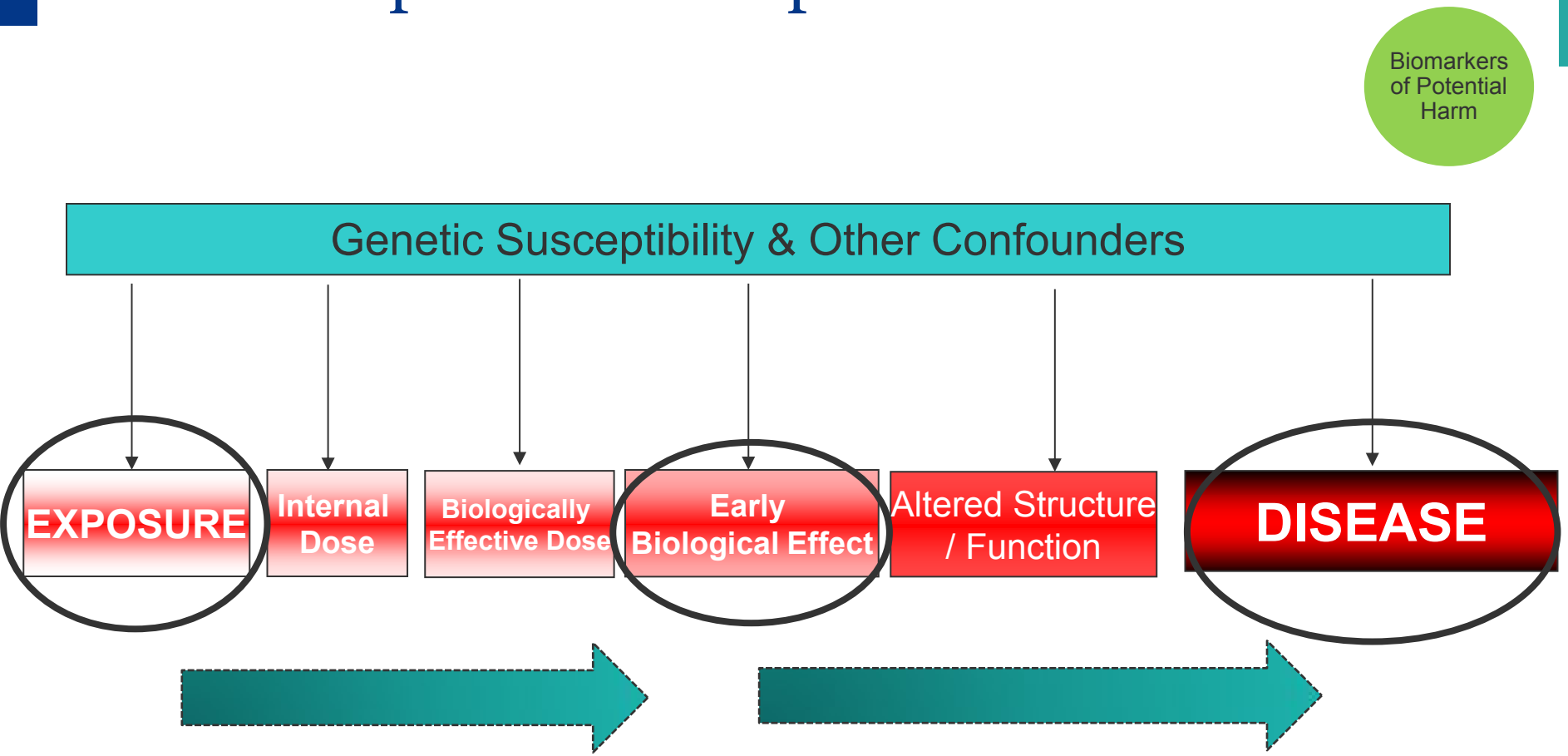
Relationship Between Exposure and Disease



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Early Indicators of Disease Risk

