Specific IP Issues with Molecular Pharming: Case Study of Plant-Derived Vaccines

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ABSTRACT

The public sector is making substantially increased investments in health technology innovation through public/private partnerships to bring improved health technologies to underserved people in developing countries. These product-development partnerships, however, face a common problem: how to manage intellectual property (IP). Such management involves many issues. In relation to a case study, presented in this chapter, of plant-derived hepatitis B virus vaccine, the challenges involve obtaining freedom to operate, securing new intellectual property, and deploying intellectual property to developing countries. We conclude that while challenges abound, the IP issues are fairly clear and can be addressed with straightforward IP management approaches. The cost of managing the intellectual property is expected to be minimal on the price of the finished vaccine. In the medium term, an IP protection strategy might offset costs and generate modest income. Most important for the partnerships is to develop a clear, transparent IP policy, with emphasis on the licensing principles, so that products can be made available to developing countries at affordable prices.

1. INTRODUCTION

The goal of molecular pharming is to develop valuable new drugs and vaccines for significant diseases in developed and developing countries. A number of substances have already been produced in plants and include flavors, nutraceuticals, biodegradable plastics, and metabolites. From a health perspective, plants have been engineered to produce therapeutic proteins for clinical evaluation including human serum proteins (epidermal growth factor), monoclonal antibodies, such as antigenic peptides for rabies virus, tuberculosis and HIV, antibodies to treat cancer, cardiovascular diseases, gastric lipase in the fight against cystic fibrosis, and hepatitis B antibodies, and a range of vaccines.[1] Recombinant protein drugs are one of the fastest growing segments of the pharmaceutical industry, currently generating over US$20 billion in annual revenues. They are the so-called third generation of recombinant plant products.[2]

From a global perspective, plant-derived vaccines represent an attractive mode of production to address diseases of the poor and to stimulate manufacturing in developing countries.[3] Over the last decade, the concept of plant-derived vaccines has grown more sophisticated and many research partnerships have emerged that involve advanced research centers in developing countries. Several potential characteristics of plant-derived vaccines could make them particularly attractive for controlling infectious diseases in developing countries.

- The vaccines would be orally active, thus eliminating the need for injection and the associated cost and safety concerns.
- Oral activity is associated with the ability of plant-derived vaccines to evoke mucosal immunity, which is valuable for a number

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of infections that are transmitted through the mucosa.
- Plant-derived oral vaccines should be heat stable, thus largely eliminating the need for a cold chain for these vaccines.
- It might be possible to make multi-antigen vaccines either by multiple gene splicing or by mixing various plant-derived vaccines.
- A very important potential aspect of plant-derived vaccines is that developing countries could launch and carry forward their development and ultimately their production.
- Plant-derived vaccines could be produced on a very large scale and at very low cost, perhaps as little as a few cents per dose.

Indeed, a multi-disciplinary team led by Charles Arntzen[4] recently carried out detailed calculations of the comparative costs of the production of vaccines by traditional methods and by plants. The chapter here is an extension of that report. In that study (as indeed in this chapter), hepatitis B vaccine (HBV) was used as a model. The cost-of-production study computed the costs for facilities in the United States, Korea, and India capable of producing 75 million doses per year. The "effective cost" was also computed (in other words, the cost per dose to deliver in a developing country immunization program and the percent savings that could be enjoyed over the effective cost using plant-derived vaccines). The results are summarized in Table 1. It shows that the potential economic benefits of plant-derived vaccines justify the establishment of a comprehensive program to bring one or more products to the market soon.

It is not surprising therefore that government- and foundation-funded molecular pharming represents a new generation of public sector initiatives that seek to rectify a widely acknowledged imbalance: a lack of investment in R&D for health technologies for the poor. Since the private sector is, by definition, profit driven, it cannot, on its own, address this imbalance because of the need to make a competitive return on investment, which the market for the poor does not provide.

The public sector is now making substantially increased investments in health technology innovation through public/private partnerships. These product-development partnerships face a common problem: how to manage intellectual property (IP). This is no small challenge. IP management is a complex field in which learning, understanding, and using best practices is essential.

