Role of Nutritional Therapy in Healthcare Innovation: The Need for Reshaping Regulatory Paradigms

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Over the next decades, the world will undergo profound changes, with its population approaching ten billion, senior citizens making up one out of five, non-communicable diseases (NCDs) increasingly outnumbering infectious diseases [1], and healthcare costs threatening to reach an ever higher percentage of countries' GDPs. As daunting as these figures might appear, new scientific insights and technological opportunities coming at an unprecedented pace promise new perspectives and potential solutions to currently unmet needs. 'Omics' diagnostics will revolutionize the way we approach prevention, personalize nutrition in healthcare, and how a patient is to be defined. Novel nutrition therapeutic findings will transform disease management, and the microbiome will become a new force in targeting holistic healthcare solutions.
This article presents pertinent focus areas to encourage dialogue with regulators, policy makers, healthcare professionals and other stakeholders to revisit current regulatory and policy frameworks at the food-medicine continuum and their respective interpretation, with regards to healthcare.

Three Focus Areas of Disruptive Healthcare Innovations – Opportunities & Regulatory Challenges

Emerging developments in science and technologies will affect the practice of modern disease management and the nature of patient care at a faster pace than ever seen before [2]. Disruptive discoveries in diagnostics and the human gut microbiome will bring a better understanding of the complex interplay of nutrition, health and disease and have the potential to create an innovative, affordable, cost-effective and sustainable healthcare environment [3]. Regulatory frameworks established over time will have to accommodate these new developments and adapt faster than ever to serve the needs of patients and society (Table 1) [4] [5].

1) Firstly, disruptive advances in diagnostics (incl. "omics" biomarkers, IT/Big Data) will change the way we are going to undertake disease prevention, in particular developing a differentiated, targeted way to address the non-communicable, mostly chronic, disease (NCD) pandemics. The goal is to improve health and prevent, delay or reduce severity of diseases. "Omics" technologies such as genomics, epigenomics, proteomics, metabolomics can be used to more completely characterize physiological states and to show how nutrition alters the balance between health and disease [6]. The definition of what constitutes a "patient" is a pivotal element in determining the regulatory classification within product development. Advances in diagnostics such as 'omics' will imply new mechanisms to better define the "future" patient, i.e. where health ends ("homeostasis") and disease starts (for example, whether persons diagnosed with a genetic pre-disposition to a disease are considered (potential) patients). Regulations need to adapt to make this clearer. 'Omics' diagnostics will also have direct implications to foster the move towards targeted ('personalized') nutrition for specific patient groups [6].

2) Secondly, a more holistic approach to disease management is needed, fully including nutritional therapy, such as medical foods, providing patient benefits as demonstrated in Crohn's disease [7] [8], inborn errors of metabolism [9], intractable epilepsy [10] [11] [12], severe cow's milk allergy [13], disease related malnutrition in the elderly patient [14]. Furthermore, nutritional therapy holds promise, in addition to medical care and life-style changes, to get patients healthier quicker, out of the hospital earlier, back to a productive, social life, at reduced costs to our healthcare systems [14] [15] [16] (17) [18]. Despite evidence of

benefits, medical foods are significantly underutilized, a dilemma which is aggravated by regional differences in regulatory frameworks. For instance, a deliberately narrow interpretation by regulators and payers to limit usage and reimbursement largely to enteral tube feeds and IEMs (e.g. US), or a continued prevalence of parenteral nutrition usage over enteral nutrition due to lack of regulation, awareness, and/or reimbursement (e.g. Asia) [4].

3) Thirdly, the new frontier 'human gut microbiome' has the potential to synergize dietary disease prevention as well as dietary disease management approaches. Nutrition therapies can influence the microbiome and target specific patients with certain chronic conditions, but will require a regulatory environment that is fit for purpose, flexible to translate science rapidly into applications. Science is working towards a better understanding of the complex interplay of nutrition, host factors, and the gut microbial composition. The effects measured are dependent on many different factors and it still remains largely unclear what determines the permanent changes in the gut microbiota, and how certain nutritional interventions can make such changes and induce a long term health effect [19] [20] [21].

Achieving innovative, cost-effective and sustainable healthcare systems to address the demographic challenges that await us requires accelerated policy making to foster incentives and investments for developing novel science-based healthcare solutions. This includes striving for global convergence of regulations as well as more flexibility in their interpretation, making changes such as:

- Accepting relevant nutritional parameters as endpoints of clinical studies in disease prevention and therapy, and
- Permitting disease prevention and treatment as indications for product categories other than medicines (e.g., for Food for Special Medical Purposes (FSMPs)).

