

Industry Views of Minor Crop Weed Control

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The level of past industry participation in registering herbicide minor crop uses has been a function of active ingredient discovery output and the combination of incentives and barriers that drive minor use registration decisions. Over the past 10 yr there have been several external factors negatively impacting the rate of new herbicide introductions by industry. These include industry consolidation, a decrease in the global value of the conventional herbicide market, adoption of Herbicide-Resistant Crop (HRC) technology, a substantial increase in required regulatory activity primarily through reregistration programs, and increased costs of discovery research and product development. The increased cost of conducting business in an increasingly competitive market has undoubtedly influenced herbicide registrants to adopt different discovery strategies. Economics dictate registration efforts only towards crops that will create a significant, positive return on investment. In most cases, development of new herbicides for minor crops is not economically viable due to low or negative return on investment and disproportionate liability risk. Therefore, to motivate increased participation, companies need incentives and mechanisms to mitigate risk and registration barriers. Increased data protection and the Interregional Project 4 (IR-4) program, a cooperative government program with the goal of developing data to support regulatory clearances of pest control products for specialty crops, are current government programs in place that provide incentives and defray cost. Other incentives should be explored to make minor crops more attractive targets. However, product registration, liability risk, and dedicating the necessary resources to adequately research crop selectivity are still major economic barriers. Creative solutions that ensure companies are not unreasonably exposed to yield loss claims would remove a primary reason why companies are reluctant to register herbicides for minor crops.

Key words: Barriers, GMOs, herbicide-resistant crops, herbicide-tolerant crops, HRC, IR-4, minor crops, patents, specialty crops, weed control, industry view.

New herbicide discovery and development efforts are almost exclusively directed towards major crop market uses due to the rigorous financial hurdles required of pesticide industry corporations (Rotteveel and Powell 2003). Minor crops are rarely considered during the discovery and initial development phase but are considered at later stages of the product life cycle, depending on various factors. Most existing minor crops uses are typically the result of serendipitous selectivity uncovered after initial active ingredient registration. Still, without certain incentives, development of herbicides for use in minor crops can be a difficult choice for pesticide companies because the financial payback is usually insufficient when weighed against the cost of registration for a single small acreage crop (Baron et al. 2003). Additionally, many minor crops have the distinction of having a relatively high value, increasing the liability risk for the potential registrant in the event crop yield losses are incurred (Bischoff 1993). Even with these impediments, numerous minor crop registrations obtained over the years have provided at least some weed control tools for growers (Holm et al. 2005). Current unmet needs, changing weed control issues, and loss of older products necessitate the need for new herbicide tools for these markets in the future (Hall et al 2000). However, recent changes in the pesticide industry and the herbicide markets likely have decreased the potential prospects for new herbicide discovery for both major and subsequent minor uses in the future. This paper discusses the impact of these changes, and ideas for incentives and elimination of barriers to industry participation.

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Challenges to Future Herbicide Development for Minor Crops

Because minor crop registrations usually result from exploitation of herbicides originally targeted for major agronomic crop markets, the number of potential future minor crop registration opportunities more than likely will be proportional to the industry-wide production rate of new herbicide active ingredients. Recent industry trends point to lower output of new conventional herbicides in the future, however. For example, although the global rate of new herbicide active ingredient commercial launches over the period of 1980 to 2001 was an average of about 6 per yr, the average rate of launches over the following 5 yr, 2002 to 2006, was 2 per yr. The lower output rate is indicative of several recent industry trends. Industry consolidation accelerated during the mid to late 1990s, and even though the total number of herbicides already in the market usually was not reduced, consolidation did reduce the total number of discovery operations. The decreased rate of new active ingredient output did not start until the early 2000s, after the discovery compounds which were in development before consolidations went through the registration process, because the typical development timeline from discovery to launch is 6 to 8 yr. Concurrent with the consolidation trend was the commercialization of HRC technology in the late 1990s, most notably with glyphosate-resistant crops (Dill 2004; Duke 2005). Soybeans, corn, cotton, and canola markets were most affected by the strong adoption of this technology because value of non-HRC herbicides in these markets was significantly reduced (Duke 2005). As a result, discovery research and development of selective herbicides for these crops has

likely been reduced or eliminated by many pesticide companies.

Economic pressures have also influenced the overall level of investment in selective herbicide discovery. The total global value of the conventional chemical crop protection market has shown a modest decline in recent years (Dow AgroSciences, unpublished data). Global herbicide sales were flat (0.7% growth rate) for the 5 yr following the year 2000 and are predicted to remain relatively flat for the next 5 yr. These trends likely are due, in part, to a maturing industry but also can be attributed to the increasing number of herbicides becoming nonproprietary as patent protection ends. Generic pressure is expected to increase in the future, especially for some key products coming off, or about to come off patent. Competition with generics has usually led to lower margins and loss of income stream on some products. Lower sales and profitability are likely to further constrict discovery and research and development resources, sometimes forcing companies to redirect or invest less in these areas.

