Phillips McDougall

The cost and time involved in the discovery, development and authorisation of a new plant biotechnology derived trait

A Consultancy Study for Crop Life International

September 2011

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Introduction

The first plant biotechnology trait with applications in modern Agriculture was introduced in 1995. Since that time the number and complexity of biotechnology derived traits utilised in the agricultural sector has increased significantly. Expenditure by companies on new trait discovery and development programmes has also increased.

This study was designed and carried out to determine the cost and duration associated with the discovery, development and authorisation of a new plant biotechnology derived trait that had received cultivation approval in two countries and import approvals from at least five countries.

The study excluded costs and time to develop and to obtain regulatory approval for breeding stacks involving multiple events which are the final product in most crops today.In addition the study was also targeted at determining the number of genetic units that are processed and the time involved in each stage of the overall R&D process.

Study Definitions

By utilising plant biotechnology techniques, researchers have been able to identify specific genes of interest, characterise their properties, and insert those genes within the genome of a particular plant. The result of which allows the implanted gene to express itself in the cell, and thereby confer the genetic trait to the host plant. Successful application of this technology has led to the development of a number of commercially important traits that enable plants to protect themselves against the action of specific herbicides, insect pests, viral attack, or to improve the nutritional properties. New plant varieties developed using these methods are commonly referred to as genetically modified plants.

The discovery, development and authorisation of a new plant trait using modern genetic engineering techniques is a complex and time consuming procedure. The overall R&D programme involved can be split into three main stages, first the research programme leading to the discovery of a new genetic sequence with useful biological properties, second its development and finally its authorisation by the appropriate regulatory authorities.

The discovery or research process to develop a new plant trait involves the identification of a genetic sequence that can be used to confer a new or altered biological activity or to suppress the expression of native genes for a plant metabolic pathway. Candidate genetic sequences are initially subjected to a series of biological research tests or screens which are designed to demonstrate the biological activity of the potential trait. The screening process is likely to involve a number of increasingly stringent biological tests that are designed to ensure that the new genetic trait has sufficient biological activity to merit further development.

Candidate genetic sequences are subsequently combined with different promoter sequences in order to develop the most suitable genetic construct. These optimised genetic constructs are introduced into the target crop for subsequent evaluation under greenhouse and/or field conditions

From these tests a number of genetic events will be identified or selected on the basis of their biological activity for introgression into the company's most elite germplasm. The resulting product-quality hybrids or varieties are further evaluated under field conditions to confirm the biological and commercial potential of the trait of interest.

The procedures described above are designed to produce a novel genetic trait suitable for full development in the target crop. In addition to developing a trait with commercial efficacy, the overall R&D process also involves agronomic testing to confirm commercial potential and a comprehensive suite of regulatory studies to ensure that the event satisfies the statutory requirements of the regulatory bodies in the countries where it will be cultivated and in countries which are major export markets for commodities derived from or produced by the plant. In addition intellectual property work will be undertaken to patent the plant biotechnology trait and protect the invention.

The results of the regulatory studies will be subsequently submitted to the various regulatory bodies for review. On approval the new trait is authorised or deregulated by the regulatory body bodies for cultivation or import, and commercialisation of the crop varieties containing the new genetic event can then take place.

The table on the following page contains a glossary of the main terms used in describing the research and development process for a new plant biotechnology event.

