Golden Rice: A Product-Development Partnership in Agricultural Biotechnology and Humanitarian Licensing

IP (intellectual property) constraints are often perceived as barriers to market entry, especially when it comes to developing countries. This case study examines the IP management component in the development of Golden Rice[1] (or beta-carotene-containing rice) and the transfer and introduction of Golden Rice to developing countries.

Rice, one of the most widely grown food crops, contains neither vitamin A nor beta-carotene, yet it is a staple food crop for billions of people, especially in Asia. Here, and in other developing countries, vitamin A deficiency (VAD) is a major problem affecting primarily children under age five and pregnant and lactating women. Thousands of impoverished people lose their eyesight because of VAD. Severe VAD (xerophthalmia, or night blindness) leads to permanent blindness: 500,000 people, 250,000 of them children, lose their sight every year due to VAD.[2] The deficiency also leads to a depressed immune system that increases the incidence and severity of infectious diseases and infant mortality rates.

There are several avenues for mitigating VAD, including programs to fortify food with vitamin A and beta-carotene and to distribute vitamin A supplements to affected populations. For the supplement distribution, more than US$100 million are spent every year. An alternative, and complementary, approach is to insert relevant genes in rice. This allows farmers to grow beta-carotene-rich rice. By enhancing those varieties primarily grown or consumed by poor people, beta-carotene can be delivered at essentially no cost once the Golden Rice has been developed and bred into local varieties.

Interestingly, rice plants synthesize beta-carotene in foliage and other parts of the plant, but not in the grain, and all but two steps of the biosynthetic pathway are present in the grain. By the addition of only two genes, phytoene synthase (*psy*) and phytoene desaturase (*crt* I), the pathway is reconstituted and beta-carotene accumulates in the endosperm (the endosperm being the edible part of the grain).[3]

INTELLECTUAL PROPERTY FEATURES OF THE CASE

The development of Golden Rice led to a significant change in the relationship between the public sector and intellectual property. A freedom to operate (FTO) review of pro-Vitamin A-containing Golden Rice was commissioned by the International Rice Research Institute, a center of the Consultative Group on International Agricultural Research (CGIAR), with funding from the Rockefeller Foundation (led by one of us [AK]). The review showed that about 70 patents and patent applications were applicable to the improved rice when *all* patents issued in or applied for in *all* countries, including patents on commercially accessed research tools, were considered.[4] The published analysis also showed, in accordance with analysis by Zeneca (which later merged with Novartis to form Syngenta) that, in practice, only a few, if any, patents pertaining to Golden Rice were applicable in developing countries, together with a few material transfer agreements.

Obtaining Freedom to Operate

Fortunately, these potential—and arguably perceived—constraints were resolved in a few months in the year 2000 by a straightforward IP management strategy comprising four goals:

- identification of major IP components (the above-mentioned FTO review)
- interpretation, with Zeneca, of the relevance of the FTO review to the proposed humanitarian use in developing countries

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- in licensing for humanitarian use, led by Zeneca, of IP components it did not already own
- licensing by Zeneca, as Syngenta, via the inventors of the assembled (or bundled) intellectual property to public sector institutions in developing countries that could use the rights for the benefit of resource-poor farmers, and others, deficient in vitamin A

The patented key technologies for Golden Rice production include core patents related to the specific biosynthetic pathway. These patents were filed by the inventors, Potrykus and Beyer. Their work built on myriad other technologies that were published in issued patent documents and scientific literature. These core patents were licensed to Zeneca, which already owned its own plant-biotechnology-related patents. Zeneca then negotiated access to all possibly necessary patents, including intellectual property from Bayer AG, MonsantoCompany, Novartis AG, Orynova BV, and Zeneca Mogen BV.

All of these companies, including Zeneca (which, coincidentally, almost immediately merged with Novartis Agribusiness to form Syngenta), provided access to their technologies, free of charge, for defined humanitarian research and use of Golden Rice in developing countries. It is important to note that, contrary to what many commentators state, the licensing process was relatively uncomplicated, with the involvement of commercially experienced people.

