



# Microbiome et al.: Regulatory pathways for innovation at the food-drug continuum

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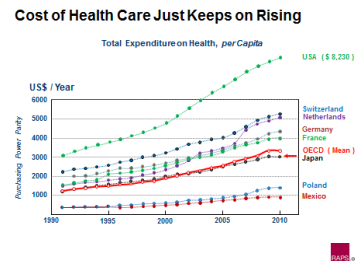
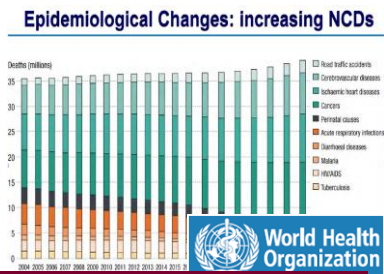
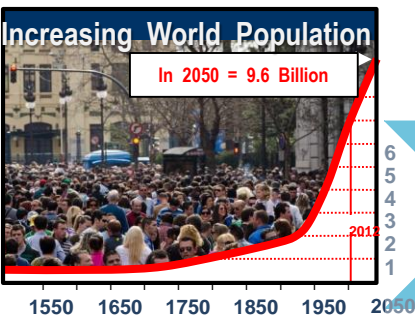
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**OECD Workshop - Microbiome, Diet and Health:  
Assessing Gaps in Science and Innovation**

Brussels, May 30-31, 2016

# Changing HealthCare Paradigms ...

## Address Unmet Need → Opportunities & Challenges



«Pharma Model»

Treatment vs. Prevention

«Nutrition Model»

Case Law  
Pharmaceutical

«Society Model»

Genographics

Blockbuster Market Access

Safety & Claims

NCDs, Lifestyle & Prevention

Precision, Orphan drugs

«omics» (R)evolution Prevention

HealthCare Costs

**Disruptive Innovations**

Gray Zones

3D Printing, IT/Big Data ...

Microbiome, nano, Medical Treatment & Lifestyle inter-connections

«-omics»/NGS/Diagnostics, key role of Genetics, Nutrition, Medical Treatment & Lifestyle inter-connections

→ timely, appropriate, affordable healthcare solutions to patients/society

# HealthCare Systems being dysfunctional by 20?!

- Get vested stakeholders out of silos to find concerted solutions

Stakeholder	Stuck with / in / on / - ...	
Scientists/industry	long-term investments	resources, opportunity costs
Regulators	current framework	evidence / ltd. room for interpretation or switch categories
Policymakers/ Politicians	short-term incentives	vs. long-term vision
HCPs/Society	treatment paradigm	vs. disease prevention (primary, secondary, tertiary)
Payers	current framework	evidence & certainty incentive to pay
Patient/Society	-	not organized or vocal enough, not heard



## Microbiome et al.: Regulatory challenges to innovation at the food-drug continuum

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1. are current regulatory frameworks sufficient?
2. are there gaps to be addressed?
3. is there a need for an international approach?

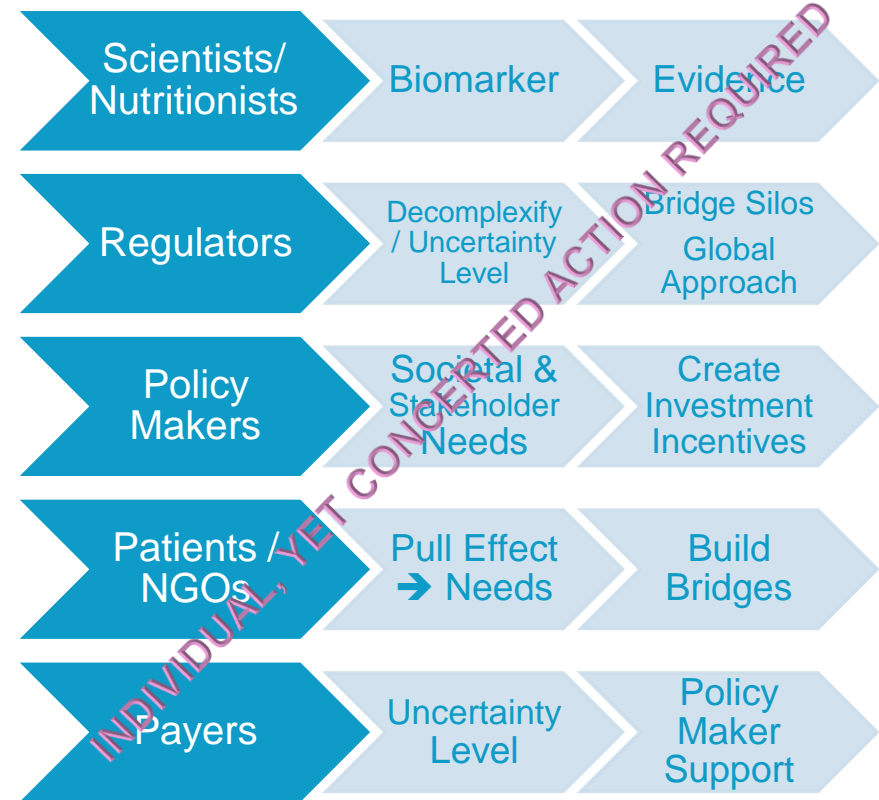
# A HealthCare Framework should benefit Consumers & Patients