Glossary of Terms

Term	Definition
Allele	One of two or more alternative forms of a gene
Constitutive expression	The continual expression of a gene
Construct	The genetic sequence created to facilitate the production of specific gene products once inserted in a cell containing at minimum a promoter, a gene of interest, and a terminator
DNA	Deoxyribonucleic acid - Genetic code that is organised into structures
Endogenous genes	Native genes within an organism's genome
Gene expression	The generation of functional gene products from DNA/genes
Gene sequence shuffling	The random shuffling of a gene sequence
Genetic event	One or more unique genetic lines produced by transforming a specific construct into a plant cell
Genetic sequence	Typically a structure comprising of DNA organised into a gene or genes
Genome	Sum of the total genetic material within a cell
Homozygous	An organism that possesses two identical alleles for a particular trait
Hybrid	Progeny generated by crossing two different two inbred lines
Inbred	A genetically pure line, homozygous at all or most genetic loci
in silico	Performed on computer or via computer simulation
Introgression	The utilisation of conventional breeding methods to incorporate a genetic event into a commercial crop variety or inbred line
Progeny	Descendents or offspring
Promoter	A genetic sequence used to control the expression (timing and rate of transcription) of another genetic sequence
Random activation tagging	The random insertion of plant regulatory sequences throughout the host genome to activate endogenous genes and provoke pronounced and detectable phenotypes
Regulatory protein	A protein (transcription factor) that may activate or deactivate the transcription of a gene
Regulatory sequences	Small sequence of DNA responsible for the binding of regulatory proteins
RNA	Ribonucleic acid - Intermediate molecule in the production of gene products or for gene regulation as RNAi
Temporal expression	The activation of a gene and the production of its gene product at a specific time during the host organism's development
Tissue specific expression	Expression within a specific plant tissue
Trait	A distinguishing characteristic or quality conveyed by a gene sequence
Transcription	The generation process of RNA from a DNA sequence
Transcription factor	A regulatory protein that may activate or deactivate the transcription of a gene
Transgene	A gene introduced into a species from itself or from another organism by biotechnological processes
Transgenic	Crop plants containing additional genetic sequences derived from that crop or another organism
Unit	For the purpose of this study, Unit describes the relative candidate gene, construct, or genetic event for each activity stage of the R&D process as described in appendix 2

Study Scope

As described above, the primary aim of this study was to collect and evaluate data on several key parameters in the discovery and development process for a new plant biotechnology trait. The parameters to be investigated were:

- Cost of discovery, development and authorisation.
- The number of units processed by companies in order to commercialise one plant biotechnology derived trait.
- The time involved in each activity stage of the R&D process for a new plant biotechnology trait.
- The total time from initial discovery through to the authorisation and first commercialisation for novel plant biotechnology traits.

Methods

The study was carried out according to the protocol which is attached as Appendix 1.

The data for this investigation was collected from the results of a questionnaire (see Appendix 2) which was sent to the following group of Crop Life member companies.

The companies included in this survey were:

- BASF Corporation
- Bayer CropScience
- Dow AgroSciences
- DuPont / Pioneer Hi-Bred
- Monsanto Company
- Syngenta AG

On receipt, the results of each company response were added to a matrix in which each company was assigned a code number. Each company result was subsequently aggregated and the mean value of each particular category was calculated. The results of the responses are shown in the report as mean values however the variance within the actual responses is documented as Appendix 3.

In the case of Part 1 of the study, namely the evaluation of the cost of new product discovery and development, where a company response contained incomplete information on sub categories, the mean values were calculated on a pro rata basis to ensure that the mean category totals agreed with the sub category values.

Study results – Part 1

Cost of New Trait Discovery and Development

Six companies were surveyed to determine the situation for the cost of discovering, developing and registering a new plant biotechnology trait that was introduced or scheduled to be introduced in the 2008-2012 timeframe.

All of the companies responded however in some cases the company responses did not contain information on each sub category and as a result sub category mean values were calculated on a pro rata basis according to the number of responses received.

The actual number of responses and the mean values of the company responses are shown in the table below:

Discovery, Development and Authorisation Costs of a Plant Biotechnology Trait

Category		Cost ($m.)	Number of Responses
Discovery	Early discovery	17.6	5
	Late discovery	13.4	5
	Total Cost	31.0	5
Construct optimisation		28.3	5
Commercial Event production & Selection		13.6	6
Introgression Breeding & Wide-Area Testing		28.0	6
Regulatory Science		17.9	6
Registration & Regulatory Affairs		17.2	6
Total		**136.0**	

All six companies responded to the survey questionnaire, with five providing detail on the costs relating to the discovery and construct optimisation costs.

