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

Manfred Ruthsatz

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

Changing Healthcare Paradigms...

Address Unmet Need ➔ Opportunities & Challenges

Disruptive Innovations

- Better understanding key role of Genomics, Nutrition, etc.
- 3D Printing, IT/Big Data, etc.

NCDs, Lifestyle & Prevention

HealthCare Costs

- Precision, Orphan drugs
- (R)evolution Prevention

«Society Model»

«Nutrition Model»

«Pharma Model»

HealthCare solutions to patients/society

timely, appropriate, affordable

Case Law: Pharma vs. prevention

Safety & Claims

Precision, Orphan drugs

In 2050 = 9.6 Billion

Increasing World Population

In 2050 = 9.6 Billion

Increasing World Population

Gray Zones
HealthCare Systems being dysfunctional by 20?! - Get vested stakeholders out of silos to find concerted solutions

<table>
<thead>
<tr>
<th>Stakeholder</th>
<th>Stuck with / in / on / - …</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientists/industry</td>
<td>long-term investments → resources, opportunity costs</td>
</tr>
<tr>
<td>Regulators</td>
<td>current framework → evidence / ltd. room for interpretation or switch categories</td>
</tr>
<tr>
<td>Policymakers/Politicians</td>
<td>short-term incentives → vs. long-term vision</td>
</tr>
<tr>
<td>HCPs/Society</td>
<td>treatment paradigm → vs. disease prevention (primary, secondary, tertiary)</td>
</tr>
<tr>
<td>Payers</td>
<td>current framework → evidence &amp; certainty incentive to pay</td>
</tr>
<tr>
<td>Patient/Society</td>
<td>- → not organized or vocal enough, not heard</td>
</tr>
</tbody>
</table>
Microbiome et al.: Regulatory challenges to innovation at the food-drug continuum

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 $\Rightarrow$ Simplify it to Incentivize Product Development yet not so Complicated $\Rightarrow$ Product «Intended Use» Counts

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

be «SAFE $\Rightarrow$ 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 $\Rightarrow$ 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»
$\Rightarrow$ Intellectual Property; «glocal» patient CTs…

(2) Define acceptable level for «(UN-)CERTAINTY» of evidence
$\Rightarrow$ 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) & the Food-Drug «Borderlines» for the Regulator! Food-Drug «Continuum» for Patient & Society!
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
### 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)?

---
8 Manfred Ruthsatz, OECD, May 31, 2016
**Example: «Modify* the Gut Microbiome for the ...**

<table>
<thead>
<tr>
<th>Biological Drug</th>
<th>• ... treatment, cure, prevention of IBD / ... C.diff. »</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSMP/Medical Food (tube feeding or ONS)</td>
<td>• ... dietary management of IBD»</td>
</tr>
<tr>
<td>Food Health Claim (EU NHCR Art.14; US)</td>
<td>• ... risk (factor) reduction of IBD» (~«Disease Prevention»)</td>
</tr>
<tr>
<td>Food Health, S/F Claim (EU NHCR Art.13; US S/F)</td>
<td>• ... normal bowel function/increase in faecal bulk»</td>
</tr>
</tbody>
</table>

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

---

9 Manfred Ruthsatz, OECD, May 31, 2016
Medical Nutrition → Can be a de-facto Disease Prevention or Management/Treatment - Complementing Drugs

Enteral Nutrition (EN)
(\textit{i.e.} tube feeds and/or ONS) & Parenteral Nutrition (I.V.)
Health Care Professionals’ key role for proper intended use (compliance, safety)

Nutrition as disease-related malnutrition management
- Short bowel syndrome, stroke
- COPD
- Surgical patients
- Older patients

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’


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

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

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?

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

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)

---

Manfred Ruthsatz, OECD, May 31, 2016
An Example of a Successful Multi-Stakeholder Model in Progress

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, EUCMS, ESPEN, PCEU, HOPE, EFAD, ECAN 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 2013
- 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.

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
- **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 ...)

14 Manfred Ruthsatz, OECD, May 31, 2016
## Glossary

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