Compliance costs for regulatory approval of new biotech crops

To the editor:

The regulatory approval process for new biotech crop varieties is said to be slow and expensive, presenting important barriers to the development and commercialization of new cropping technologies. For some crops these barriers may be prohibitive, resulting in technological orphans. Alternative approaches to regulating new crop biotechnologies could be less expensive, but to date the private and social costs of the current regulatory system have not been analyzed or measured, let alone compared with alternatives. In fact, estimates of the compliance costs for the full regulatory approval of a biotech crop do not exist, as such information has been closely guarded by biotech developers.

Here, we make two contributions to knowledge concerning the private costs of complying with the current regulatory approval system for agrifood biotechnologies[1]. First, we characterize the structure of such compliance costs and identify key dimensions of their variability. Second, we provide estimates of representative compliance costs for selected maize biotechnologies. Our estimates are based on reviews and analyses of dossiers submitted to regulatory agencies, and firm-level data on associated expenses. Bayer Cropscience (Monheim am Rhein, Germany), DuPont (Wilmington, DE, USA), Monsanto (St. Louis) and Syngenta (Basel) provided confidential information on compliance costs. These four firms and their subsidiaries (that is, Aventis Cropscience (Research Triangle Park, NC, USA), Agrevo (Berlin), Plant Genetic Systems (Ghent, Belgium), Asgrow (Des Moines, IA, USA), Calgene (Davis, CA, USA), DeKalb Genetics (DeKalb, IL, USA), Seminis (Oxnard, CA, USA), Zeneca (Jealott's Hill, UK) and Northup King (Gilroy, CA, USA)), own or co-own almost 80% of all biotech traits that have received regulatory approval across the globe.

Structure of compliance costs

All biotech crops are submitted to a battery of tests and regulatory scrutiny before commercialization. The associated processes of experimentation, submission and regulatory review undertaken by biotech firms translate into compliance costs. Significant variance in compliance costs is expected as they will tend to vary from one regulatory submission (dossier) to another with differences in the number and type of field trials, analytical tests, bioinformatic analyses, animal studies and other comparative safety assessments, which are, principally, determined by:

- Which crop has been modified (e.g., maize, soybeans, tomato)?
- What novel trait has been introduced (e.g., insect resistance, herbicide tolerance, change in composition)?
- How many (and which) countries are petitioned for regulatory approvals?
- What kind of regulatory approvals are being pursued (e.g., production, importation)?

Despite their significant variance, we sought to define general categories of compliance costs that are characteristic of all regulatory submissions. To identify these general categories of compliance costs, we first interviewed lead scientists and regulatory affairs practitioners on the basics of regulatory submissions. We also obtained and analyzed representative dossiers for various novel maize traits submitted over the past ten years. Using these representative dossiers and relevant cost data provided by biotech developers, we next added structure to the compliance costs by identifying aggregate categories that were characteristic across all types of dossier submissions. Last, we evaluated the degree of overlap among multiple submissions for the same technology across various national regulatory systems and the incremental compliance costs associated with each additional international market where regulatory approval was sought.

Following these steps, we organized private compliance costs, both variable and fixed, into the categories listed in **Table 1** and **Table 2**, which adequately characterized all reviewed dossiers.

To provide representative figures for each of these categories, we standardized private compliance costs along certain key dimensions (trait, crop and countries petitioned). Specifically, we evaluated, and report here, compliance costs incurred by the cooperating biotech developers seeking regulatory approval of herbicide-tolerant and insect-resistant maize in ten key producing and importing countries (Argentina, Australia, Canada, China, the European Union (EU), Japan, Korea, the Philippines, Taiwan and the United States). Compliance costs for successfully

Table 1 Compliance costs for insect-resistant maize

Cost categories	Range of costs incurred ($)
Preparation for hand-off of events into regulatory	20,000–50,000
Molecular characterization	300,000–1,200,000
Compositional assessment	750,000–1,500,000
Animal performance and safety studies	300,000–845,000
Protein production and characterization	162,000–1,725,000
Protein safety assessment	195,000–853,000
Nontarget organism studies	100,000–600,000
Agronomic and phenotypic assessments	130,000–460,000
Production of tissues	680,000–2,200,000
ELISA development, validation and expression analysis	415,000–610,000
EPA expenses for PIPs (e.g., EUPs, tolerances)	150,000–715,000
Environmental fate studies	32,000–800,000
EU import (detection methods, fees)	230,000–405,000
Canada costs	40,000–195,000
Stewardship	250,000–1,000,000
Toxicology (90-day rat)—when done	250,000–300,000
Facility & management overhead costs	600,000–4,500,000
Total	*7,060,000–15,440,000*