As shown in the above table, the results of this part of the study reveal that the mean cost associated with the discovery, development and authorisation of a new biotechnology derived crop trait introduced in the 2008-2012 timeframe is $136.0 m.

Overall the highest costs were associated with the discovery stages with the aggregated cost of $31 m., followed by genetic sequence construct optimisation procedures with a cost of $28.3 m. However collectively the costs of meeting regulatory requirements amounted to $35.1 m. (25.8% of total costs).

Study results – Parts 2 to 3

Part 2: Throughput

This part of the questionnaire was designed to determine the number of units typically being assessed in each stage of the R&D process in order to obtain one commercial event for subsequent commercialisation. Each company was asked to provide information as it related to the event used to provide the commercial data in the first part of this study, namely one introduced or scheduled to be introduced in the 2008-2012 timeframe. In addition for comparative purposes each company was asked to provide data for an event introduced before 2002.

The mean results of the survey are shown in the table below:

Mean Number of Units Evaluated

Activity Stage	For an Event introduced before 2002		For an Event introduced between 2008-2012	
	Mean Number of Units Evaluated	Number of Responses	Mean Number of Units Evaluated	Number of Responses
I Early Discovery	1638	2	6204	4
II Late Discovery	302	3	4005	5
III Construct Optimisation	135	3	511	5
IV Commercial Event Production & selection	2853	3	1302	5
V Introgression Breeding & Wide –Area Testing	4	3	2	5
VI Regulatory Science	2	3	1	5
VII Registration & Regulatory Affairs	1	3	1	5

Five of the companies were able to provide data on the number of units associated with each stage of the R&D process leading to the introduction of new crop trait between 2008 and 2012. The number of responses received for an event introduced before 2002 was significantly lower.

The data shows a considerable increase between the 2002 and 2008-12 time frames in the number of units in the discovery stage for each event commercialised. It also demonstrates an increasing efficiency in the industry with fewer events in the production & selection stage (Stage IV) for the events commercialised in 2008-2012 compared to events introduced before 2002.

Part 3 (a): Time Involved in Each Activity Stage

This section of the questionnaire was designed to determine the time involved in each of the activity stages in the overall process of discovering, developing and authorising a new plant biotechnology trait for subsequent commercialisation. Each company was asked to complete the questionnaire with data for:

- an event sold before 2002
- the event used as the basis for the data in section one, namely an event introduced in the 2008-2012 timeframe
- the duration it takes to complete activity stage currently (2011)

The mean results of this section of the survey are outlined in the table below:

Duration of Each Activity Stage in the Plant Biotechnology Trait R&D Process (months)

Activity Stage	Duration for an event sold before 2002		Duration for an event introduced between 2008-2012		Duration required to complete each stage in 2011	
	Months	Number of responses	Months	Number of responses	Months	Number of responses
I Early Discovery	38.0	3	33.9	5	25.8	5
II Late Discovery	17.3	3	20.0	5	20.9	5
III Construct Optimisation	18.0	2	27.0	4	32.8	5
IV Commercial Event Production & Selection	24.0	2	30.0	5	34.0	5
V Introgression Breeding & Wide –Area Testing	40.0	3	37.2	5	42.0	4
VI Regulatory Science	50.5	2	37.2	5	47.0	4
VII Registration & Regulatory Affairs	44.5	2	48.8	5	65.5	4
Total Cumulative Time	232.3		234.1		268.0	

Part 3 (b): Overall Duration of New Plant Biotechnology Trait R&D Process

Although the results of the previous section outlined the time involved in each activity stage in the discovery, development and authorisation of a new plant biotechnology derived trait, because various activity stages overlap in real time, the cumulative total did not reflect the actual duration of the overall R&D process.