Table 1. Comparison of Production and Effective Cost for Three Countries and Two Presentations

	Korea or India	United States		Korea		India	
	Yeast-derived 10-dose vials	*Plant-derived single-dose packet*	*10-dose packet*	*Plant-derived single-dose packet*	*10-dose packet*	*Plant-derived single-dose packet*	*10-dose packet*
Cost	$0.27	$0.15	$0.06	$0.09	$0.04	$0.075	$0.03
Effective Cost	$0.42	$0.16	$0.08	$0.10	$0.05	$0.08	$0.04
% savings for plant-derived vaccine against yeast-derived for effective cost		62%	81%	76%	88%	81%	90%

Source: Arntzen et al., 2006.[5]

IP management involves many issues, including patenting, the protection of confidential information, and the formation of cooperative R&D programs. For any area where many organizational actors converge, there are three primary challenges to IP management:

1. **Securing new intellectual property.** New research initiatives will naturally develop new intellectual property. It is essential to public sector goals that this intellectual property be identified and secured, either by filing the appropriate patent applications or by obtaining licenses from patent holders. If, for example, one group develops a method for promoting the synthesis of an antigen, and another group develops a technique for purifying the antigen from plant material, it is essential to be able to bring together both intellectual properties for developing the final product. This IP challenge can be largely overcome by undertaking an inventory of the existing intellectual property of key groups. To accomplish this work there must be access to technical experts who can identify the specific ways the intellectual property can be useful for product development.
2. **Freedom to operate (FTO).** If a molecular pharming initiative is to achieve its goals, the partnership will need to undertake a thorough Freedom-to-Operate review to provide a clear picture about which patents do, may, and do not stand in the way of developing products. These assessments are always associated with a high level of uncertainty, for a number of reasons, including the large number of patents that may exist, the numerous jurisdictions (countries) in which the patents have been or have not been filed, and the varying practices of patent offices. A blocking patent may exist and might be voided in key markets only through long and costly legal battles. The value of an FTO assessment is that it provides a good sense of the IP issues relevant for any development project, which helps minimize costly, unforeseen problems.
3. **Deploying intellectual property.** Public sector groups are often dedicated to achieving social goals, such as developing safe and effective health technologies to address disease. Further, these groups would like to see these products made widely available at affordable prices to all levels of society. To accomplish these ends, public sector groups should use humanitarian licensing practices. For example, if a group helps to develop a new monoclonal antibody against the rabies virus, it could license the technology to companies in Europe and the U.S., but the group could also reserve the right to license companies in developing countries under different terms. These countries may enjoy some advantages, such as lower costs of production. Licensing to companies in developing countries could also help to make the product available to the poor at prices near the marginal cost of production.

2. SPECIFIC INTELLECTUAL PROPERTY ISSUES WITH PLANT-DERIVED PHARMACEUTICALS

2.1 *Background*

As with most biotechnology products, the IP situation in plant-derived vaccines is complex. Managing IP and tangible property presents added challenges and expense because plant-derived vaccines build on many distinct areas of innovation, including:

- Engineering of proteins and specific antigens (including immunogens and specific genes encoding antigenic proteins). Many patents in this area are the same as those that apply to vaccine production through conventional means.
- Antigen production and accumulation in plants (including the expression of foreign genes and the optimization of genes). The technologies associated specifically with the expression of antigenic determinants in plants are the subject of several issued patents.

- Genetic transformation of plants (including vectors for use in plant transformation, transformation protocols, molecular toolkits, and various equipment). Basic plant transformation technologies have been under development for more than 20 years. The procedures commonly in use today are covered by a range of issued and pending patents. Virtually all of the groups that have been involved in plant-derived vaccine activities have utilized the agrobacterium-mediated approach to plant transformation.
- Selectable marker systems (that allow for the identification of plant cells that have successfully taken up the DNA, and comprising the gene expression systems), such as kanamycin (nptII), mannose-phosphate-6-isomerase, among others.
- Transcription regulatory elements (to ensure that the introduced genes are expressed in plants), including promoters (constitutive and/or tissue specific), and transcription terminators (terminator nucleotide sequences), which are quite often NOS or rubisco E9 terminator sequences.
- Sub-cellular targeting systems (used to "guide" the transcribed products into specific cellular organs), such as rubisco subunits and plastid signal sequences
- Related technologies (such as adjuvants, and product formulation and immunomodulatory technologies).
- Bioprocess engineering for extraction and processing.

An additional complication is that most plant-derived vaccine projects are developed through the collaborative efforts of a range of research institutions, including private companies and academic institutions. Materials often change hands periodically during the development program, possibly in conformity with material transfer agreements that stipulate certain restrictions. Research agreements must be developed for all of these collaborative efforts. The agreements must address what will happen if such inventions are developed jointly. Further, nasal administration of vaccines may require access to a number of patents, which may be difficult to obtain.

