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"Collaborative Innovation"—Regaining the Edge in Drug Discovery

Hanno Wild, Christoph Huwe, and Monika Lessl*

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Why Bother?—Rationale to Engage in Collaborative Innovation

It is well documented that the pharmaceutical industry currently faces serious challenges as indicated by decreasing output and rising costs of new medical entities.[1] This development is based on the fact that targets and diseases that are now being pursued to address unmet medical needs are more complex than those in the past. Heightened risk perception in society, increasing regulatory requirements, and reimbursement issues associated with increasing overall healthcare costs have exacerbated this situation, and the demonstration of the net clinical benefit of new drugs increasingly requires large and expensive late-phase clinical studies.

While these issues are relatively easy to describe, it is much more challenging to provide solutions that will help to pave the way towards breakthrough innovation and cost control. Some notable recommendations include the reduction of nontechnical attrition (project terminations for business or strategic reasons),[2–4] the combination of the best features of small and large pharma companies,[5–7] and the promotion of internal innovation by favoring leadership (inspiration) over management (controlling).[5,7] The special role of chemistry for the future of the pharmaceutical industry has also been discussed.[8–10]

Herein we would like to focus on "Collaborative Innovation", a concept we expect to provide significant contributions to help address these challenges. This approach should enable the generation of breakthrough innovations based on scientific issues too complex for one organization alone to handle in a cost-efficient manner.

[*] Prof. Dr. H. Wild, Dr. C. Huwe, Dr. M. Lessl
Bayer HealthCare AG, Global Drug Discovery
Global Candidate Generation and Exploration
42096 Wuppertal (Germany)
E-mail: hanno.wild@bayer.com

Evolution in the Making—From the Extended Workbench to Strategic Alliances

While historically the best and sometimes only way to assemble the technology and expertise required for drug discovery and development was to build it in-house, today many of these elements are available externally, and it might even be more cost efficient to access them by means of partnering. This was the initial motivation for companies to outsource selected aspects of drug discovery to service providers. Typical examples include the production of extensive compound libraries for screening, selectivity screens, sometimes also lead optimization, toxicology, and animal pharmacology, and in some cases whole projects. Outsourcing is also used as a means of flexibly increasing and decreasing the capacity of the R&D organization without changing the internal headcount.

While the contract research and fee-for-service-based outsourcing model continues to have its utility, more recently a trend towards more value-added collaboration models and strategic partnerships with significant contributions and long-term commitments from both partners can be seen. This trend is supported by an increasing interest both in industry and academia, and is encouraged by governments, who are increasingly focusing on unmet medical needs and the cost effectiveness of healthcare systems.[11]

No Stone Unturned—"Outside-In" Concepts

Currently the primary focus of the pharmaceutical industry with regard to partnering is placed on bringing assets in, and consequently a variety of collaboration models have been developed in addition to more traditional collaborations on individual projects, for example strategic alliances, innovation incubators and industry-on-campus models, crowdsourcing, and precompetitive consortia.

In contrast to regular collaborations between two partners on a specific scientific project, **strategic alliances**[12] are more long-term-oriented, risk-and-reward-sharing agreements based on significant contributions in terms of content, resources, and financials from both partners. These partnerships incorporate both complementary expertise and common goals, and therefore are a promising model to initiate and

progress projects from discovery through development to the market. When moving from technology transfer towards true exchange of knowledge and risk–benefit sharing, partnerships are built to benefit from expertise that is not available in the individual organizations, and that would be difficult to obtain in a cost-efficient and timely manner; this enables the partners to pursue highly innovative projects that they would not have engaged in on their own. Bayer HealthCare's strategic alliance with the German Cancer Research Center (DKFZ)[13] directed at joint drug discovery and development in cancer therapy is a notable example of this approach. In this partnership Bayer HealthCare provides its proven drug discovery and development, marketing, and sales capabilities, while the DKFZ contributes its insight into the molecular mechanisms of cancer, innovative target ideas, and clinical experience, resulting in a powerful combination of expertise. Other examples of strategic alliances include Bayer HealthCare's strategic partnership with OncoMed Pharmaceuticals to discover, develop, and commercialize novel anticancer stem cell therapeutics, the alliance of Novartis and MorphoSys to establish a therapeutic antibody pipeline, and the partnerships of Pfizer and the University of California at San Francisco, of Gilead Biosciences and Yale University, and of AstraZeneca and Cancer Research Technology Ltd.