Licensing

Within a short time, 16 further licenses, including licenses with the right to further sublicense (for example, the license issued to IRRI), were issued to public sector licensees. Thus national programs in Bangladesh, China, India, Indonesia, the Philippines, South Africa, and Vietnam obtained licenses for use of the technology in local rice varieties important in VAD areas.

Terms of the humanitarian license agreement

The Golden Rice Humanitarian Board, although not a legal entity, provides a forum for discussion of strategic and tactical issues relating to the humanitarian project. Both Potrykus and Beyer have the right to issue licenses. Two licensees also have that right, as does Syngenta, which has not exercised its right. All the licenses are in the same form, as proposed by Syngenta and agreed to by the inventors.

The essential elements of the licenses include the following points:

- Syngenta retains commercial rights, although it has no current plans to commercialize Golden Rice. Humanitarian use, and research leading to it, is allowed.
- Humanitarian use is defined as use in developing countries by resource-poor farmers (earning less than US$10,000 per year from farming).
- The technology must be introduced into public seed varieties, as a way to optimize public sector benefit and use.
- No technology fee (or surcharge) may be charged for Golden Rice, as a way to optimize public sector benefits.
- Sale of Golden Rice is authorized by farmers, as a way to reach urban poor.
- Farmers are allowed to reuse harvested seeds.
- Golden Rice may not be released in a country that lacks biosafety regulations and where official government review has not been made to ensure health and environmental safety.
- Export of Golden Rice is not permitted, except to other licensees for humanitarian research and subsequent use. (Export of crops is a commercial activity. The purpose of the humanitarian project is to assist resource-poor people in overcoming VAD).
- With regard to improvements to the Golden Rice technology:
  - Humanitarian use of any improvements to Golden Rice is guaranteed under the same terms of the original agreement (and thus any improvements to the technology will serve the humanitarian purpose). Syngenta has acted on this—donating to the humanitarian project new transformations, including the intellectual property and results reported in Paine and colleagues.[5]
  - Commercial rights to improvements of the technology are granted back to Syngenta.
- No warranties are given by the licensor or licensors (as is common for licenses), and each party is responsible for what it controls.

KEY LESSONS LEARNED

The rapid resolution of the IP constraints surrounding Golden Rice demonstrated, first of all, how effective IP management, coupled with strong collaborations between the public and private sectors, can help achieve global access to new technologies and products for humanitarian goals. The IP constraints identified by Kryder and colleagues[6] did not delay the development of the product, and their clarification and resolution required only managerial and influencing skills and the resulting goodwill of IP owners.

More specifically, three specific lessons have been learned:

1. Intellectual property and patents did not delay the development and introduction of Golden Rice by a single day. Notwithstanding this, the resolution of the potential IP constraints could not be ignored.
2. Other constraints are much more critical to the introduction of Golden Rice, in particular, and to potentially life-saving food biotechnology

applications, in general. These constraints are, in decreasing order of importance:

- the necessity of governments to establish a sustained and positive policy priority for the adoption of all relevant, including novel, technologies in agriculture
- the importance of the establishment of affordable, workable, and science-based regulatory systems designed to comply with international obligations *and* to address local needs and concerns (The unnecessarily burdensome, overly politicized regulatory requirements for genetically modified organisms [GMOs] and the absence of consideration of benefit has led to years of delay in the introduction of Golden Rice technology. Yet there is no evidence to justify such a burdensome regulatory system.)
- the need for the capacity and funding of national agricultural rice research institutions to keep segregated different versions of genetically modified crops, including conducting field trials with them
- the anticipated need to develop effective seed distribution systems for reaching farmers in remote areas, including the presence of private sector entities willing to invest in seed distribution systems (However, a major aim is also to have farmers pass the seed on to neighboring farmers to reach "infrastructure remote" areas often associated with VAD.)