Despite the complexity, the task is manageable. Corporations typically manage their intellectual property in a strategic manner. This entails, among others, significant in- and out-licensing activities to obtain FTO as part of an integral element in their product development strategy. In contrast, public institutions are generally less experienced with FTO procedures. A better understanding of IP management will allow these institutions to take advantage of the flexibilities in IP systems. In the United States, for example, groups can undertake research without a license on patented technologies if the goal is to generate data for the regulatory requirements of the U.S. Food and Drug Administration (FDA).

While a patent thicket exists for plant-derived vaccines in industrialized countries, very few of these patents have been filed in developing countries. The absence of many patents in developing countries simplifies matters significantly with respect to humanitarian use and also facilitates commercial applications in developing countries. It does not, however, reduce the overall need for IP management in order to obtain FTO.

There are several models of humanitarian-use licensing where patent rights are effectively pooled. One example is the approach used by the developers of the biotech rice containing pro-Vitamin A, called "Golden Rice." The developers of Golden Rice encountered many of the FTO issues that face developers of plant-derived vaccines. An FTO assessment revealed that Golden Rice was related to over 70 patent applications and issued patents, most notably in the United States and Europe, and that patent applications were owned by over a dozen institutions. Few patents were applied for or issued in developing countries. However, because the material was developed in Europe, it could not be transferred for use in developing countries without proper licenses. There were a few reasons for this, not the least of which was that several material transfer agreements were limited to research use only. Thanks to the publicity surrounding Golden Rice and the seriousness of vitamin A deficiency in developing countries, these patent constraints were

resolved in only a few months. The public and private organizations that held relevant patents made them available at no cost to the inventor, who, in turn, granted one single license for all the necessary intellectual property to developing country institutions. Golden Rice serves as a useful model of how to approach the owners or assignees of proprietary technologies for royalty-free access for humanitarian uses.

One important difference between nutritionally enhanced rice and plant-derived vaccines is that the vectors and gene-expression components used to produce Golden Rice were assembled without advance consideration of intellectual property and FTO. Thus, the way forward with plant-derived vaccines should proceed more smoothly than it did with Golden Rice with respect to IP issues. Preliminary analysis and continued review of the IP landscape, however, are essential elements in the development of plant-derived vaccines. While it is relatively easy to put the different pieces into place, managing the process, in tandem with scientific advancements and the development of the product, remains a major challenge.

Based on a preliminary review of a specific plant-derived vaccine against hepatitis B virus, it was concluded that (1) the IP issues are fairly clear, although additional FTO analysis will be required to address specific cases, (2) the issues can be addressed with straightforward IP management approaches, and (3) the impact on the cost of finished vaccine is expected to be minimal. If a great deal of the work is conducted in developing countries, the IP management issues will be significantly simplified, since a number of the relevant patents may not have been filed in developing countries and thus the need for licenses would be reduced significantly (unless the products are exported to countries where a patent thicket existed).

2.2 *Types of intellectual property and material property rights associated with plant-derived vaccines*

Increasingly, IP rights influence every stage of vaccine development. In this section, the specific aspects of IP management are considered as tools to (1) achieve freedom to operate, (2) capitalize on new inventions, and (3) achieve the highest possible level of accessibility and affordability in developing countries. The relevant IP includes patents, trademarks, know-how/trade secrets, plant variety protection (PVP), and tangible property (such as research materials obtained through agreements). For practical purposes, we consider IP management at three different levels:

- incoming third-party intellectual property
- newly generated intellectual property, and
- outlicensed intellectual property

2.2.1 *Third-party intellectual property*

Third-party intellectual property considerations relate to tangible and intangible property and the relevant contractual obligations.

Tangible property. The components of tangible property typically comprise plants, genes, vectors, and the conditions under which such material property was obtained. In most cases, public germplasm or varieties are available (including corn, tomatoes, and tobacco). Whereas scientists in public research institutions typically prefer to obtain such materials from colleagues, the resulting material transfer restrictions should not be underestimated. In the private sector, it would be more typical to have genes synthesized, which avoids the material transfer restrictions on the genes.

Other tangible property issues involve the machinery required for bioprocesses.

Intangible property. The intangible property aspects are often more complex. Among the reasons for this complexity is that intangible property takes many forms, including utility patents, trademarks, trade secrets/know-how, plant variety protection/plant breeders' rights and plant patents (including utility patents on plants).

- ***Utility patents.*** Much of the third-party intellectual property will be in the form of utility patents. A detailed FTO opinion will be based on the specific antigen, process, and market in which the products are to be sold. In countries where certain patents are not issued, licenses will not be required either for the production or the sale of such vaccines.