Biomarkers of Potential Harm

- Three of the major diseases related to smoking
  - Lung Cancer
  - Chronic Obstructive Pulmonary Disease (COPD)
  - Cardiovascular Disease (CVD)
- These diseases are complex but some underlying mechanisms are common, e.g.
  - Chronic Inflammation
  - Oxidative Stress

References available on request

Selective List of BOPH

Biomarkers of Potential Harm

Biomarker	Biological Effect	Disease Association
White Blood Cell Count	Inflammation	Cardiovascular disease / Cancer / COPD
Fibrinogen	Inflammation	
HS C-reactive protein	Inflammation/Tissue injury	
von Willebrand factor	Inflammation/Endothelial cell damage	
8-epi-prostaglandin-F_{2a}	Oxidative Stress/Lipid peroxidation	
11-dehydro thromboxane-B_2	Inflammation/Platelet activation	Cardiovascular disease
Triglycerides	Atherosclerosis	
HDL and LDL Cholesterol	Atherosclerosis	
DNA adducts	Pre-neoplastic perturbations	Cancer
Urinary mutagens		

References available on request

White Blood Cells and HDL-C

Biomarkers of Potential Harm

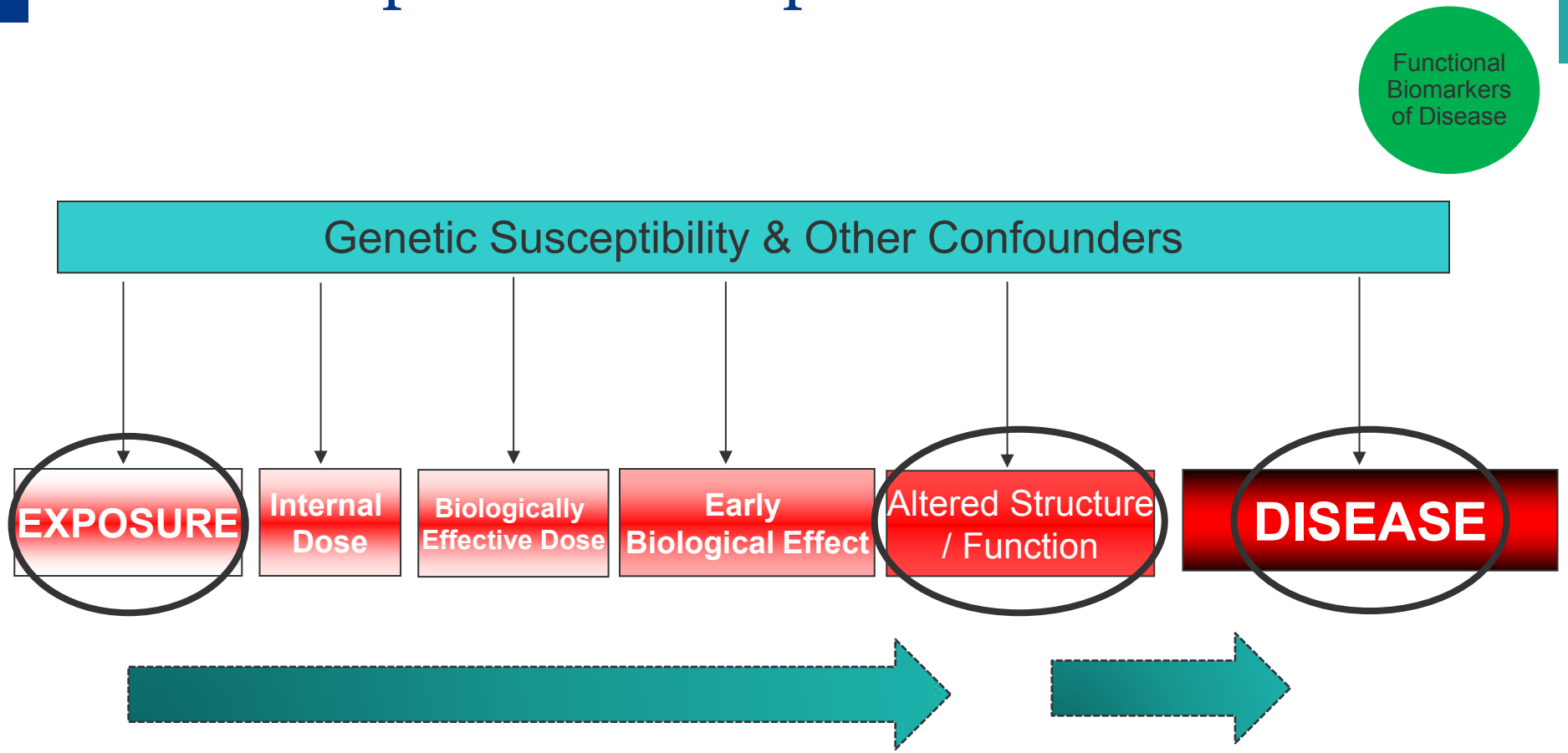
- "A decrease of WBC count of 1,000/μL has been associated with a decrease of 14% in the risk of cardiovascular disease death."

