Open Innovation in the Life Sciences

A paradigm shift in the life sciences: nutraceuticals and cosmeceuticals lead the way

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To date, the open innovation approach has been implemented successfully in the chemicals and automotive industries. Life science sectors such as pharmaceuticals, cosmetics, food and biotechnology are now using this strategy in various ways and with various degrees of porosity. Faced by ever-increasing demands for greater specialization and internationalization, the life sciences market is focusing primarily on developing targeted products generally described as "stratified medicine" or "precision medicine". Such requirements, especially in terms of time and cost savings, need effective strategies, and "translational medicine" is one such concept encountered frequently within the development process. Tests and assessments are derived from existing knowledge to keep the product "lean" and support it with minimal effort through development to market approval. This produces a set of requirements for investigative strategies to which nutraceuticals und cosmeceuticals are already well-adapted.

In 2011, Germany invested 2.9 % of its gross domestic product in research and development. The latest report from Germany's Commission of Experts for Research and Innovation (EFI) flags the pharmaceutical industry as a major contributor, plowing 14 % of its product revenue into internal R&D projects. This figure places pharmaceuticals far above automotive, chemicals and mechanical engineering, securing it the #1 spot and a status as Germany's most research-intensive segment. Nor is this trend merely a German phenomenon. In its ranking of the most innovation-friendly industry sectors published in late 2012, the EU Industrial Investment Scoreboard places the pharmaceutical industry first within the EU, the United States and Japan, with an R&D quota of 15 %. What are the changes and challenges now facing the life sciences industry, headed by pharmaceuticals as its leading segment?

OILS: Open Innovation in the Life Sciences

As a general concept, the idea of open innovation was first discussed by Chesbrough in 2003 [1]. His paper introduced the idea of a paradigm shift from an inward-looking and closed process of innovation ("closed innovation") to an outwardly-oriented process ("open innovation") (fig. 1). The latter requires making company boundaries temporarily porous. While projects furthering innovation have been based mostly on internal ideas and resources to date, a trend towards outsourcing has been seen in recent years, also coupled with the implementation of conceptual ideas.

Accessing innovation: challenges in the life sciences

Rising complexity in development work coupled with recently available technologies and increased time and cost pressures has accelerated the process of outsourcing high-level R&D resources. To date, access to the technologies and resources in question has been possible only for internal units within large corporations. The idea behind OILS is to broaden access to the mid-sized enterprises operating in these industry sectors, thus closing a gap in the value chain by drawing on the services of specialists (fig. 2).

Since present-day bottlenecks are typically found in project management, OILS opens up this bottleneck as a variable, multi-disciplinary link in the chain. Schuhmacher et al. [2] provide an overview classifying the use of external sources of innovation by multinational pharmaceutical companies as regards ideas, technologies and R&D project involvement. The overview groups companies by their "introverted" and "extroverted" preferences on the subject of innovation, and the rate of externally-acquired R&D projects.

Throughout the life sciences market, stakeholder collaboration – including that among industry suppliers and partners – is undergoing rapid change. In the cosmetics and food sectors, this change process is to an extent complete. Accordingly, the process of innovation will now first be illustrated with reference to the interfaces used by nutraceuticals and cosmeceuticals in terms of their methods of investigation.

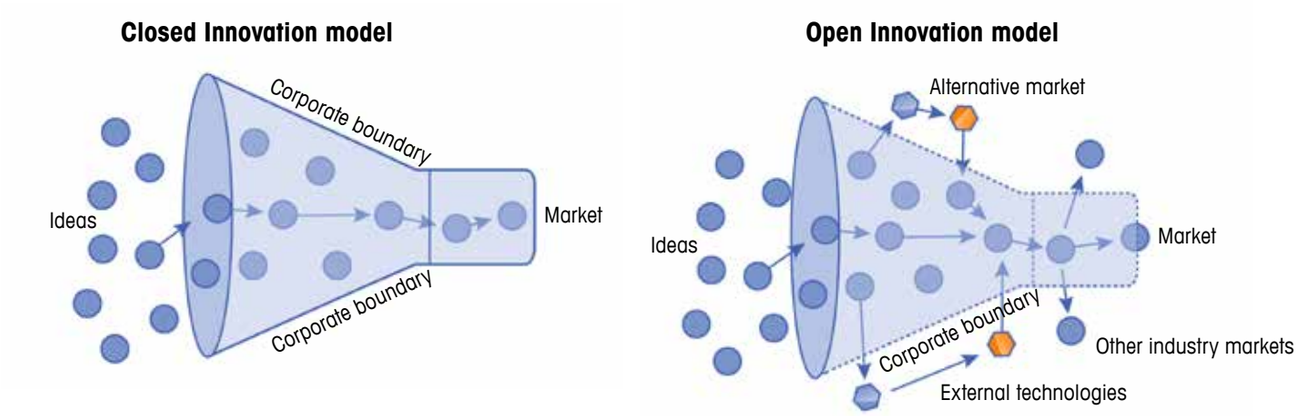

Fig. 1 The process of innovation in a closed funnel model, from the initial idea through to the product market launch, and (right) as part of a temporarily porous process within open innovation