Innovation incubators and industry-on-campus models[14] are ways of promoting interactions between academia and industry by providing assistance to access to funding, lab space, and drug-discovery technologies. As a good example, Bayer Healthcare has just started its CoLaborator model, a shared lab for start-up life science companies whose technology platforms, drug targets, or drug candidates align with Bayer's strategy. The goal of the CoLaborator approach is to support start-ups in establishing their research labs; the likely sources of these companies are spin-offs of academic labs and and venture capital groups. In addition, CoLaborator scientists will have access to Bayer's global research network. In return, Bayer seeks preferred access to partner with the emerging companies. The CoLaborator is located at the Bayer HealthCare U.S. Innovation Center in San Francisco; a second site in Berlin, Germany, is currently planned. Other examples of innovation incubators include the QB3 Garage (http://www.qb3.org/startups/qb3-garage), a network comprising the University of California at Berkeley, Santa Cruz, and San Francisco to promote basic research in quantitative biosciences and its quick commercialization by supporting the formation of start-up companies, and the Biogen Idec Innovation Incubator (bi^3, http://bi3.biogenidec.com), which aims to facilitate access of start-up companies to funding, lab space, and drug-discovery technologies, with Biogen having a purchase option of the hosted companies.

The concept behind **crowdsourcing**[15] is to utilize the expertise of the larger scientific community, often using the internet as a platform, instead of a single partner to address an issue. For a crowdsourcing approach to be successful it is crucial to precisely define the problems, expectations, offerings, and intellectual property (IP) policy, and to have low bureaucratic hurdles and short response times. For example, Bayer HealthCare's Grants4Targets (http://www.grants4targets.com) initiative[16] brings together drug discovery and development expertise and novel target ideas, which are supported by a one-year grant. After the duration of the grant during which the IP rights remain completely with the applicant, promising targets might be pursued by means of separate collaboration agreements. Other examples of crowdsourcing models include the Innocentive platform (http://www.innocentive.com), the first example of crowdsourcing in the pharmaceutical industry initially started by Eli Lilly and now an independent organization, the Medical Research Council Technology's Call for Targets program (http://www.callfortargets.org), Eli Lilly's Phenotypic Drug Discovery approach (PD^2, http://www.pd2.lilly.com), and GlaxoSmithKline's Pharma in Partnership program (PiP, http://www.pharmainpartnership.gsk.com).

Finally, the concept of **precompetitive consortia**[11,17] has led to a paradigm shift over the last decade with respect to what is regarded as the competitive field of pharmaceutical research. These consortia are formed by parties from industry, academia, patient organizations, and regulatory agencies who share a common interest in developing general tools and standards for drug discovery and development, for example predictive models, biomarkers, and data management systems. They address problems that are too complex to be solved by any individual institution alone. For example, Bayer HealthCare is participating in the Innovative Medicines Initiative (IMI, http://www.imi.europa.eu), a joint initiative of the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA), and with a budget of €2 billion the world's largest public–private partnership in healthcare research and development, aiming at speeding up the development of safer and more effective drugs for patients. The currently funded projects involving several hundred international partners are directed at solving issues related to target and biomarker identification and validation, lead structure identification and characterization technologies, drug efficacy and safety, knowledge management, and education and training. Other examples of precompetitive consortia include Enlight Biosciences (http://www.enlightbio.com), a company founded by a group of pharmaceutical and venture capital companies in order to develop novel platform technologies for pharma R&D, and the Asia Cancer Research Group (ACRG, http://www.asiancancerresearchgroup.org), a nonprofit organization established by Eli Lilly, MSD/Merck & Co., and Pfizer to foster the development of treatments of cancers common in Asia.

It is important to emphasize that none of the collaboration models described above is suitable as a one-fits-all solution. Instead, the appropriate model for the specific question to be addressed must be selected for maximum impact and probability of success.

Letting Go—"Inside-Out" Concepts

Partnering as an opportunity to retrieve some of the significant R&D investments made earlier has been intensively pioneered by industries besides the pharmaceutical industry, with IBM, Dow Chemical, and Texas Instruments being notable examples, each collecting significant annual

licensing revenues in the process.[18] However, several strategies are currently used by the pharmaceutical industry as additional development or commercialization channels.

Outpartnering of development projects is a common way of strengthening the available development and sales capabilities of an asset, ideally based on complementary expertise and market access. As an example, Bayer HealthCare's oral, direct factor Xa inhibitor rivaroxaban (Xarelto) was co-developed and is co-marketed with Johnson & Johnson.