## – The Task of a Multistakeholder Engagement

### Regulations & processes to be

- Science based & proportionate
- Predictable - clear, transparent, efficient, include precise timetables
- Enforceable
- Facilitating free movement of goods

Clearly define needs & build on **multi(ple) stakeholder** competencies



# Regulatory is Complex → Simplify it to Incentivize Product Development yet not so Complicated → Product «Intended Use» Counts

All that counts for product compliance  
= meet «intended use»\*  
*i.e. food, drug, medical device*

be «SAFE → for its intended use»  
*[for drugs also RISK-BENEFIT]*

«Not mislead consumer/patient»  
*i.e. CLAIM & related EVIDENCE*  
*[for drug reimbursement also HEALTH ECONOMICS]*

*Drug = «any substance(s) presented as  
... treating or preventing disease»;  
in cases of doubt → it's a Drug!*

**Missing Notion:** «decomplexify» &  
«incentivise» development to get a  
compliant (food) product for «patients»

(1) to the market in a  
«TIMELY» manner; «ROI»  
→ Intellectual Property; «glocal» patient CTs...

(2) Define acceptable level for  
«(UN-)CERTAINTY» of evidence  
→ IT; Phase IV, post-market surveillance ...

(3) Nutrition for Disease Prevention,  
Therapy & Holistic approaches  
(Drug + Nutrition + Services)

\*Wording is key. Notion includes also the nature of  
the effect (e.g. physiologic, pharmacologic, toxic)

# Increase Flexibility between Food & Drug Frames for Innovative Solution-Focused Dietary Disease Management

## Regulatory Design & Gaps

«Intended use» designed @ very start of development:  
‘changing horses midstream?’ →  
~ start from scratch to meet compliance requirements



«Disruptive innovations» in dietary disease management:  
difficulty to meet all category requirements in switching frames

- ❖ Nutrition vs. drug CMC (monographs; analytics; G(X)P; ...); clinical endpoints
- ❖ Nutrient «cocktails» not adapted to [mono-]dose-response drug requirements
- ❖ Health vs. disease dosage continuum: nutritional → pharmacologic → toxic
- ❖ Patho-mechanism of action («DNR») proof for medical food, yet not drugs



# Gut Microbiome – A Great HealthCare Solutions Potential

- yet we need to address basic development issues to fit into current frame

## Base Line Thoughts

- Who are we dealing with, the Patient or Microbiome? a symbiosis?
- What is a «Healthy Microbiome» / dysbiosis? health & disease impact

## Disruptive Science

- Understand mechanism of action, functional equivalence, physiologically relevant endpoints, dynamics of microbiome
- Gut microbiota - a determinant of individual metabolism, e.g. nutritional phenotyping to quantify “DNR”, nutritional needs

## Quality, Safety, Efficacy

- What do we want to regulate? Safety 1st, e.g. free of major pathogens? Manufacturing: large scale; product consistency with live bacteria
- Fiber or probiotic effects on the microbiome, always a nutritional effect?
- Classify «non-gut» related systemic microbiome effects alike?

## Gold Standards, Precedents, Analogies, Learnings?

- Pro-, Pre-, Symbiotics / Antibiotics
- First 1000 days, functional ecology, variability
- The payers' view(s)?



# Example: «Modify\* the Gut Microbiome for the ...



## Biological Drug

- ... treatment, cure, prevention of IBD / ... C.diff. »

## FSMP/Medical Food (tube feeding or ONS)

- ... dietary management of IBD»

## Food Health Claim (EU NHCR Art.14; US)

- ... risk (factor) reduction of IBD» (~«Disease Prevention»)

## Food Health, S/F Claim (EU NHCR Art.13; US S/F)

- ... normal bowel function/increase in faecal bulk»

\* incl. e.g. FMT from healthy to sick individuals



# Medical Nutrition → Can be a de-facto Disease Prevention or Management/Treatment - *Complementing Drugs*

Nutrition as disease-related malnutrition management

Short bowel syndrome, stroke

COPD

Surgical patients

Older patients

**Enteral Nutrition (EN)**  
(i.e. tube feeds and/or ONS) &  
**Parenteral Nutrition (I.V.)**

Health Care Professionals' key role for proper intended use (compliance, safety)