- ***Plant variety protection/plant breeders' rights, plant patents (United States only) and utility patents on plants (mainly United States).*** Depending on which crop is being used, different types of intellectual property may apply. For example, it is becoming increasingly common for companies and universities alike to seek utility patents on inbreds and hybrids of corn, and for varieties of soybeans, cotton, fruit trees, and ornamental plants. If such protected material were used, a license may need to be obtained to use the plant or export it for production in other countries. Similarly, with the advent of new PVP regulations (under the 1991 UPOV [International Union for the Protection of New Varieties of Plants] treaty), a variety with PVP could not be used to produce plant-derived vaccines within the duration of the certificate's validity, because inserting one gene or a set of genes would make it an "essentially derived" or protected line.[6]

  However, many of the IP problems described here can be avoided if appropriate strategies are pursued from the outset. This could, for example, entail the use of public germplasm instead of proprietary varieties. Such a step may not be a feasible nor cost effective since some newer varieties might be the highest yielding or provide the highest regeneration efficiency during genetic modification work.
- ***Trade secrets/know-how.*** Some of the critical steps of bioprocesses lie in the know-how or trade secrets. Know-how refers to the knowledge of how something is produced, and not the specific components that constitute a product. Know-how can be licensed through appropriate confidentiality or secrecy agreements. Requirements for licensing, however, vary widely from country to country and certain information may not be legally protected in many jurisdictions.

Cost implications. Traditionally, in-licensed intellectual property has considerable impact on the cost and pricing of vaccines. Estimates of the licensing fees vary widely—from as high as 20% of sales prices for newly introduced vaccines, to as low of 2% for haemophilius influenzae type B. However, this comparison of royalty rates does not help much when it comes to plant-derived vaccines, since the total royalties of all in-licensed IP will depend on the type of product, the number of patents, and type of market. Manufacturing costs per vaccine can be reduced by economies of scale/increased production, but, in such cases, royalty fees are unlikely to be affected since they are generally fixed percentages of the sale price of each dose.

In terms of possible royalty rates for the hepatitis B model that has been mentioned in this chapter, it is perhaps premature to speculate on royalty ranges and licensing terms, since such speculation may influence the type of deal that could be obtained. Nevertheless, it seems that reasonable royalty rates *in aggregate* would add no more than 1% to 5% to the estimated total production costs.

Finally, in addition to the costs related to in-licensed IP, IP-management-related expenditures will be incurred during the R&D phase. These include expenditures for FTO opinions, which will need to be commissioned well ahead of production. Typical FTOs cost $20,000 to $100,000, depending on the complexity of the technology.

3. DETAILED ANALYSIS FOR HEPATITIS B VIRUS VACCINE

3.1 *Research*

Since the decision of the Supreme Court of the United States on *Merck v. Integra Life Sciences* in 2005,[7] analysts contend that, with the broadened definition by the Supreme Court of the Hatch-Waxman Act[8] as it relates to data exclusivity, research in preparation of FDA approval is exempt from the requirement for research licenses. Although this broad conclusion has not been tested within specific circumstances in the lower courts, it is reasonable to assume for hepatitis B that there are no IP constraints during the research phase, until clinical trials are complete and, possibly, the submission of an investigational new drug (IND) application to the FDA.

3.2 *IP components*

3.2.1 *Patents related to the hepatitis B vaccine (HBV)*

Many of the existing patents related to HBV are unlikely to be relevant for a number of reasons. First, several surface antigens are either in the public domain or their patents are limited to parenteral[9] administration, rather than oral delivery, or the claims do not cover their production in plants. In addition, the patent issued in 1989 to Merck & Co, and the 1986 Chiron patent for the first recombinant vaccine (hepatitis B), will have expired by the time a plant-derived vaccine reaches the market. Furthermore, these patents seem to be limited to the production of virus-like particles in yeast only. A full FTO assessment will nevertheless be required to provide clearer answers and reveal other intellectual property related to the specific methods of production envisaged here.

3.2.2 *Plant transformation and antigen production in plants*

A preferred method of production for the HBV is through stable lines produced through agrobacterium-mediated transformation. The IP thicket related to agrobacterium is relatively complex and still evolving; at least one of the interference proceedings of agrobacterium-related patents filed prior to March 1995 is still ongoing, and no details on possible claims have been made public.[10] However, based on counterpart patents issued in Eurpoe, it is fair to assume that at least one license could be required from either Monsanto or Syngenta (since they, or companies they acquired, are presumed to have filed patents for agrobacterium-mediated transformation prior to March 1995).