The opposite side of the economic equation includes the expenses required to bring new products to market and to defend existing portfolios. Estimated at about 23 million dollars in the late 1970s, the cost to discover, develop, and bring a new active ingredient to market has risen dramatically over the years, growing to 154 million dollars by 1995 and an estimated 184 million dollars in the year 2000 (Crop Life America, unpublished data). Additionally, the cost of maintaining registrations through reregistration activities is becoming an increasing proportion of research and development budgets. These increased costs in an overall flat pesticide market would force companies to be more selective in the breadth and direction of future research and development investments. For instance, some companies might have shifted scarce discovery resources away from herbicides in favor of other crop protection areas not imminently threatened by biotechnology replacement, or away from conventional chemistry in favor of biotechnology-related research.

The driving forces outlined above most likely have resulted in an overall decline in industry investment in herbicide discovery and continued movement towards a lower rate of new active ingredient output in the future. As a result, the future pool of new herbicide active ingredients to be exploited for minor crop use will be smaller compared to what has been available in the past. Although the innovation pace might be reduced by this trend in the foreseeable future, the dynamic nature of weed control problems will continue to reward innovative solutions.

Registration Concerns and Issues

As mentioned previously, the decision to support a new minor crop registration requires the registrant to carefully consider several influencing factors including registration costs, impacts on other registered uses, and liability exposure. New crop uses usually require residue trial data over multiple locations. In addition to the costs of conducting residue trials, there are also other direct and indirect costs associated with creating a regulatory submission package, such as residue analyses, report writing, exposure risk assessments, tolerance

petitions, label production, and regulatory manager support. In cases where IR-4 supports the minor crop use, many of these costs are defrayed. Registrants must still provide the necessary regulatory support to gain and maintain registrations, however, and these activities are increasingly measured for financial return.

Regulations outlined in the Food Quality Protection Act (U.S. EPA 1996) concerning aggregate risk also have impacted minor crop herbicide registrations. Aggregate risk takes into consideration both dietary and nondietary exposure risks from a given pesticide. Each additional use of the pesticide must be weighed for its effect on the allowed aggregate exposure amount. Sometimes the addition to aggregate risk from minor crop use is viewed as excessive or disproportionately high, and in turn, potentially limiting use of the pesticide in major markets with higher economic returns. Although usually not an issue with newer chemistries, each new use still must be weighed in context to existing and future potential business impacts.

Unlike other types of pesticides, herbicides have additional costs for field trials to evaluate crop selectivity. Crop injury can be difficult to predict and cannot be taken for granted; therefore, research and development costs necessary to thoroughly convince companies that injury claims will be avoided can be significant. In some cases, experience with related crops or the innate safety of the herbicide's mode of action can reduce the need for evaluation. However, most herbicide uses require thorough selectivity testing under the many potential environmental and edaphic conditions encountered in commercial use. Minor crops can possess a relatively high value per acre, necessitating a precise assessment of selectivity, especially because many of these crops are grown over varied climates. The cost of adequate field research programs in addition to potential losses from crop injury claims can be perceived to easily offset future financial returns. This aspect alone can deter companies from labeling a minor crop use even if all other registration costs are minimal.

Addressing Incentives and Barriers to Participation

Because development of new herbicides for minor crops usually is not economically viable due to low or negative return on investment and disproportionate liability risk (Bischoff 1993), participation by companies usually requires incentives and mechanisms to mitigate risk. There are several government-based incentive programs in place. The IR-4 program is a very necessary component because it defrays the costs of residue trials and analyses as well as residue tolerance petitions. However, IR-4 annual budgets are usually not large enough to cover the cost of all requested projects. Therefore, the list of projects is prioritized for funding, with most requests deferred for future consideration. In spite of the funding limitations, the IR-4 program has been effective and needs to remain viable because unfunded projects are rarely acted upon by industry.

"Extended" data protection mechanisms, which can result in additional years before generic entry into the market, are a relatively recent addition to the Environmental Protection

Agency (U.S. EPA) registration system. The new system, implemented in 1996, still provides 10 yr of initial active ingredient core data protection and now rewards the initial registrant 1 additional yr (up to 3) of protection per three minor crop registrations. Because the 18-yr patent period for an active ingredient is often almost halfway completed before a first registration, and the registration process for a generic compound cannot begin until this core data protection period ends, an additional 3 yr of protection against generic entry can motivate companies to consider minor crop uses. In addition to the initial active ingredient registration, companies usually file subsequent patents involving mixtures, formulation, synthesis process, etc. These patents potentially provide longer protection periods than the additional years gained from minor crop registrations through the new registration data protection mechanisms, and therefore in many cases these strategies are preferentially pursued because they provide worldwide protection. As a result, the incentive can be less attractive for companies to take advantage of the data protection mechanism by registering minor crop uses.