ELISA, enzyme-linked immunosorbent assay; EPA, US Environmental Protection Agency (Washington, DC); EUP, experimental use permit; PIP, plant-incorporated protectant.

guiding a single maize event through the regulatory process are reported in the form of ranges in **Table 1** and **Table 2**. The costs of withdrawn events are not included in the figures. To preserve the confidentiality of firm-level data used, we do not report the means of the total compliance costs or of the individual cost categories. When possible, compliance costs unique to a country because of its specific regulatory requirements are separately reported (e.g., EU requirements for development of detection methods).

It should be noted that the compliance costs reported here are representative. The cooperating biotech developers, for instance, own or co-own all 24 maize events that have been approved in the United States. Given the data we use, however, the compliance costs we report are representative of recent approvals (e.g., MON 863, NK 603 or TC 1507) and not as much of older ones (e.g., MON 810, BT 11, 176 or T25). Even so, these more-recently approved events represent a large share of all commercialized maize biotech traits today. For instance, of the 78,750,000 maize acres grown in the United States in 2006, 52,350,000 were planted with biotech hybrids. Of those, 37,864,000 (72%) were planted with single or stacked events whose regulatory compliance costs are considered in this study.

The magnitude of compliance costs

Several observations can be readily made from the compliance costs reported in **Table 1** and **Table 2**. First, there is a wide variance in the total compliance costs incurred by biotech developers. Indeed, the reported variance is much higher than expected considering that key sources of variation in compliance costs (e.g., the type of modified crop, the specific countries where regulatory approval is pursued and the types of traits introduced) have been minimized. The variance is even larger within the individual compliance cost categories. To be sure, some firm-level differences in the individual cost categories and total compliance costs are the result of differential accounting and budgeting practices among firms.

More importantly, however, these differences are also attributable to the variable strategies followed by biotech developers as they pursue regulatory approval of their innovations. These strategies are shaped by the (apparently distinct and often evolving) developers' expectations of the appropriate number and types of field trials, analytical tests and assessment studies that are likely to satisfy the various national regulators. For instance, some firms regularly submit toxicology (90-day rat) studies whereas others consider them irrelevant and do not include them in their dossiers. Similarly, compliance costs can vary drastically depending on the number of events advanced by the developers through various regulatory stages as a strategy to manage uncertainty.

Table 2 Compliance costs for herbicide-tolerant maize

Cost categories	Range of costs incurred ($)
Preparation for hand-off of events into regulatory	20,000–50,000
Molecular characterization	300,000–1,200,000
Compositional assessment	750,000–1,500,000
Animal performance and safety studies	300,000–845,000
Protein production and characterization	620,000–1,725,000
Protein safety assessment	195,000–855,000
Agronomic and phenotypic assessments	130,000–460,000
Production of tissues	680,000–2,200,000
ELISA development, validation and expression analysis	415,000–610,000
Herbicide residue study	105,000–550,000
EU import (detection methods, fees)	230,000–405,000
Canada costs	40,000–195,000
Stewardship	165,000–300,000
Toxicology (90-day rat)—when done	250,000–300,000
Facility and management overhead costs	560,000–4,500,000
Total	6,180,000–14,510,000

Second, among all variable compliance cost categories, four dominate: first, production of tissues; second, compositional assessment; third, protein production and characterization; and fourth, molecular characterization. Indeed, these four cost categories represent ~60% of all variable costs.

Third, overhead costs for facilities and management are also very significant as they represent between 10% and 20% of the total compliance costs for various firms. Clearly, such costs are most challenging to measure as facilities and regulatory management are shared across multiple traits and events for various crops, all being advanced in parallel at their individual development speeds. Overhead costs also include regulatory outreach and other relevant activities.

Although accounting and budgeting nuances make measurement of overhead costs difficult, their accurate assessment is essential for the identification of potential scale and scope economies. Our preliminary assessment indicates that there are no discernible fixed cost advantages and thus we could not detect economies of scale and scope. This may be the result of the regulatory slow-down that has occurred in recent years, suggesting that, at least temporarily, a larger than necessary management and facility capacity is being maintained by larger biotech firms. It may also be the result of the limited variance in the firm size studied here or other data limitations.

Fourth, the gap in the compliance costs between insect-resistant and herbicide-tolerant maize is lower than expected. Indeed, it appears that over time, firm strategies on how to develop regulatory dossiers for those two types of traits have converged and so have the relevant compliance costs incurred.