Additionally, **out-licensing and optional back-licensing** of projects is an option to balance overall portfolio risk. As a notable example, the renin inhibitor aliskiren was out-licensed by Novartis to the biopharmaceutical company Speedel in 1999, and back-licensed after a successful phase and II clinical development program in 2002, in order to start phase III development and later marketing.

Finally, **spin-offs** can be used to generate value from de-emphasized research and business areas. Examples include Bayer's antiinfective spin-off Aicuris and Roche's biopharmaceutical spin-off Actelion, both of which have recently closed licensing deals with MSD/Merck & Co.

It should be noted that in addition to the pure financial benefit, such strategies have also been recognized as motivators to "let go" of projects.[19] It is much easier for scientists in the pharmaceutical industry, typically inherently motivated by the idea to provide care for patients, to accept the termination of a project for strategic reasons in their own organization, if the project is continued by a partner and continues to have a chance to reach the patient.

While creating a successful out-licensing program has often proven rather challenging, key success factors have been described, including establishment of a clear licensing strategy, securing of upper management support, assignment of a dedicated licensing group, formation of licensing opportunity identification and implementation project teams, and ultimately transformation of the corporate culture.[18]

As an example, at Bayer HealthCare a dedicated group within Global Drug Discovery aims at creating value from de-prioritized pre-Proof-of-Concept (pre-PoC) assets and to progress them through partnerships employing flexible deal models, while licensing transactions for later assets (post-PoC) and marketed drugs are managed by a Global Business Development and Licensing group.

The Full Monty—Exchange in Both Directions and across the Full R & D Process

In order to truly utilize the benefits of Collaborative Innovation, the exchange of know-how and assets should be pursued in both directions and along the full R&D process, albeit not necessarily with the same partner. For example, a target could be proposed by an academic partner, the drug discovery process could be done jointly, the development and commercialization of the resulting drug could be undertaken by the industry partner, potentially in collaboration with additional partners, and additionally the compound could be out-licensed to another party for development in an indication outside of the strategic interest.

Such a model would be a true example of what is often coined the "Open Innovation" model.[20] In this way all options are considered and the chances of succeeding in providing innovative healthcare solutions in an increasingly difficult environment are maximized. However, as promising as such an approach is, it is not always followed, because it requires a high degree of flexibility and partnering expertise on all sides, and the growing dependence on the partner's productivity and organizational stability as well as the risk coinciding with know-how transfer must be accepted and managed. It should also not be underestimated how difficult it can be to handle IP and know-how in such a complex environment and how to develop adequate risk- and profit-sharing models for all participants.

Getting Buy-In—Gaining Commitment of the Internal R & D Organization

One key aspect of collaboration management is to gain support for partnering activities across the internal R&D organization, starting from lab heads across middle management up to the executive level, in order to overcome the occasional tendency to prefer internal over collaboration projects, the well-recognized "NIH" (not invented here) syndrome. This skepticism might be due to a lack of trust between new partners, and different philosophies, experience levels, and approaches of the partnering organizations, especially between industry and academia. In contrast, it is crucial to understand and accept externally originated assets as part of the portfolio instead of a threat. This can be promoted by organizational measures, and by providing incentives for collaborative research and rewarding an open mindset. As an example, at Bayer HealthCare the evaluation of potential licensing and collaboration opportunities is an integral part of monthly portfolio management meetings, and one of the regular Global Drug Discovery awards is specifically dedicated to the team that has initiated a successful collaboration project.

Making It Work—Professional Alliance Management

Ultimately, however, successful collaboration projects are the best way to encourage the pharmaceutical industry to continue moving towards a Collaborative Innovation approach, and this should be enabled by employing professional alliance management at all partner organizations. Key factors for the successful management of collaborations include putting an emphasis on partner relationship and cultural fit, strategic fit of the organizations, operational management, learning capabilities, valuing communication, and enthusiasm and commitment. This should already start during partner selection and is especially important at the beginning of a collaboration when trust-building is crucial and later in order to maintain a successful long-term relationship. Based on experience, these goals can optimally be met by implementing a dedicated alliance management group.

In a Nutshell—Making Sense of it All

The pharmaceutical industry strives to improve the life of patients by fighting increasingly complex diseases. In the light of the growing challenges to achieving this goal, it is crucial to join forces on a global level and to combine different approaches in a flexible way. This requires the right mindset of all involved parties, a combination of internal excellence with external openness, and the right organizational setup.

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