3. Recognizing that universities are not set up to develop products, Syngenta was instrumental in converting the proof-of-concept results generated at ETH Zurich and University of Freiburg into deliverable products. Although Syngenta retained commercial exclusivity for the technology, the company decided not to develop a commercial product of Golden Rice for markets in developed countries. Syngenta's continued support of the project with advice and scientific know-how has proven absolutely essential for the success of the product-development partnership.

From a broader perspective, the FTO review of Golden Rice, in particular before "commercial analysis," served as a wake-up call to the public sector to pay more attention to IP management as a powerful tool for meeting public sector goals. Concern about potential constraints on public sector research and innovation in agriculture spurred the public sector's interest in intellectual property. One important response was work that led to the formation of the Public Intellectual Property Resource for Agriculture (PIPRA). Supported by, among others, the Rockefeller and McKnight foundations, PIPRA is a public sector initiative that recognizes that continuing and enhancing relationships with the private sector, and between the public sector institutions, are critical components of the utilization of intellectual property to meet public sector goals. As part of its initial work, PIPRA began a study of the structure of IP ownership in agricultural biotechnology. In the words of the study's authors, Richard C. Atkinson and colleagues: *This study found that roughly one-fourth of the patented inventions were made by public-sector researchers, which is substantially larger than the IP portfolio held by any single agricultural biotechnology company. It is, however, highly fragmented across institutions and across technology categories. And much of this IP has been licensed, often under terms that are confidential but which have likely resulted in greatly restricted access to the underlying technologies.*[7] *This study suggested that, apart from a few important exceptions, public-sector scientists have invented many of the types of technologies that are necessary to conduct basic biological research and develop new transgenic plant varieties. For instance, they have developed technologies to transfer genes into plant cells; have characterized specific DNA elements that drive unique patterns of gene expression; and have identified many genes that confer important plant traits. Such discoveries underscore the fact that public-sector research institutions have been significant sources of technological innovation.*[8]

We believe that this study involving Golden Rice shows how public and private sector innovations can be put to work directly to help the poor with more focused public sector IP management. Indeed, IP management is merely one of the components needed to bring innovation to the poor.[9] Other factors, such as regulatory requirements, can be much more costly and do constitute tremendous barriers to the poor benefiting from innovations that are becoming commonplace in much of the world. ■

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1 Golden Rice was invented by Ingo Potrykus, then at ETH in Zurich, Switzerland, and Peter Beyer of the University of Freiburg, Germany. See also www.goldenrice.org.

2 childinfo.org/areas/vitamina/ .

3 Potrykus I. 2001. Golden Rice and Beyond. *Plant Physiology* 125:1157–1161.

4 Kryder D, SP Kowalski and AF Krattiger. 2000. The Intellectual and Technical Property Components of pro-Vitamin A Rice (GoldenRice™): A Preliminary Freedom-to-Operate Review. ISAAA Briefs No 20. ISAAA: Ithaca, NY. www.isaaa.org/kc/bin/isaaa_briefs/index.htm.

5 Paine JA, Shipton CA, Chaggar S, Howells RM, Kennedy M, Vernon G, Wright SY, Hinchcliffe E, Adams JL, Silverstone a, Drake R. 2005. Improving the nutritional value of Golden Rice through increased pro-vitamin A content. Nature Biotechnology 23(4):482–487.

6 See *supra* note 4.

7 Only within the temporal and spatial limits allowed by the patent system (note added by the authors of this case study).

8 Atkinson RC, RN Beachy, G Conway, FA Cordova, MA Fox, KA Holbrook, DF Klessig, RL McCormick, PM McPherson, HR Rawlings III, R Rapson, LN Vanderhoef, JD Wiley and CE Young. 2003. Public Sector Collaboration for Agricultural IP Management. *Science* 301(5630):174–175.

9 Current Golden Rice transformation events in the humanitarian project's development process were all designed and made by Syngenta to need access to no third party intellectual property.