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# Benefit-Harm-Uncertainty Management: Biomarker Challenges and Opportunities in a New Regulatory Oversight Framework

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**Health Canada**

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Canada

# CMOD Meeting Themes Today

**Personalised medicine**

**Disease burden**

**Regulatory oversight**

**Practical challenges**

**Integrating emerging technologies into drug development  
and regulatory landscape**

# OBJECTIVES

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- 1) Suggest HC's proposed regulatory oversight frame:
  - a) shelters contextual drivers (e.g. disease burden) for meaningful regulatory decisions; and
  - b) aligns with personalised medicine trendsby:
  
- 2) outlining the HC proposed regulatory framework for Benefit-Harm-Uncertainty Management
  
- 3) Identify some practical regulatory challenges/ opportunities for biomarkers in this frame that relate to uncertainty management in integrating emerging technologies

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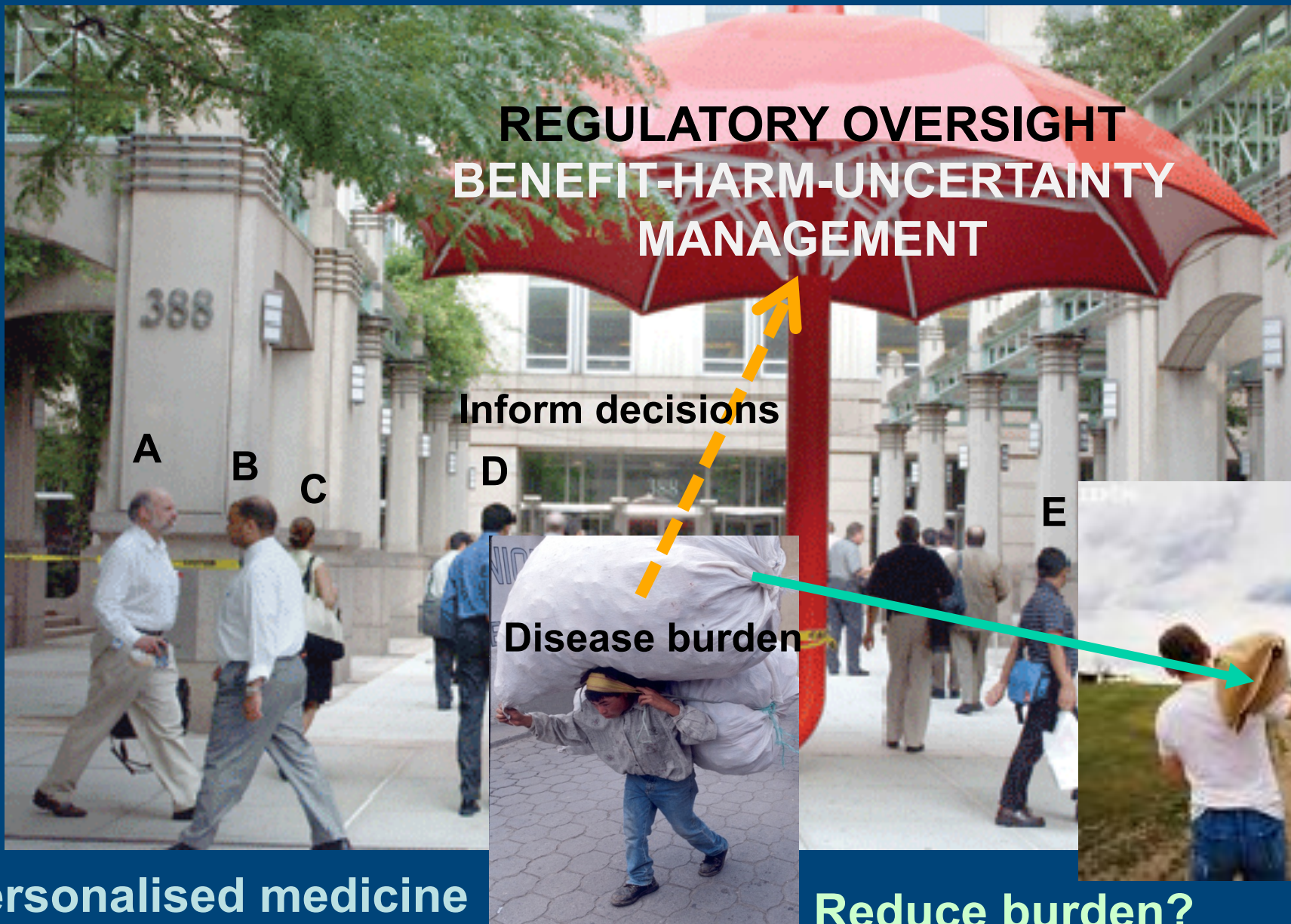
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# Proposal: The Future of Patients' Therapy Needs