(Brown *et al* J. Clin. Epidemiol. 2001;54:316-22.)

- "Epidemiological studies suggest that for every 2-3% increase in HDL-C (independent of LDL-c) there is a 2-4% reduction in cardiovascular disease events."

(Charland *et al* Curr Med Res Opin. 2010; 26:365-75.)

Relationship Between Exposure and Disease



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Selective List of Functional Biomarkers*

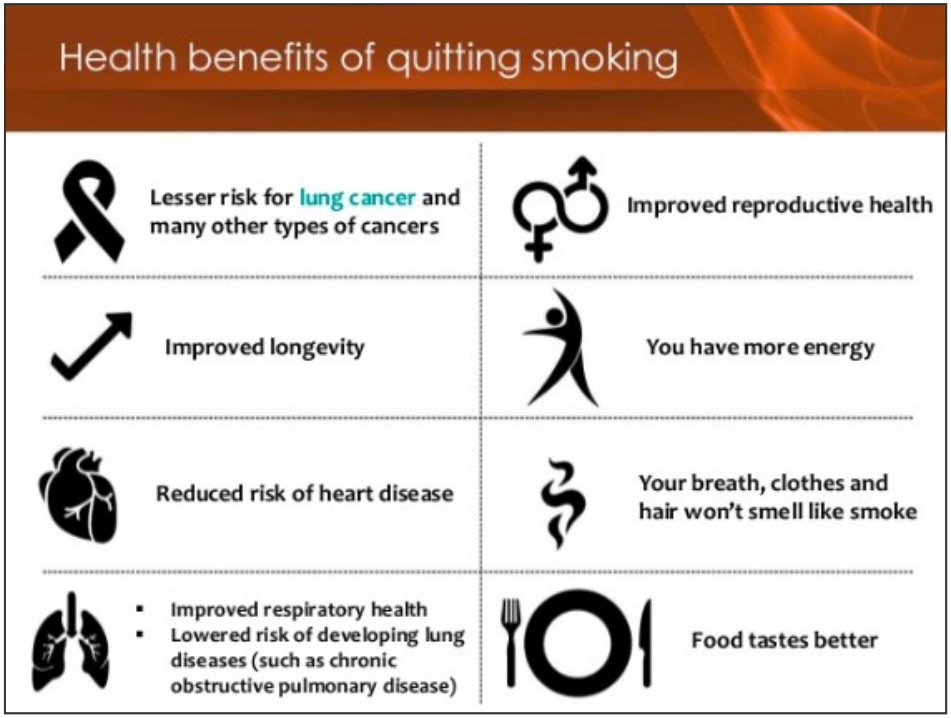
Representative Biomarker	Biological Effect	Disease Association
%FEV_1 / FVC	Pulmonary Function	COPD
Post-bronchodilator FEV_1 or FVC		
$FEF_{25-75\%}$		
FeNO		
Mucociliary Clearance		
Flow-mediated dilation Laser Doppler Flowmetry Venous occlusion plethysmography	Endothelial dysfunction	Cardiovascular disease
Carotid Intima-media Thickness	Atherosclerosis	
Heart Rate Variability		
Cardiopulmonary plethysmography	Atherosclerosis and Pulmonary function	CVD and COPD