These changes will give nutrition therapy its rightful place in a holistic approach to disease management, enhance co-operations between academia and industry, and provide a huge incentive for both public and private investments in novel nutrition therapy research.

The Way Forward – A Conclusion

Our regulatory frameworks have historically aimed for and demonstrated consumer and patient protection. Even so, disruptive findings in diagnostics and innovative nutritional approaches make the once separate silos of food (health) and drug (disease) systems move closer together, and hence require an evolving and forward looking policy, revisiting the historic pharmaceutical and nutrition "models".

The opportunity for **multi-stakeholder, public-private partnership** engagement to address divergent expertise, interests, with improved quality of healthcare and patient-centered outcomes is growing, and is required given the magnitude and complexity of issues (outlined in Table 1). Current comprehensive efforts across boundaries largely focus on technology and medicine, including the Global Coalition for Regulatory Science Research (GCRSR) [22] [23] or the US Congress' "21st Century Cures" targeting cancer and orphan disease treatments [2]. There is great merit in researching solutions that embrace nutrition [24], as well as fully implementing existing evidence such as the ENHA's Optimal Nutrition Care for All (ONCA) initiative [25], which addresses the negative impact of disease related malnutrition. Key to the ONCA campaign's progress, also embedded into EU Commission strategies [26], is aligning diverse stakeholders across multiple member states to form national alliances. The goal is to develop a nutritional care plan to facilitate greater malnutrition screening and nutritional care implementation, which include FSMPs, and actively promote public awareness, appropriate reimbursement policies and medical education [25].

The recent Mérieux Foundation and OECD Microbiome, Diet and Health Initiatives [20] [21] provide a promising way for an open dialogue to promote a science and technology based, yet flexible, regulatory and policy guidance framework in the food-medicine continuum, that includes nutrition therapy, as well as addresses incentives for investment, including intellectual property protection.

By sharing the voice of regulators, policymakers, payers, R&D, developers, medical associations, healthcare professionals (HCPs), as well as patients [5] multi-stakeholder platforms have the great potential to align on big objectives triggered by major scientific findings to better serve the needs of society. The regulatory as well as payers' framework need to adapt rapidly, in particular addressing current legal limitations on the use of disease prevention claims for nutrition and dietary disease management, as well as to create favorable development conditions for the human microbiome to provide innovative solutions in healthcare.

Glossary

CMA (Cow's Milk Allergy), CMC (Chemistry Manufacturing and Controls), ENHA (European Nutrition for Health Alliance), FSMP (Food for Special Medical Purposes), HCP (Health Care Professional), ICH (International Council for Harmonization), IEM (inborn error of metabolism), IMDRF (International Medical Device Regulators Forum), MNI (Medical Nutrition International Industry), MODA (Modification of Diet Alone), MSUD (Maple Syrup Urine Disease), NCD (Non-communicable Disease), ONCA (Optimal Nutrition Care for All), ONS (Oral Nutritional Supplements), PKU (Phenylketonuria), RAPS (Regulatory Affairs Professionals Society).

Disclaimer

This article does not, by any means, represent an official opinion of any organization the author is affiliated with, yet it underlines the importance to expeditiously work on and create an environment to engage with all vested parties to help investing into sustainable solutions in healthcare, including nutrition, considering the pace demographics and diversity based needs in our environments are shifting.