# OBJECTIVES

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# What Canadians want from their drug regulator\*:

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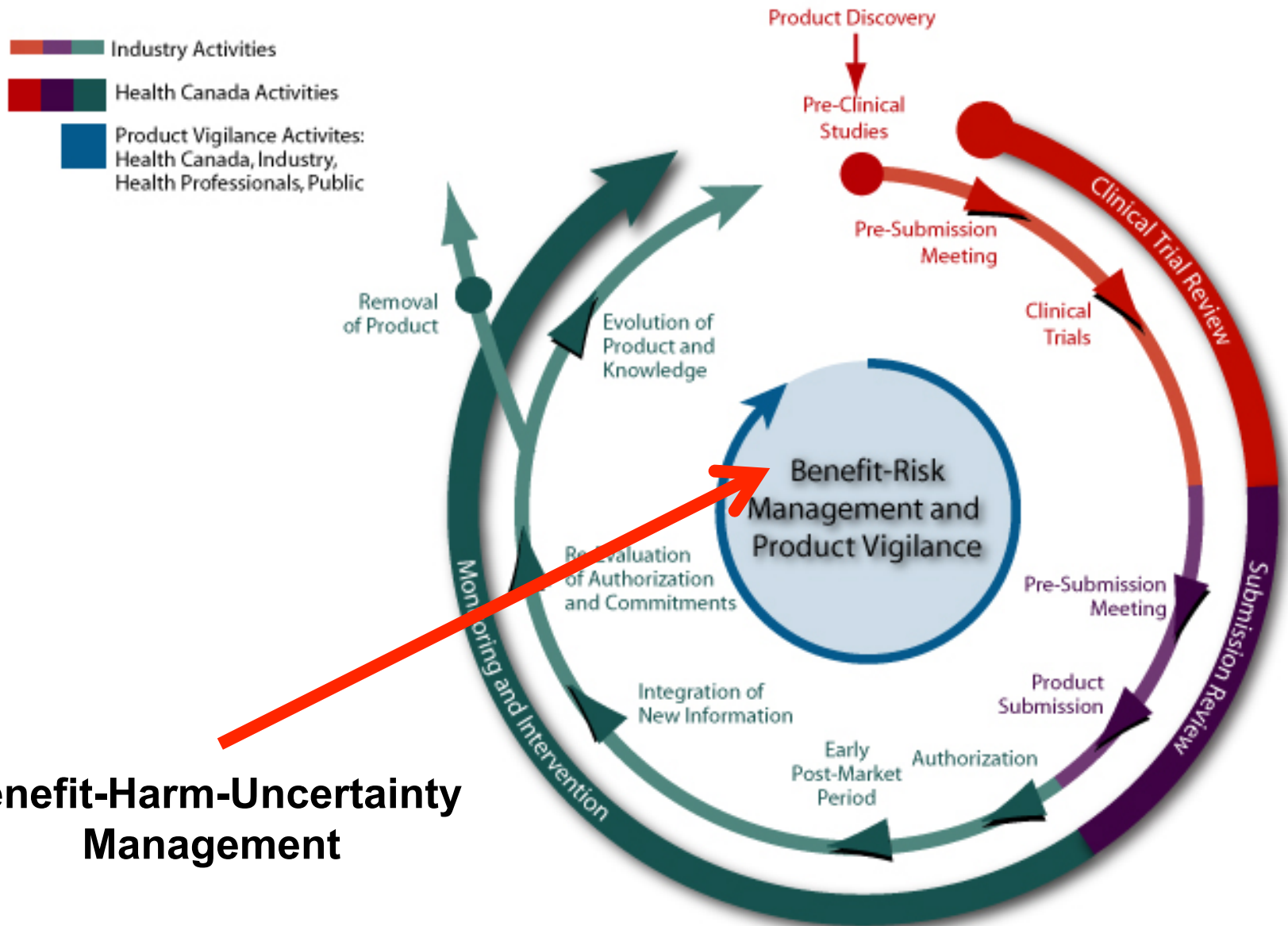
We understand that Canadians want a modernised drug regulatory system that can protect and promote health through measures that:

- can **optimise benefits and minimise risks** in the use of drugs
  - can **optimise the decision-making of end-users** about if, when and how to use drugs
  - can allow for **alignment of regulatory activities with other partners (decision-makers) in healthcare system in Canada**
    - e.g. manufacturers, payers, healthcare practitioners, patients
- **patient-focussed approach to regulatory decision-making that is scientifically, socially relevant and responsible**

\* PLP outreach initiatives (2006-2007)

# → HC's Vision for Modernized Regulatory Oversight

Lifecycle Approach Model



**Benefit-Harm-Uncertainty Management**

# “Benefit-Risk”: What is it?

## A Working Definition

Regulatory science to identify and improve

- evidence,
- technical/value judgements and
- decision processes across life-cycle

to enable better informed, more meaningful, better communicated regulatory decisions so that other healthcare partners - including patients - can make their own best decisions.