The final section of the questionnaire was designed to determine the actual time involved from the early discovery of new trait until the first commercial sale. The mean values of the responses received from each company are outlined in the following table and figures:

Number of Years Required to Discover, Develop and Authorisation a new Plant Biotech Trait (Mean Values)

	Canola	Corn	Cotton	Soybean	All crops
Number of years from discovery of trait to first commercial sale	11.7	12.0	12.7	16.3	13.1

Based on the results of the complete survey, the mean value for all crops for the total duration of the R&D process was 13.1 years. However, there was considerable variation in the responses between companies and between crop species. Overall variability in the responses received varied from a low value of seven years to the comparatively high value of 24 years.

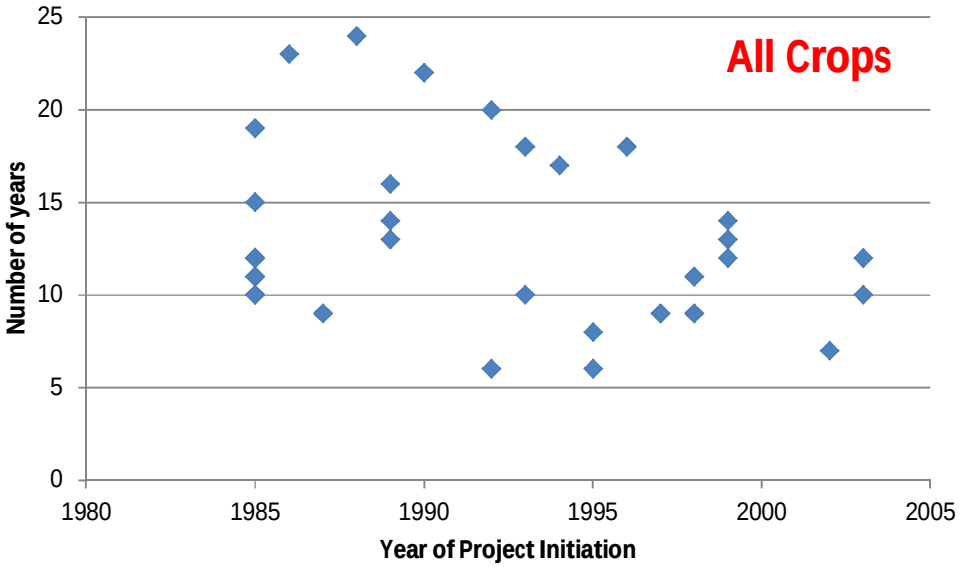
The table above outlines the variability among the project mean values for the various crops. Based on these results, the overall time duration needed to discover, develop and register a new trait for canola was 11.7 years, whereas the equivalent values for corn, cotton and soybean were 12.0 years, 12.7 years and 16.3 years respectively.

The figure on the following page outlines the actual responses received for all crop species. It shows the total time undertaken for a new trait to progress from the beginning of the discovery process until the stage where it may be commercialised.

The data in the figure below differs from that contained in table Part 3 (a), in that this analysis depicts the actual time required to develop a new trait in real time. In contrast the total value in table in Part 3 (a) shows the cumulative total for the time devoted to each concurrent stage within the overall plant biotech trait R&D process.

The y axis indicates the total number of years from the initiation of each new trait project until the actual first commercial sale of seed containing the new trait. The x axis indicates the year in which the project began.

Number of Years Required to Discover, Develop and Register a new Plant Biotech Trait



Discussion

Since their first introduction in 1995, genetically modified crop varieties have become an important factor in global agriculture. Research and development activity and expenditure associated with biotech trait development has increased significantly in the intervening period, however there is currently no accepted standard for the costs and time involved in the development of a new trait.

One of the main aims of this study was to establish a value for the relative cost of the development and authorisation of a new plant biotechnology trait. This valuation is based on a survey of the companies who have been responsible for the discovery and introduction of virtually all of the biotech crop traits and varieties that are currently commercially available.