Lifesaving intervention

Increased ventilatory capacity

Less complications

More active, better quality of life, decreased mortality

Induction of remission

Reduced symptoms, catch-up growth

Normal growth and development

Nutrition as disease management

Crohn's disease

Cow's milk allergy

PKU

**US FDA: IND Guidance (2013) - Section VI, Part D ("Foods") → AGA (4/2014) 'negative consequence ... to human food/nutrition research ... field of GE & gut microbiome'**

**ECCO/ESPGHAN (2014)**  
"Consensus Guidelines on pediatric Crohn's medical management: **exclusive enteral nutrition as Induction therapy of 1st choice**"

**De facto nutrition «treatment (prevention) of disease»: yet permitted → «For the dietary management of ...»**

# New Diagnostics require to revisit «Disease Prevention»

«Prevention of Disease = Medicine» !(?) → Diagnostics / «omics (r)evolution creating new gray zones?  
Where does health end, disease start (homeostasis)? What does it mean for early interventions & regulations?

PREVENTION Level	Definition (US NLM - Medical Subject Headings (MeSH)): <b>Methods to ...</b>
<b>Primary</b>	<b>... avoid occurrence of disease.</b> <i>Most population-based health promotion efforts (e.g. vaccination)</i>
<b>Secondary</b>	<b>... diagnose and treat existent disease in early stages</b> before it causes significant morbidity
<b>Tertiary</b>	<b>... reduce negative impact of existent disease</b> by restoring function/disease-related complication

Already Status Quo:

## Nutrition & Disease Prevention

**Disease (Symptom) Prevention:**  
e.g. Cow's Milk Allergy; PKU & other I.E.M.s; Crohn's Disease

**Disease (Risk Factor) Prevention:**  
sterols & CVD (US, EU: few claims approved for foods («DR(F)RCs»))

**Prevention (Disease Consequences)**  
- falls/hip fracture in osteoporosis

## Consequences for Patients & Society?

**Nutrition:** to what extent are

- **Developers** ready to invest into complex nutrition & disease studies, i.e. uncertain success with ltd. **incentives/ ROI** (incl. development costs; access)?
- **Regulators & Payers** ready to accepting limited evidence & related «**uncertainty**»?

# We require Multi-Stakeholder Innovation & Need Based Actions to Revisit HealthCare Regulatory & Policy Framework

## 1. Build Bridges behind common goal

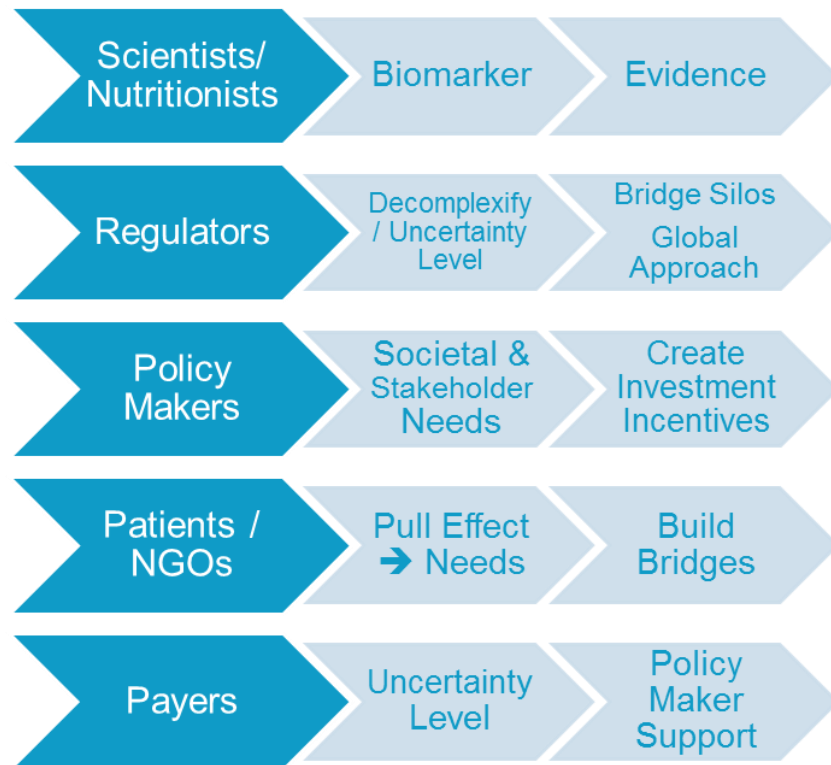
- Foster investment into new/disruptive science, solutions