# “Benefit-Risk” Trends (2007-2011)

- Regulators (HC, FDA, EMEA), industry, downstream decision-makers now moving towards:
  - benefit-risk management, with explicit acknowledgment of uncertainties, through life-cycle
  - standard qualitative frameworks for structured benefit-risk optimization
    - better understanding of terms and deliberative approaches for analyses, judgements and decision-making processes

**Benefit-Risk Assessment (evidence, judgements)**



**Benefit-Risk Management (regulatory options, decisions)**



**“Benefit-Harm-Uncertainty” Management**

# HC's Vision for Modernized Regulatory Oversight

**Benefit-Harm-Uncertainty Management, providing the regulatory oversight to facilitate:**

**1) Patient-focussed approach:**

- **personalised strategies to optimize benefits, minimize harms and manage uncertainties**

**2) Contextualized approach:**

- **consider, amongst other things, disease burden on patient, health system**

**3) Life-cycle approach:**

- **integrate emerging technologies into drug development and the regulatory landscape to reduce uncertainties**

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➔ **Benefit-Risk Assessment** (evidence, judgements)

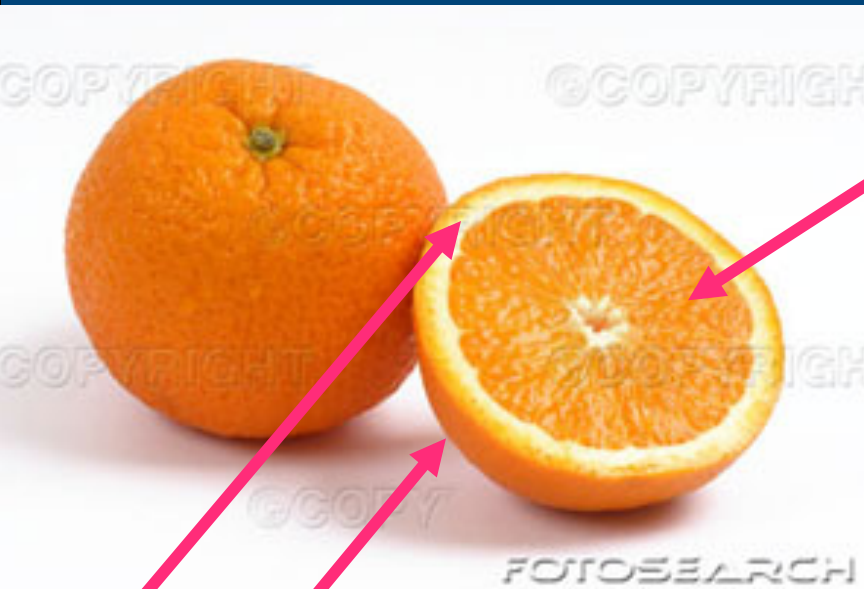


**Benefit-Risk Management** (regulatory options, decisions)



**“Benefit-Harm-Uncertainty” Management**

# Benefit-Risk Assessment: Evidence



## 1°: drug performance (explicit)

- foundational, traditional,  
Safety  
Efficacy  
Quality

## Higher-order: context consideration (less explicit)

2°:

performance framing: situational / health system issues  
e.g. conditions/ **burden of disease**; use; target pops; treatment  
environment; **clin/practical utility**; reg tools available

3°:

beyond drug performance: out-span drug scientific issues  
e.g. access; choice; hope; benefit-risk perceptions; **risk /  
uncertainty tolerance** (trade-offs); ability to accrue SEQ on  
market

# Benefit-Risk Assessment: Judgement:

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## Regulators' "weight of evidence" questions include:

- *have studies been designed to generate meaningful, relevant evidence?*
  - *is the outcome evidence "substantial"?*
  - *is the evidence "robust"?*
  - *is it possible to optimise benefits and minimise risks? If so, how?*
  - *what additional evidence is considered necessary to be collected?*
  - *when is there enough evidence?*
    - *is further evidence necessary from Phase I-III clinical trials or is delaying collection to Phase IV appropriate (if approvable)?*
- There is likely no single right answer
- The answer(s) will depend on context(s).....
- Other benefit-risk considerations can modulate interpretations of core SEQ evidence