The currently used plasmid is a derivative of the antigen pBin19 and may be covered by Monsanto patents. The promoter that drives the gene expression (CaMV 35S) and the selectable marker that allows for the selection of transformed cells (nptII) are both covered by Monsanto patents. Other patents may also cover the applications; these will be identified during an FTO. However, broad patents are not known to these authors that cover all transgenic corn, tomato, or tobacco. There might be some differences in agrobacterium-related patents depending on whether a monocotyledoneous or dicotyledoneous plant is used. These differences, however, will not materially affect the conclusions related to the key licensing requirements.

3.2.3 *Broad plant-made pharmaceutical patents*

Three of the most often cited patents related to plant-made pharmaceuticals for oral administration are the Curtiss-Cardineau patents (U.S. patents No. 5,654,184, 5,679,880 and 5,686,079), assigned to Washington University in St. Louis, but now owned by Dow. However, all claims of the three patents are limited to oral administration of "transgenic plants" or of "transgenic plant tissue." It is unclear whether the Curtiss-Cardineau patent would cover the oral administration of antigens "extracted" from plant tissue.

3.2.4 *Bioprocess facility*

Many aspects of a bioprocess facility (which is required for the extraction, purification and processing of the vaccine) are covered by the very broad U.S. patent No. 6,617,435 B2 and U.S. application No. 2004/0166026 A1 and, possibly, patents that are continuations, divisionals, foreign counterparts, reissues, reexaminations, and continuations-in-part of known patents. The former is assigned to the now-defunct Large Scale Biology (LSB) Corp. in Vacaville, California; the latter, if issued, also would be assigned to the successors of LSB Corp.[11] Since much of this bioprocess facility design would draw on the trade secrets and know-how of LSB Corp., a license from LSB Corp. or its successor would be highly desirable.

3.2.5 *Cost implications*

Production of plant-derived hepatitis B vaccines through plant transformation and antigen production in plants is expected to require a number of licenses. These should be obtainable, especially because the proof of concept has already been demonstrated and confidence built into the technology. In aggregate, licenses for HBV

technology, plant transformation and broad molecular pharming patents, the total royalties should not add more than 1% to 3% to the cost of production. This estimate is based on common industry licensing practices.

Bioprocess patents are in a different category because know-how is important for the construction and operations of bioprocess facilities. Nevertheless, favorable terms for a license that would not exceed 1% to 3% of the cost of production could likely be obtained.

3.3 *New intellectual property*

3.3.1 *Utility patents*

During the development of plant-derived vaccines, certain new inventions will emerge that might be patentable. Aside from the typical inventions related to antigens, plant transformation systems, and related technologies, innovative business models and production processes might also be developed. Care should be taken in making decisions about whether or not the inventions should be patented, kept as trade secrets, or made public and consideration given especially to the best ways to make the plant-derived vaccine available at affordable prices to the neediest countries in the developing world. This goal is more likely to be achieved if a certain level of control over the vaccine is retained.

3.3.2 *Trade secrets/know-how*

Many critical aspects of the operations of bioprocessing facilities are valuable knowledge. In some jurisdictions, this knowledge can be protected under trade secret law. It is customary for any pharmaceutical production plant to keep its standard operating procedures as trade secrets, given the considerable time and resources involved in fine tuning operations. By extension, employees of such plants will need to be informed of procedures for keeping information confidential and should have related clauses in their employment contracts.

3.3.3 *Trademarks*

One expense that might be worth considering is the creation of a quality seal for all plant-derived vaccines that are made using the processes outlined in this chapter. Such trademarks could be valuable and would afford a level of quality assurance and control not otherwise available.

3.3.4 *Cost implications*

Obtaining IP protection through utility patents, and trademarks incurrs legal and government filing fees (especially if trademarks are pursued in multiple countries). (Trade secret protection, on the other hand, costs nothing.) There will also be expenses related to ongoing licensing negotiations. Nonetheless, the added cost for the protection of new intellectual property will undoubtedly be small compared to overall production costs. The expenses would likely add no more than US$10-100,000 per year to the cost of production. In time these costs can be recovered, and the IP may even lead to a modest royalty stream if licensed.

