

# Opportunities for the use of biomarkers and surrogate endpoints in the EU

*Agence française  
de sécurité sanitaire  
des produits de santé*



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# Surrogates vs Biomarkers (1)



**Biomarkers**: objectively measured characteristics of normal biological processes, pathogenic processes, or pharmacologic response to a therapeutic intervention

- Examples: CRP, HDL, IMT data
- Regulatory Significance: **Not** sufficient for new drug registration because correlation with outcomes has not been firmly established through intervention trials

# Surrogates vs Biomarkers (II)



Surrogate endpoints: biomarkers that substitute for (predict) clinically meaningful endpoints (clinical endpoints directly measure how patients function, feel or survive)

- Examples of surrogates: LDL-C or blood pressure
- Regulatory Significance: Sufficient for new drug registration because correlation with clinical outcomes has been established

# Uses of biomarkers (1)



Biomarker research will facilitate a science-driven approach to drug development

- Can identify mechanism of action of drugs
- Can identify high risk subpopulation (“prognostic factor”)
- Can identify subpopulations more likely to respond (or not respond) to a drug (“effect modifier”)
- Can indicate drugs more likely to have certain adverse effects
- May play a role in dose selection, dosing schedule

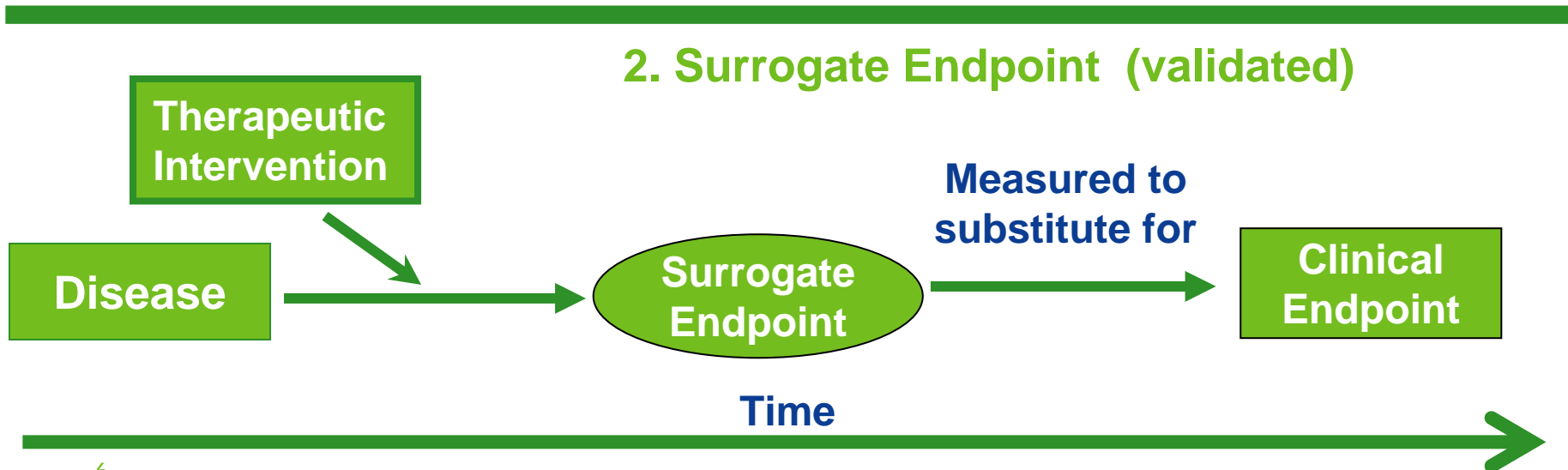
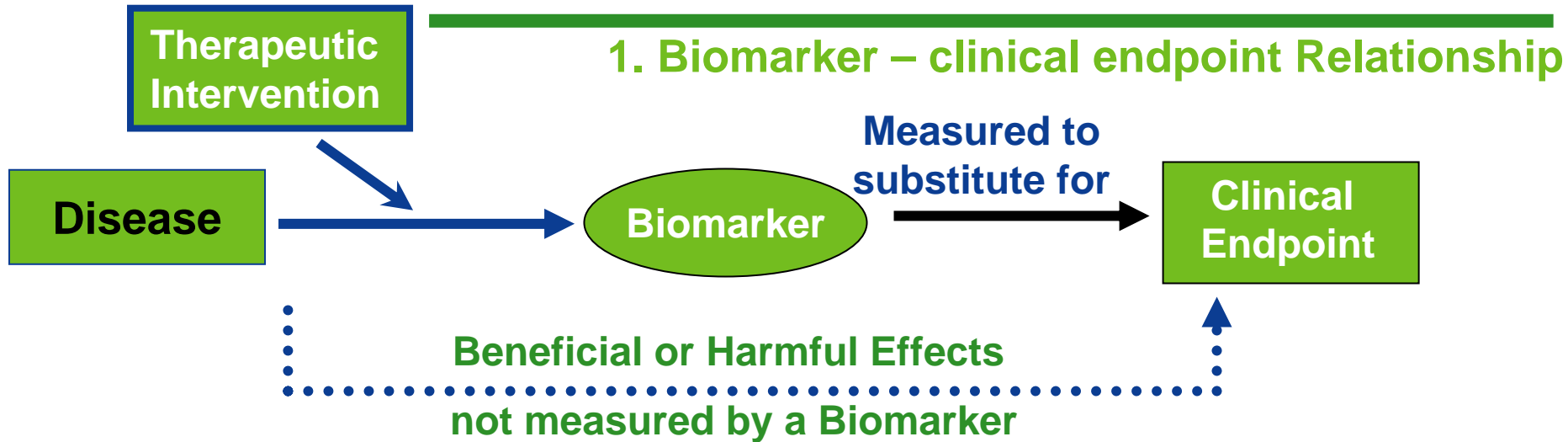
# Uses of biomarkers (II)