## 2. Refine Food Drug Continuum

- Disease Prevention (primary, secondary, tertiary)
- Flexibility for nutrients («Less is More»): remove technical development barriers (Quality/Safety, not disease based)

## 3. Medical Food/FSMP Specifics

- Dietary Disease Management & Therapy
- Strengthen «Certainty»: Phase IV evidence vs Pre-market registration; define level of uncertainty
- Strive for Global Convergence; Market Access
- Incentivise Use Pathways: expand existing solutions (DR Malnutrition: EN vs. PN; HEOR; treatment vs. prevention)





The European  
Nutrition for Health Alliance

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## An Example of a Successful Multi-Stakeholder Model in Progress

HOME NEWS MALNUTRITION ABOUT ENHA GOVERNANCE TOPICS EVENTS PUBLICATIONS ACTIVITIES CONTACT

### MEMBERS

- EUROPEAN UNION
- ILC
- hope
- EUGMS
- ESPEN
- EFAD
- mi
- AIM
- PGEU GPU

### ACTIVITIES:

#### The Optimal Nutritional Care for All (ONCA) campaign

Launched in 2014, the Optimal Nutritional Care for All (ONCA) campaign is a multi-stakeholder initiative to facilitate greater screening for risk of disease-related malnutrition/undernutrition and nutritional care implementation across Europe. ENHA is the driving force behind the campaign, and has appointed a Steering Committee from its membership to lead the initiative through strategic guidance and engagement with partners at national level. The Steering Committee is made up of representatives from ESPEN, EUGMS, ESPEN, PCEU, HOPE, EFAD, EGAN and MNI.

#### Why was the campaign launched?

Up to 2010, ENHA worked extensively with members of the European Parliament and other stakeholders to organise political support to get disease-related malnutrition/undernutrition on the European health agenda. At a conference organised in November 2010 together with European Parliament members and the Belgian EU Presidency, one of the conclusions was to translate political support into action in the form of implementation at national level. Since 2011, ENHA developed collaborations with selected countries including Belgium and Ireland to engage in this implementation process. Several countries in Europe are now making progress in various ways towards improving nutritional care. ENHA felt that the time is right to speed up the process to make sure that all patients in Europe receive optimal nutritional care.

#### What are the key steps in the campaign?

The ONCA campaign aims to engage with diverse stakeholders in selected focus countries to:

- Encourage them to form/strengthen a national alliance of stakeholders and develop national nutritional care plans
- Facilitate these stakeholders to benchmark current status in order to develop an aligned view on the current state of play with respect to nutritional care in a given country
- Bring these stakeholders together at Implementation Conferences in Brussels and Berlin.
- **Bring these stakeholders together at a Workshop in Dubrovnik, Croatia on the 17 April 2015**
- Use these events to define and reconfirm the nutritional care strategies for subsequent implementation at national level

#### Which countries are involved?

There are thirteen countries currently involved in the ONCA campaign; Belgium, Czech Republic, Croatia, Denmark, France, Germany, Israel, the Netherlands, Poland, Slovenia, Spain, Turkey and the UK.

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# ONCA

‘Every patient  
who is malnourished or  
at risk of undernutrition  
is systematically screened  
and  
has access to appropriate,  
equitable, high quality  
nutritional care’

# Conclusion – Actions to Enable Innovation

Demographics & Co(nsequences)  
require Microbiome  
as a key ally for an innovative  
disease management

**Disruptive innovations:**  
better understanding  
of interconnections

→ Genetics, Nutrition,  
Medical Treatment  
& Lifestyle

Healthcare regulatory &  
policy frameworks are largely  
sufficient, yet inconsistent or  
unprepared in some cases

Simplify → “Phase IV”  
Market Access

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**Nutrition & Disease**  
Prevention  
(primary, secondary, tertiary)  
Management/Therapy  
Stratification  
Microbiome

Accelerate policy making  
to catalyse incentives &  
investments for developing  
healthcare solutions

Leverage  
**Multistakeholder**  
Expert Venues

Facilitated by  
**Glocal Platforms**  
(WHO/Codex, EU, US ... -  
OECD, RAPS, Mérieux ...)

# Glossary



Acronym	Category
CMC	Chemistry Manufacturing Control
CVD	CardioVascular Disease
DNR	Distinctive Nutritional Requirements
DR(F)R Claim	Disease Risk (Factor) Reduction Claim
G(X)P	Short for GMP, GCP, GLP, i.e. Good Manufacturing, Clinical, Laboratory Practices
HEOR	Health Economics Outcomes Research
S/F Claims	Structure Function Claims (USA)