Selected Issues*	Potential Development Hurdles	Proposed Action	References
Framework Innovation & Implementation	- Precautionary principle costs time for patient therapy - Non-harmonized or non-existing global frameworks (e.g. for medical food/FSMP) - To avoid technical barriers, a decision 'Food or Drug' must be taken early in development - No change of category possible midstream w/o starting development quasi from scratch (e.g. nutrient 'cocktails' to fulfill drug CMC requirements) - Nutrient is considered a 'drug' once a clinical disease endpoint is investigated (US)	- Balance risk & speed to market: leverage Post-Marketing Surveillance (Phase IV) not to miss opportunities to get promising solutions to market; manage data quantity & uncertainty ('Big Data') - Convergence of regulations, guidelines e.g. by Codex Alimentarius (i.e. ICH and IMDRF/GHTF analog for drugs and medical devices, respectively) - Compliance criteria with focus on patient & society benefit: define safety & quality based technical testing criteria, rather than food-drug category, mode of action or efficacy based (e.g. analytics/CMC, purity criteria, monographs)	Hall (editorial 2016) (3) RAPS (San José, 2016) (27) Ruthsatz and Morck (2016)(4) ECJ case law (2015) (cited in (28)) FDA IND Guidance (2013, 2015) (29) Codex Alimentarius (30) ICH (31) IMDRF (32)
Nutrition & Prevention of Disease	- Products for disease prevention fall under the drug definition - Current development focus & incentives (in particular reimbursement) privilege therapy over prevention - Difficult to reimburse Disease Prevention - Diagnostics – 'omics' biomarkers: complex validation (authority approval times may exceed drug approval times)	- Elevate the role of nutrition and include prevention to tackle disease before it happens - Early Diagnostics: define where health ends ("homeostasis") and disease starts (Patient or Consumer) - Investigate impact on regulations to accelerate product development	EU Chronic Disease Summit (2014) (33) EFSA Opinion – EU FSG 609/2013 (Art.3) (2015) (34) Kaput et al. (2016) (6) Feinberg (2013) (35)
Nutrition in Disease Therapy	- Products for disease treatment fall under the drug definition - Medical Food/Nutrition can in fact be *the* therapeutic solution of choice – but can't be legally stated - Lack of disease specific medical guidelines that incorporate evidence for nutritional intervention	- Elevate the role of nutrition in a holistic disease management approach to tackle NCDs, e.g. Crohn's, inborn errors of metabolism (IEM) (e.g. PKU, MSUD), intractable epilepsy, severe cow's milk allergy (CMA) - Establish & implement more disease specific medical guidelines where evidence for benefit of nutritional intervention exists.	ESPEN Guidelines & LLL Courses (36) Crohn's: ECCO/ESPGHAN (2014) (7), NASPGHAN (2012) (8), IEM (9), Intractable Epilepsy (10) (11) (12), CMA (13)
	- Meeting Medical Food Legal Requirements: - distinctive nutritional requirement: defining how altered nutrient levels negatively affect a known metabolic process or organ physiology thereby contributing to the disease (= a hurdle for medical food, not drugs) - 'Modification of Diet Alone' (MODA): consensus needed on what dietary modification constitutes an unrealistic burden on the patient (i.e. not 'Convenience Food')	- Better balance 'that' a product/nutrient works and is safe for its intended use, than 'how' it works - Elevate HCP's role to decide on safety and best usage for his patient: 'in case dietary change is impossible, unrealistic or very difficult' ("medical supervision"), e.g. dysphagia, intractable epilepsy, dementia	CFR (37), FDA CFSAN (2013) (38) Codex (39) EU Regulation 128/2016, EFSA Opinion (2015) (40) (34) Giordano et al (2016) (41) RAPS (Boston, 2015) (42) Cochrane (2016) (10) NICE (2016) (11)
	- Developers' 'Dilemma' in relation to return of investment: - As foods are not pre-approved by authorities, their value proposition is difficult to sell to (private) payers, regulators. - Orphan drugs' dilemma for rare diseases: often overlooked by developers until development incentives were defined (e.g. marketing exclusivity, tax credits).	- FSMP were demonstrated to be cost-effective: NICE identified nutrition as one of the most cost effective investments (saving >£28,000 per £100,000 invested) - Take learnings from Orphan Drugs' value propositions: progress toward treating many disease areas that were previously underserved.	NICE Guidelines (43) (44), NAIT/ASPEN (2010) (15), Cangelosi (2011) (16), Elia et al. (2016, 2016) (17) (18), MNI (2014) (14) Orphan Drugs (45)
Human Gut Microbiome as Therapeutic Target	Scientific-medical knowledge is emerging but still lacking - Defining a healthy microbiome (incl. validated biomarkers) - Host-microbiome interaction, cause & effect relationship - Integrating 'Big Data' into the evidence package - Communication & consumer acceptance, awareness	- Accelerate validation of biomarkers (healthy & dysbiotic microbiomes) - Review regulatory & policy frameworks & make them fit for purpose, more flexible to translate science into nutrition therapy applications	Nature (2015) (19) Mérieux Foundation (20) & OECD (21) Microbiome Initiatives (2016)

Table 1: Nutrition Therapy to Innovate Healthcare for the Benefit of Patients & Society: Reshaping the Regulatory Framework.
* The terms FSMP (e.g. EU) & medical food (US), as well as medicines & drugs, respectively, are used synonymously throughout this article.

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