Finally, the compliance costs incurred by biotech developers and reported here appear to be quite high, considering that they represent only part of the regulatory burden of novel biotech crops. Specifically, only direct compliance costs are reported here, counted as such by most biotech developers only after a formal assessment process with strict standards known as 'good laboratory practices' has commenced. Informal preregulatory safety assessments of various discovered proteins and events are regularly carried out but are normally budgeted as R&D costs. Similarly, indirect private compliance costs from unnecessary and unexpected regulatory delays are not presented here. These costs include

increased expenditures (e.g., for seed inventories that are carried over), foregone profits from delays in commercialization, costs for channeling and segregating biotech crops away from certain markets in cases of partial approvals, and others. Such indirect regulatory costs are likely significant but more difficult to estimate than direct ones.

Conclusions

Economists have estimated the social benefits from biotech crop varieties to be in the billions of dollars, with the benefits shared among consumers, agricultural producers and the biotech innovators that have developed the new crop varieties[1,2]. In spite of this apparent success, however, many observers have been disappointed at the rate of development and commercialization of new biotech crops[3]. Indeed, the accumulating evidence suggests that agbiotech innovation and product development have recently slowed down, and high compliance costs for regulatory approval have been cited as a key culprit[3–6]. Assessments of whether compliance costs are 'high' or 'low' are arbitrary and subjective unless they are made against an appropriate benchmark. The figures reported here are, no doubt, large in an absolute sense, especially because they represent costs incurred by biotech developers upfront and on top of R&D expenses, whereas commercial success is an uncertain outcome. Clearly, further research is needed to assess how such costs vary from one crop to another and whether they are large enough to discourage development of biotech traits in certain crops with limited market size, leading to unrealized potential productivity gains and technological orphans.

Further research is needed to assess how compliance costs vary from one crop to another and whether they are large enough to discourage development of biotech traits in certain crops with limited market size

An additional important question that needs to be addressed is whether compliance costs have increased over time. To answer this question, one must evaluate changes in the compliance costs over time. Such assessments are extremely difficult considering the relatively small number of regulatory approvals that have been spread over a relatively long period of time. Nevertheless, some incomplete data and our cursory comparisons of dossiers that have been submitted over time indicated certain differences. Most obvious are expansions of the molecular characterization of the genetic modification studies and of the stewardship plans with parallel increases in the compliance costs. Other supportive safety assessments also appear to have become more complex and voluminous, but we do not have sufficient data to accurately measure any relevant cost changes, if any have occurred. Clearly, these last issues are important in their own right and deserve additional detailed research.

ACKNOWLEDGMENTS

This research was supported by the Illinois-Missouri Biotechnology Alliance from a USDA special grant.

COMPETING INTERESTS STATEMENT

The authors declare no competing financial interests.

Nicholas Kalaitzandonakes[1], Julian M Alston[2] & Kent J Bradford[3]

[1]Department of Agricultural Economics and Director of the Economics and Management of Agrobiotechnology Center, University of Missouri-Columbia 131 Mumford Hall, Columbia, Missouri 65211, USA. [2]Department of Agricultural and Resource Economics and Agricultural Issues Center, 2157 Social Sciences & Humanities Building, 1 Shields Avenue, University of California, One Shields Avenue, Davis, California 95616, USA. [3]Department of Plant Sciences and the Seed Biotechnology Center, 1107 Plant Reproductive Biology, 1 Shields Avenue, University of California, One Shields Avenue, Davis, California 95616, USA.
e-mail: KalaitzandonakesN@missouri.edu

1. Falk-Zepeda, J.B., Traxler, G. & Nelson, R.G. *Am. J. Agric. Econ.* **82**, 360–369 (2000).
2. Huang, J., Rozelle, S., Pray, C. & Wang, Q. *Science* **295**, 674–677 (2002).
3. Jaffe, G. *Withering on the Vine: Will Agricultural Biotechnology's Promise Bear Fruit?* (Center for Science in the Public Interest, Washington DC, 2005). <http://www.cspinet.org/new/pdf/withering_on_the_vine.pdf> (Accessed January 12, 2007).
4. Bradford, K.J., Van Deynze, A., Gutterson, N., Parrott, W. & Strauss, S.H. *Nat. Biotechnol.* **23**, 439–444 (2005).
5. McElroy, D. *Nat. Biotechnol.* **21**, 996–1002 (2003).
6. Miller, H.I. & Conko, G. *Issues Sci. Technol.* **21**, 76–80 (2005).