Registrants could be further motivated to include minor along with major crop uses in a registration package if the EPA registration process was augmented further to allow reduced data requirements through the use of surrogate data (from residues on closely related crops), waiving tolerance and registration maintenance fees, reduced initial registration fees, and expediting the EPA submission package review if a minor crop use is included (Bischoff 1993). The current registration fees for initial active ingredient food uses, including the recently implemented EPA “fee for service” program (Pesticide Registration Improvement Act) costs, are substantial at \$500,000 for an initial compound submission. Although a reduction in these fees could be motivating, the new fee for service program promises to have predictably shorter review times compared to the past, so a request to further reduce package review time based on inclusion of minor crops might be difficult for EPA to consider. Moreover, hastening a product launch into the market usually has more financial impact than research and development expenses.

An extended patent period for the initial active ingredient registrant if minor crop uses are added before the 18-yr patent protection expires is another potential idea that could be explored. Patent extension could be more motivating than the recently added data protection mechanisms depending on how much time is left in the patent life. It might be more problematic to implement because it involves a different government agency, the U.S. Patent and Trademark Office, and could be legally challenged by generic manufacturers.

Barriers to industry participation in minor crop use registrations include the direct and indirect costs of registration already mentioned, however the main barrier is liability exposure from potential crop injury or yield losses. These risks are assumed for any registered use; however, most agronomic crop values range in the hundreds of dollars per hectare, whereas many minor crops are valued in the thousands of dollars per hectare. Also, because major crop products are usually priced for optimum market penetration, the sales and profit potential of these products in minor crops is disproportionately small compared to the size of potential

losses where one significant claim could erase years of profits. This barrier is inadequately addressed with current liability protection solutions which minor crop commodity groups have championed in order to gain registrations for their crops, such as “waivers of liability.”

Minor uses deemed of low risk usually are registered using federal labeling or state special local need (SLN) labels. To mitigate liability exposure with higher-risk uses, the typical registration approach has been to use only SLN labeling with separately attached waivers of liability, including user signatures or indemnification language. These types of waivers are not allowed on federal labels, so the only way some minor crop uses have been registered is through SLN labeling. The EPA limits the number of states using SLN labeling for any particular product crop use, however. In addition, signed waivers of liability are cumbersome and difficult to manage for registrants because they must administer the process of delivering the label, collecting user signatures, and storing records. An improved approach recently has been allowed. The EPA approved indemnification language that could be included directly on the SLN label rather than requiring a separate waiver with signatures or indemnification language (U.S. EPA 2006). Although user signatures are no longer needed, to further distance themselves from liability exposure, registrants sometimes ask that third parties, such as grower associations, request the SLN label from the state, rather than requesting it themselves.

Even though all of these improved approaches increase the likelihood of a successful legal defense for registrants against liability claims, they do not necessarily help to avoid costly litigation, however. Therefore, in order to remove liability exposure as a registration barrier, more innovative approaches need to be considered. For instance, the United Kingdom and other European countries have adopted the concept of “Specific Off-Label Approval (SOLA)” (PSD 2005). SOLAs are employed for uses not supported by the manufacturer but have been petitioned for by grower groups who also usually pay for any supporting data. Approvals are granted by the regulatory authorities and electronic copies of the SOLA (including use directions) are posted on their website. Most importantly, before downloading the SOLA, the user is advised on the website that “the use in this case is undertaken at the user’s choosing, and the commercial risk is entirely theirs.” Allowing SOLAs appears to be a pragmatic approach balancing the needs of growers and registrants. Introduction of this concept in the United States would probably require strong support from registrants, grower associations, and other entities since legal study and most likely change of pertinent laws would be necessary.

Summary

Future herbicide discovery efforts, the pace of innovation, and new active ingredient introductions will be reduced in the future. More than ever, the high cost and risks associated with developing and maintaining supportive data package necessitate focus on major crops. Even more imperative, therefore, is placement of proper incentives and removal of certain barriers to participation in order to help facilitate new minor

crop registrations with the few new and remaining products. Reducing liability barriers must be part of the equation. Continued funding of the IR-4 project along with enhanced manufacturer registration and intellectual property incentives will be necessary to ensure adequate tools exist for successfully meeting future minor crop needs.

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