Nutraceuticals and cosmeceuticals

The term "nutraceutical" refers to a foodstuff or food product that provides health and/or medical benefits – including the potential prevention and/or treatment of an illness or disease. Products range from discrete foodstuffs or dietary supplements to specially-prepared food products. Familiar examples include antioxidants (resveratrol in products made from red grapes or anthocyanins in berries), cancer prevention with broccoli (ingredient sulforaphane) or reducing the risk of cardiovascular disease by consuming alpha-linoleic acid.

The neologism "cosmeceuticals" refers to cosmetic products with medically-proven effects on human health. These products contain substances that actively influence biological systems. For many pharmaceutical companies, the development of cosmetics products already forms a significant part of research and manufacturing. Here, companies can reuse existing structures and methods already in place for their drug development work. Cosmeceuticals constitute a seamless transition from beauty and care products to medicine. Yet companies face a balancing act in terms of ingredients, since the legislation governing care products differs significantly to that for drugs, which often need to undergo years of trials as well as a final approval process. Typically, a cosmeceutical therefore contains enough active ingredient to produce a measurable effect but not enough for the product to be considered a medicine.

In the grey area where definitions of foodstuffs, cosmetics and drugs overlap, these products form a group that generates considerable debate about its classification. These are known as "borderline" products. A product can only ever be one thing or another. Whether a foodstuff, a cosmetic, a medical product or a drug – it cannot be simultaneously one and/or another. Drugs are primarily defined in terms of their function. For a functional drug, objective attributes such as the drug's pharmacological, immunological or metabolic effects are definitive in accordance with EU law. The likelihood of a risk to health must also be taken into account when classifying something as a drug. Accordingly, intelligent methods of investigation are required in order to guarantee safety and product functionality.

Intelligent test strategies for borderline products

Between the extremes of perfect health and illness, there are any number of ways of being less than healthy (fig. 3). Frequently, these are triggered by acute or chronic stress. The symptoms will be familiar to most of us: sleeping patterns are disrupted, and there is an impact on well-being and physical fitness. We can learn to recognize and take seriously the initial signs of changes relevant for our health, so as to take action before it is too late. Following the principle of taking the least-dangerous approach

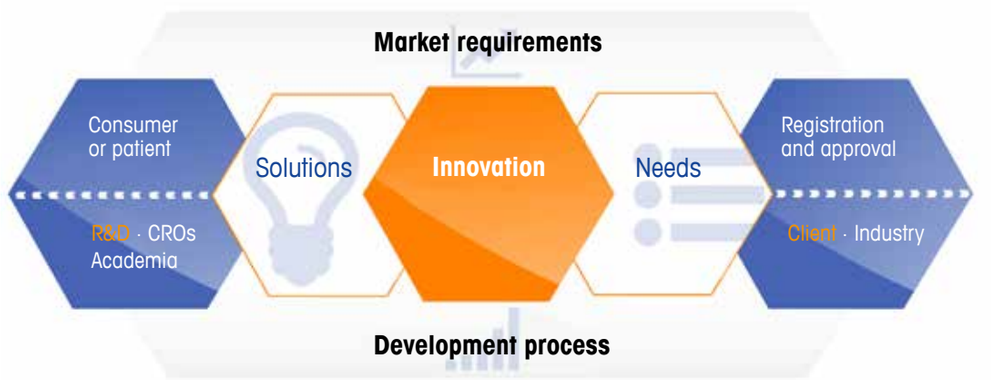

Fig. 2 Incorporating the process of innovation, driven by technical development work (active/functional ingredients and manufacturing processes) and the requirements of the market. Establishment of a tailor-made program of investigation and analysis, based on industry-relevant issues of interest and the early involvement of regulators; development of a solution strategy (safety, function and efficacy) for the consumer, followed by proof of technical feasibility and evidence supplied by the CRO as a service provider

to interventions, OTC (over-the-counter) products are of particular interest: such products do not endanger the health of the user if used appropriately, even if consumed while not under medical supervision. Borderline products that are found in such OTC products include vitamins, mineral supplements, novel and functional foodstuffs, as well as traditional plant-based remedies. Today, all of these are produced on an industrial scale under the assumption that their positive effects on health in the body are known and have been proven in clinical trials.