4. CONCLUSIONS

The chapter's survey of intellectual and material property issues was based on a cursory FTO review. We attempted to highlight key issues and estimated the possible costs associated with the resolution of these. As the current research emphasis evolves into a product development program with more downstream considerations, a detailed FTO will be required leading to in- and out-licensing of intellectual property. To successfully move the candidate vaccine through the various stages from research to commercialization will also require the development of a global access strategy to reach developing country markets.[12] For this, various components will need to be integrated, including regulatory aspects, manufacturing, access to markets/distribution, and trade. IP management then essentially becomes nothing but a useful tool for reinforcing the vaccine development and deployment/marketing strategy. ■

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1 Arntzen C, B Dodet, R Hammond, A Karasev, M Russell and S Plotkin. 2004. Plant-derived Vaccines and Antibodies: Potential and Limitations. *Vaccine* 23:1753-1885.

2 The *first generation* products are the agronomic traits (such as insect resistance, herbicide tolerance, and drought tolerance), and the *second generation* are nutritionally enhanced plants (including omega-3 fatty acid enrichment, vitamin A and E production, high oleic soybean oil, low saturate canola oil, and high beta carotene oilseeds).

3 ASU. 2006. *Blueprint for the Development of Plant-derived Vaccines for the Poor in Developing Countries*. Prepared by PROVACS-Production of Vaccines from Applied Crop Sciences, a Program of The Center for Infectious Diseases and Vaccinology. The Biodesign Institute at Arizona State University: Tempe. www.biodesign.asu.edu/centers/idv/projects/provacs.

4 Arntzen C, R Mahoney, A Elliott, B Holtz, A Krattiger, CK Lee and S Slater. 2006. *Plant-derived Vaccines: Cost of Production*. The Biodesign Institute at Arizona State University: Tempe. www.biodesign.asu.edu/centers/idv/projects/provacs.

5 Ibid. It is interesting to note that a sensitivity analysis that reduced the yield of antigen in the plant by a factor of three was also conducted. This is equivalent to increasing the required dose by a factor of three; all other variables such as capital and labor costs have little impact on final cost if they are varied within reasonable ranges. This sensitivity analysis shows that under worst-case conditions, the cost per dose of a product made in the US and prepared in a ten dose packet would rise to $0.09 from $0.06.

6 See, also in this *Handbook,* chapter 4.7 by M Blakney.

7 Justice Scalia drafted the Court's opinion. He wrote: "*As an initial matter, we think it apparent from the statutory text that 35 U.S.C. § 271(e)(1)'s exemption from infringement extends to all uses of patented inventions that are reasonably related to the development and submission of any information under the FDCA. Cf. Eli Lilly, 496 U.S., at 665-669, 110 S.Ct. 2683 (declining to limit § 271(e)(1)'s exemption from infringement to submissions under particular statutory provisions that regulate drugs). This necessarily includes preclinical studies of patented compounds that are appropriate for submission to the FDA in the regulatory process. There is simply no room in the statute for excluding certain information from the exemption on the basis of the phase of research in which it is developed or the particular submission in which it could be included.*" Refer to 545 U.S. 193, 125 S.Ct. 2372, *Merck KGaA v. Integra Lifesciences I, Ltd., et al.* No. 03-1237. Argued 20 April 2005. Decided 13 June 2005.

8 The Hatch-Waxman Act introduced data exclusivity for medicines in 1984 and allowed for patent extensions of up to five years to compensate for the loss of patent life in meeting regulatory requirements. This came with a trade-off: data exclusivity for pharmaceutical drugs and vaccines was reduced, allowing producers of generic medicines to use the abbreviated new drug approval (ANDA) process of the U.S. Food and Drug Administration (FDA) to gain approval for generic equivalents within six months. See also Derzko NM. 2005. The Impact of Reforms of the Hatch-Waxman Scheme on Orange Book Strategic Behavior and Pharmaceutical Innovation. *IDEA* 45:165–265.

9 In other words, administration of a vaccine by a route that bypasses the gastrointestinal tract such as through the use of injections, patches, creams or sprays.

10 The filing date is important, since patents filed prior to March 1995, once issued, would be valid for 17 years from the date of issue (or 20 years from the filing date, whichever is longer) and may lead to so-called submarine patents that seem to appear from nowhere. This is because any patent filed prior to March 1995 is not published until issued. The rules changed as of March 1995: Any non-provisional patent application filed since then is published 18 months after filing.

11 It is likely that Kentucky Bioprocessing has at least non-exclusive licenses to a number of LSB Corp.'s patents.

12 Mahoney RT, A Krattiger, JD Clemens and R Curtiss III. 2007. The Introduction of New Vaccines into Developing Countries IV: Global Access Strategies. *Vaccine* (in press).