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**Benefit-Risk Assessment (evidence, judgements)**



**→ Benefit-Risk Management (regulatory options, decisions)**



**“Benefit-Harm-Uncertainty” Management**

# Benefit-Risk Management: Regulatory Options

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Spectrum of possible regulatory approaches to manage B-H-U

» REJECT OUTRIGHT

» ACCEPT OUTRIGHT



Evidence  
Labelling  
Access route  
Marketing conditions  
Decision Process  
Communications

• usually multi-phased and multiplex:

First: strategies to optimise B-H profile, manage uncertainty

Then: strategies to manage optimised B-H-U profile

# Benefit-Risk Management: Regulatory Decisions

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## ***FICTION (FALSE ASSUMPTIONS)***

**Regulatory decision is passive, binary, singular, e.g.**

- approve / not approve
- safety / efficacy / quality (SEQ) evidence adequate, or not
- treatment A vs treatment B
- single point in time

## ***FACT:***

**Regulatory problem-solving is active, multiplex, iterative i.e.**

- Q: “If / how to optimise B-H profile, manage (reduce, describe) uncertainties across product life-cycle?”
  - requires:
    1. retrograde analysis (submitted, other material)
    2. proactive involvement to optimise drug development path, conditions of use

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**Benefit-Risk Assessment (evidence, judgements)**



**Benefit-Risk Management (regulatory options, decisions)**



**“Benefit-Harm-Uncertainty” Management**



# Uncertainty in benefits, harms

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Several categories of drug problems, exhibiting variable degrees of uncertainty:

- **efficacy:**

- poor
- lacking granularity, unpredictable
- unconfirmed (biomarker, surrogate marker)

- **safety:**

- identified, characterised (include causality assessment)
- identified, poorly characterised
- not identified, but plausible, therefore “potential”
- not identified, unpredicted



↑ uncertainty

# Regulatory Uncertainties (Cont'd)

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## Regulatory questions:

### 1. What is our willingness to extrapolate?

How much do / can we extrapolate?

e.g. non-clinical -> clinical  
biomarker -> surrogate  
surrogate -> clinical endpoint  
efficacy -> effectiveness

### 2. When do we have enough evidence to allow market access?

### 3. Can we reduce uncertainties / communicate irreducible ones?

# Confronting uncertainty in regulatory management:

## More emerging questions:

How does uncertainty in benefits and/or harms(qualitative, quantitative) affect decision-makers' benefit-harm trade-offs?

How much/under what circumstances are patients/physicians willing to wait for more/better information?

What are patients' abilities to make decisions regarding the technical aspects of benefit-harm issues?

(When) is it important for downstream decision makers' values/needs to inform the direction and timing of evidence development?

Why is the hope of future studies /evidence sometimes perceived as an adequate risk management strategy for patients in the present?

# Tolerance for Risk, Uncertainty

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## Complicating regulatory considerations:

- Risk tolerance in context with benefits
  - but “risk” incorporates concept of uncertainty while “benefit” does not
    - skewed assumptions/perceptions about degree/extent of benefit
- Risk tolerance of whom? Based on what perceptions, assumptions? (industry, regulator, payer, HCP, patient)
- Tolerance often reflects judgements of technical, practical, personal/social value
- Risk tolerance ≠ uncertainty tolerance

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# Uncertainty in benefits, harms: roadmap for biomarkers

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Several categories of drug problems, exhibiting variable uncertainty:

- **efficacy:**

- poor
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- unconfirmed (biomarker, surrogate marker)

**Your challenge: validate, confirm benefit (pre-, post-market)**



↑ uncertainty

**Your opportunity: characterise sub-populations for greatest benefit  
.....target population refinement (pre-, post-market)**

**.....benefit optimization**

# Uncertainty in benefits, harms: roadmap for biomarkers

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Several categories of drug problems, exhibiting variable uncertainty:

- **safety:**

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↑ uncertainty

Your opportunity: identify harm-susceptible sub-populations  
.....target population refinement (pre-, post-market)

.....harm minimization

# Uncertainty in benefits, harms: roadmaps for biomarkers

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**General challenge: planning the maps for incremental evidence collection to ensure scientific/social diligence in regulatory decision-making**

**What/how much evidence at which point in regulatory market access decision?**

**Who decides? Level of inclusivity for decisions?**

**If/how to incorporate changes to the maps as technologies mature, evidence unfolds?**

# CONCLUSIONS

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**Regulatory Benefit-Harm-Uncertainty Management approach can support responsible efforts for bio/surrogate marker research and application in drug development and use**

**Challenges as well as opportunities exist for the biomarker community to apply these emerging technologies to benefit patients by reducing uncertainties**