* Note: This list consists of representative biomarkers and not intended to be exhaustive

References available on request

Health Outcomes

Health Outcomes



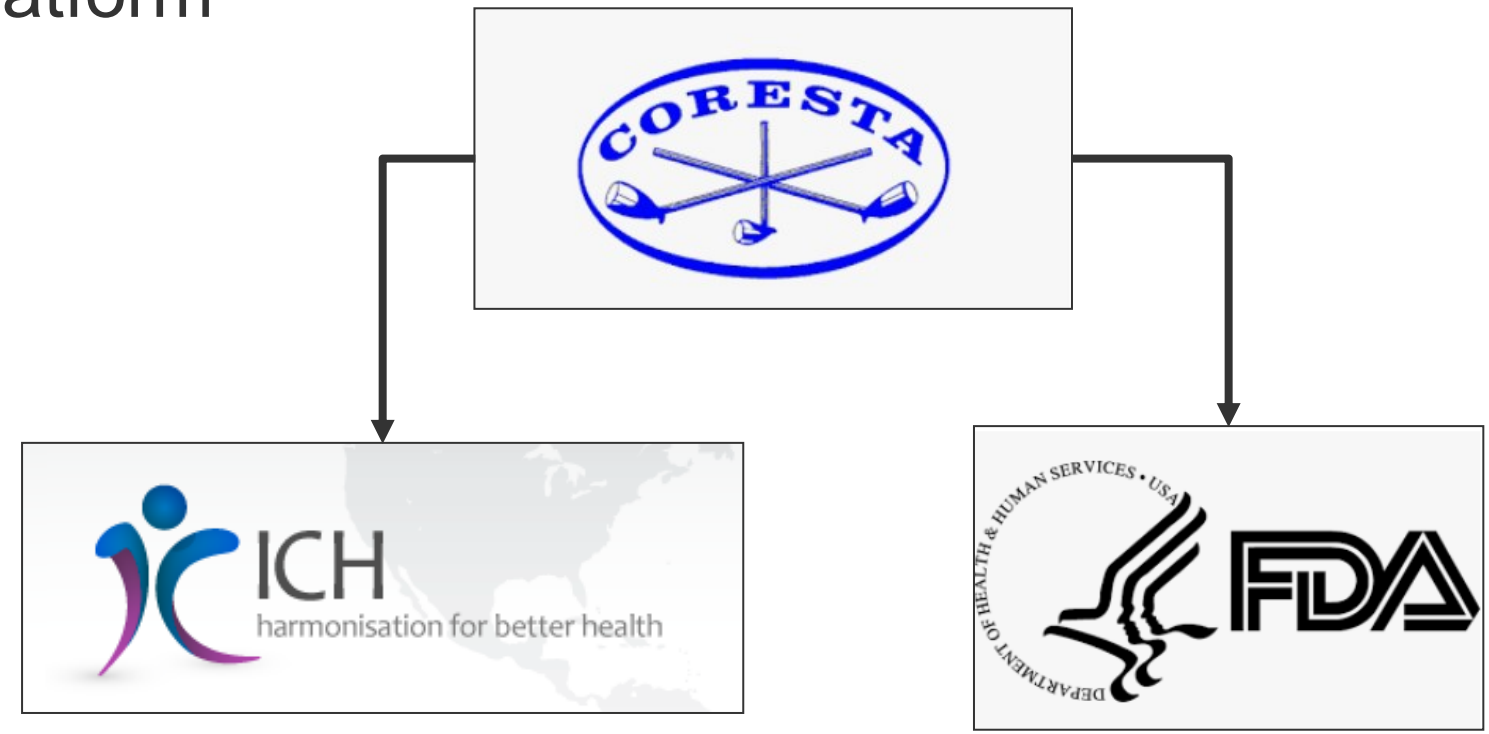
https://www.slideshare.net/IndusHealthPlus/how-quitting-smoking-changes-your-body

- Pre-market Assessments
  - Six-minute walk test
  - Cough Questionnaire
  - Quality of Life Measurements
- Post-market Assessments
  - Real-world evidence (based on product category)

References available on request

Potential solutions

- Engage with ICH and/or FDA to harmonize biomarker qualification using the CORESTA platform



ICH
harmonisation for better health

ICH* is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration.