Here, a combination of legal provisions and the intended application area determines the design of study protocols. Legislation protecting consumer health has been regularly tightened over the last few decades and the costs for clinical trials have continued to rise. Accordingly, a preliminary process of strategic consultation must go hand-in-hand with intelligent study design using meaningful target variables, with both being based on recent scientific findings. This is the only way to secure reliable study results while staying within the allotted timeframe and budget.

In this context, psychobiological models from stress research have established themselves as dependable tools in clinical trials [3, 4]. Whether used in controlled experimentation in the lab on acute stress (TSST – Trier Social Stress Test, [5]) or while accounting for chronic stress factors and their impact on the organism, statements can be obtained about the efficacy of products for both subjective outcome variables (e.g. symptoms) and physiological outcome variables (e.g. specific biomarkers) (see fig. 4). Subclinical study populations can also be characterized in more detail by specifying the duration and intensity of their exposure to stress [6]. This can be especially helpful for studies looking at OTC remedies, as this segment offers many preventive health products or products to be taken early on in the course of an illness [7].

Product developments: anti-stress deodorants

Apart from causing illness, stress also has a major impact on our well-being and appearance. Our skin and hair suffers. Or we sweat profusely. Specially-developed methods and cosmetic products can help us weather these stressful phases successfully and avoid their further escalation. As one example, we know that stress-induced perspiration differs from the sweat response to physical activity or heat because it activates the apocrine sweat glands in addition to the eccrine glands. Sweat production is accompanied by an unpleasant odor that increases the individual's stress levels in what is already a stressful situation. Skincare companies are focusing developments on specialist antiperspirants to guard against body odor and armpit wetness. The times in which cosmetic product manufacturers were allowed to make vague claims in their advertising are now long gone. Accordingly,

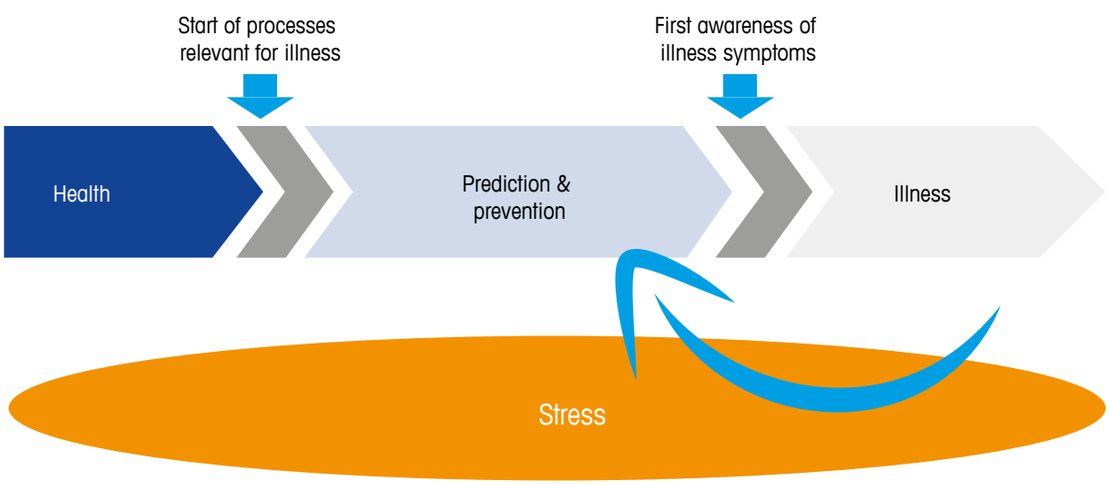

Fig. 3 Illnesses typically develop as part of a lengthy and insidious process. Effective options depend on early identification of disease-relevant processes, and interventions are generally less severe for early-stage illness. Alongside epigenetics and ageing processes, stress factors are often involved in the course of an illness – either as a primary or secondary factor. Accordingly, stress models are the ideal model for clinical trials.

Udo Bock studied chemistry at Saarland University, receiving his doctorate in 1996 in the discipline of pharmaceutical chemistry. His post-doc work included time spent on a joint research project with MUCOS Pharma GmbH & Co. KG at the Department of Biopharmaceutics and Pharmaceutical Technology at Saarland University. Positions held from 1998 to 2014 included Laboratory Manager In Vitro ADME, Sales Director and CTO at the certified (GLP, GMP) service provider Across Barriers GmbH. He completed an IHK Leadership course at the University of Koblenz/Landau and the Zurich University of Applied Sciences from 2007 to 2008. His research work focuses on the establishment and validation of in vitro methods for bioavailability and safety classification, as well as the downscaling and miniaturization of semisolid dosage forms. He has been an active board member of the Risk Assessment and Regulatory Affairs Committee within the German Society for Dermopharmacy since 2009. After forming Bock Project Management in April 2014, he has since been collaborating with companies in the life sciences sector on preclinical, clinical and regulatory projects.