Biomarkers may improve the efficiency and reduce the costs of drug development

- Prioritization of candidates
- Earlier Identification of “No Go’s”
- Enriching clinical studies with appreciation that patients may differ in their risk and likelihood of response

# Biomarker, surrogate endpoint & clinical endpoint relationships afssaps



# EMA position on biomarkers for lipid disorders

2005 NfG on Lipid Disorders -CPMP/EWP/3020/03



**LDL-C:** valid surrogate endpoint

**TG, HDL:** currently cannot be sole basis for demonstration of efficacy

## **Vascular damage/Imaging (e.g., IMT)**

- Cannot currently be considered valid surrogates
- Valuable because they bring information on how medications act & clinical protective effect

# Surrogates and biomarkers are included among the recognized components of Metabolic Syndrome



Accepted surrogate endpoint	Biomarker
	Waist circumference
LDL-C	HDL-C, TG
Systolic & diastolic BP	
HbA1c	

# Questions regarding Surrogates



**1. What are the criteria to validate a new surrogate (e.g., HDL or IMT)? One set of criteria, from ICH Guidance E9 (Stat. Princs. Clin. Trials):**

- Biological plausibility
- Epidemiological evidence of correlation with clinical endpoints
- Evidence from clinical trials that drug effect on surrogate corresponds to outcome

Should also assess the degree to which the surrogate captures the net effect of the intervention on the disease (TR Fleming)  
Difficult challenge, would require meta analysis of many RCT's

**2. If a new drug was approved in the EU based on a newly validated surrogate**

Would there be a post-approval commitment for outcome data?

**3. Could industry or industry-agency collaboration expedite validation of surrogates (or biomarkers)?**

# Questions regarding Biomarkers (I)



1. What are potential uses of biomarkers (before they are recognized as surrogates) besides internal validation of drug candidates?

Identification of high risk populations that may be more responsive to a drug therapy (enabling a smaller study)?

**Example:** Troponin T level could identify patients more responsive to antithrombotics (Abciximab or low MW heparin)

2. Related to Q1, could drug efficacy (demonstrated via outcomes or an established surrogate) in a high risk population identified with a biomarker....

- Be used as a basis of new drug approval?
- Be extrapolated to the general population?

# Questions regarding Biomarkers (II)



3. Is there a need for establishing distinct criteria for validating biomarkers (i.e., criteria that are less stringent than those for validating surrogate endpoints)?

**Ex:** Biological plausibility and Epidemiology data without Outcomes data

4. Are there circumstances in which a biomarker might provide sufficient efficacy criteria for new drug approval?

- Situations of high or unmet medical need ?
- As add-on to standard of care for unresponsive patients?

# Conclusion



**Biomarkers can facilitate a science-driven approach to drug development and accelerate it**

- risk probably acceptable due to huge savings in resources

**“Likely surrogate” endpoints may occasionally turn out to be non- predictive of clinical outcome in the long run**

- May have off-target effects that, on balance, lead to no clinical benefit
- A disease may have multiple pathogenetic “pathways” but surrogate assesses only one
- However risk can be minimized for biomarkers used as surrogates by appropriate validation

**Demonstration of a new drug’s efficacy with “likely” surrogate data must eventually be confirmed with hard clinical data, since there is no known surrogate for safety (“conditional approval” in the EU, “accelerated approval” in the US)**