Harmonisation is achieved through the development of ICH Guidelines via a process of scientific consensus with regulatory and industry experts working side-by-side

*The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Process of Harmonisation

Work Products /

ICH harmonisation activities fall into 4 categories: Formal ICH Procedure, Q&A Procedure, Revision Procedure and Maintenance Procedure, depending on the activity to be undertaken (see below).

New topic for harmonisation of ICH?	Formal ICH Procedure	Concept Paper & Business Plan required
Clarification needed for an existing ICH Guideline?	Q&A Procedure	Concept Paper required (Business Plan may be required in certain cases)
Content of an existing ICH Guideline out of date or no longer valid? / New information to be added to an existing ICH Guideline?	Revision Procedure	Concept Paper required
Change to be made to either Q3C Guideline or M2 Recommendations?	Maintenance Procedure	Proposal/Concept Paper required for Q3C maintenance. No Concept Paper required for M2 Recommendations maintenance

Each harmonisation activity is initiated by a Concept Paper which is a short summary of the proposal. Depending on the category of harmonisation activity a Business Plan may also be required. The Business Plan outlines the costs and benefits of harmonising the topic proposed by the Concept Paper.

E16 Qualification of Genomic Biomarkers

Code	Document Title	Previously coded
E16	**Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure and Format of Qualification Submissions**	

Description : The harmonised tripartite Guideline was finalised under *Step* 4 in August 2010. The Guideline describes recommendations regarding context, structure, and format of regulatory submissions for qualification of genomic biomarkers, as defined in ICH E15.

Implementation : *Step 5*

- **EC, Europe** - Adopted by CHMP, September 2010, issued as EMA/CHMP/ICH/380636/2009
- **MHLW/PMDA, Japan** - Adopted 20 January 2011, PFSB/ELD Notification No. 0120-1/ PFSB/SD Notification No. 0120-1
- **FDA, US** - Published in the Federal Register, 11 August 2011, Vol. 76, No. 155, p. 49773-4
- **Health Canada, Canada** - Implemented 08 Janvier 2016, File #: 15-113833-472
- **Swissmedic, Switzerland** - Refer to the press release on Swissmedic, Switzerland's website

Finalised Guideline: August 2010

E16

Concept Paper

Business Plan

Audio presentation on E16

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FDA Biomarker Qualification Program

Guidance for Industry and FDA Staff

Qualification Process for Drug Development Tools

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2014
Procedural

Biomarker Qualification Program

CDER Biomarker Qualification Program

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SPOTLIGHT Events & Announcements

Web content is updated for consistency with 21st Century Cures Act!

Get Started with your submission:

Resources for Biomarker Requestors

Qualified Biomarkers and Supporting Information

Requestor	Qualified Biomarker (s)	Abbreviated Biomarker Description	Abbreviated COU	Qualification Decision	Supporting Documents
Chronic Obstructive Pulmonary Disease (COPD) Biomarker Qualification Consortium (CBQC)	Fibrinogen	Plasma biomarker as assessed by immunoassay	Prognostic biomarker used with other characteristics to enrich for COPD exacerbations	Qualified 9/14/2016	9/14/2016: FDA Guidance Various Dates: FDA Reviews

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Conclusions

- Scientific evidence from biomarkers can provide relevant information
- Multiple lines of converging evidence should be considered in regulatory decision making for risk reduction. The closer these reductions are to that achieved from smoking cessation the greater the weight of evidence
- CORESTA can play a role in engaging with ICH / FDA towards harmonizing biomarker qualification