Juliane Hellhammer studied education science and psychology at the universities of Würzburg, Münster and Trier. After raising her four children, she was then active as Executive Director of the Research Center for Psychobiology and Psychosomatics from 1989 to 1999, a major scientific research facility operated by the University of Trier. From 2000 to 2003, she worked as a research assistant at the University of Trier, as a member of the project "Chronic stress and ageing: effects on hormonal, metabolic, physiological and mental psychological mechanisms", operated as part of the DFG-funded stress vulnerability and stress prevention program. In 2003, Juliane Hellhammer formed the contract research organization daacro, which conducts clinical testing for drug manufacturers and studies for both consumer healthcare and the OTC industry. Her work focuses primarily on the effects of psychotropic substances on anxiety, depression stress, as documented by numerous research papers on the subject.

meaningful trials provide the perfect environment in which to develop an authentic, marketable and successful product from an original idea. Clinical trials conducted on anti-stress deodorants by Beiersdorf and Procter & Gamble [8, 9] have substantiated the marketing statements made for these products and increased their market appeal.

Trier Saliva Lab: the potential of functional analysis

The analysis of steroid hormones in saliva was introduced into psychobiological research in the 1980s. Since the procedure proved to be exceptionally reliable, lab-independent and usable as a non-invasive method, it was

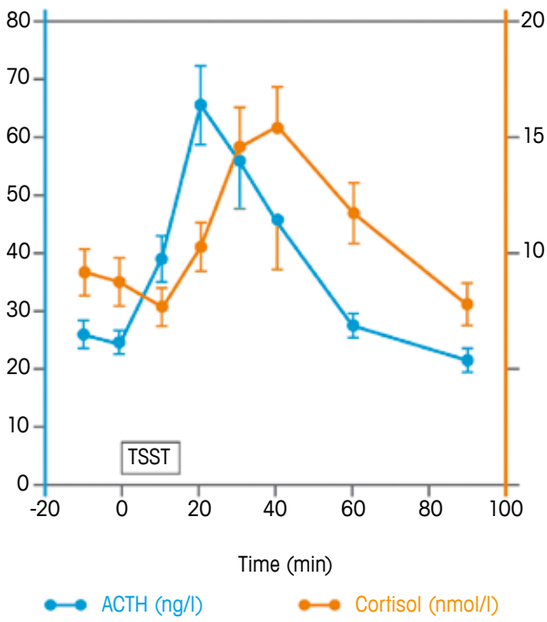

Fig. 4 The chart illustrates the levels of two hormones before and after a stress test (TSST): adrenocorticotropic hormone (ACTH), which is released by the pituitary gland, and cortisol, which is produced by the adrenal cortex. While a short-acting stress factor and the corresponding release of the hormones results in the organism adjusting appropriately to a new situation, long-term or excessive stimulation of these systems is characteristically pathogenic. Accordingly, the measurement of hormone levels is an endpoint or biomarker for the stress factor in many clinical trials. Some hormones (here: cortisol) can be measured non-invasively in saliva.

Fig. 5 Saliva collection is a pain-free technique that can be performed by non-specialists anywhere simply by following instructions. A range of collection methods are available. The method pictured is a Sarstedt-branded Salivette® for cortisol. The test subject takes an absorbent swab from a plastic container and places it in his/her mouth. Saliva production is stimulated by chewing gently on the swab for about 1 min.; the swab is then returned with the absorbed saliva to the container and the container is placed in cold storage. In the lab, centrifugation for 2 minutes at 1,000 x g yields a clear saliva sample in the conical tube.

rapidly adopted throughout the world (fig. 5). The cortisol concentration in saliva reflects the biologically-active fraction of the hormone. Permanently low changes in the level of the hormone – as seen with chronic stress, depression and anxiety disorders, for example – have an adverse effect on high blood pressure, obesity and type II diabetes, as well as on other physical and mental illnesses.

Since the 1980s, the spectrum of meaningful biomarkers measurable in saliva has been expanded continuously. As examples, alpha amylase, androstenedione, C-reactive protein, DHEA, estradiol, estriol, progesterone, 17a-hydroprogesterone, IgA and testosterone can all now be deployed in clinical trials. Here, technically competent decisions must be taken regarding the appropriate selection of parameters and their sampling times, as well as aspects of sample collection, storage and shipping.

Outlook: Stress and the human barrier function

A number of multi-year experiments and research projects [10–13] point to the influence of the human barrier function in association with rising levels of stress. This function is depressed by stress. Increased perspiration is one example of a stress-induced response (see sweating and the development of anti-stress deodorants), yet others include changes to intestinal physiology and even gut injury. In the future, we will be using cell- and tissue-based in vitro experimentation and patient studies to broaden our research in the field of stress-induced physiological change, with the aim of contributing to the safety and functionality of the borderline products in development.

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