The results of this study indicate that the overall cost to bring a new biotech trait to the market between 2008 and 2012 is on average $136 m. In comparison, a previous study undertaken by Phillips McDougall on behalf of Crop Life America and ECPA, demonstrated that the cost of bringing a new conventional chemical crop protection product to the market in the 2005-2008 period was $256 m. As with the current trait investigation, there was considerable variation in the costs derived from the data provided by the various agrochemical companies.

While the majority of the costs associated with new trait R&D arose from discovery and testing, 25.8% of the total cost arose as a result of regulatory testing and registration. Based on the results of the survey into the actual time associated with each activity stage of the R&D process, the overall time involved in regulatory testing and approval appears to have increased. If this trend is real and continues it could have a significant impact on the cost of regulatory testing and authorisation in future years.

One of the other aspects that is apparent in the results section on the time involved in each activity stage in the trait R&D process is the rise in time devoted to construct optimisation and commercial event selection stages. This could indicate the increasing complexity of techniques associated with the fine tuning of the genetic constructs.

Although the results of section 3(a) indicate the overall cumulative time involved in trait R&D has increased from just over 230 months to the current estimate of 268 months, the results of section 3(b) reveal that the actual time from project initiation to commercial launch of the trait is declining. This could well reflect the fact that companies are becoming more efficient in their project management. In turn this may not be unexpected as this is a relatively new industry.

Another feature that becomes apparent in the results of section 3(b) is the wide variability in the responses received, with some traits having a significantly extended time between project initiation and commercial introduction. Again this might not be unexpected given that modern biotechnology is a relatively new technology in agriculture. It is also likely to be a reflection of the inconsistency and unpredictability of global regulatory systems.

It should be noted that this study was designed to exclude the costs and timelines for products with multiple events combined by breeding ("breeding stacks"). For breeding stacks, the total timelines are commonly, depending on the crop, 2-3 years longer than what is represented by this data. Additional time is required to combine a new event with other approved events, to conduct the additional performance and efficacy tests of the breeding stack, to produce the additional regulatory submissions and to get approvals. While data from this study may indicate the timeline from discovery to commercial sale for a single event has become shorter, the time needed to commercialise a stacked trait product is greater.

The results of this study are indicative of the costs and timelines required to discover, develop, and authorise a new plant biotechnology trait in a large scale commodity crop, along with the associated import market approvals that are necessary for such a crop to enter the global grain trade, for example maize, soybean, rapeseed, or cotton.

Key Results of the Study

- Cost of discovery, development and authorisation of a new plant biotechnology trait introduced between 2008-2012 is $136 m.
- Discovery accounted for an estimated 22.8% of total costs and 23.0% of total cost and time involved respectively.
- Regulatory science, registration and regulatory affairs is the longest single phase in product development and is estimated to account for 25.8% and 36.7% of total cost and time involved respectively.
- The time associated with the stage in the R&D process involving registration and regulatory affairs is increasing from a mean value of 44.5 months for an event introduced before 2002, to the current estimated value of 65.5 months.
- The trend in the number of units being subjected to screening in order to develop one trait is increasing from a mean value of 1638 for an event introduced before 2002, to 6204 for an event introduced between 2008-2012.
- The time from the initiation of a discovery project to commercial launch is 13.1 years on average. This does not include the time to develop and obtain regulatory approval for stacked trait varieties which are the final product in most crops today.
- The time taken between project initiation and commercial launch has declined.

Appendix 1: Study Plan

Study Protocol

(1) Introduction

The aim of the study is to:

- Identify the level of R&D expenditure required to bring a single new plant biotech event to a major market.
- Determine the number of units typically being handled and evaluated in each Activity Stage of the R&D process to obtain a commercial event and to determine what kind of dynamic changes have occurred in the past decade.
- Determine how long it takes and how long it has taken in the past to conduct each Activity Stage in plant biotechnology trait-product R&D and to determine whether the length of time required to complete certain Activity Stages has increased significantly in the past decade.
- Quantify the total calendar time required to discover, develop and de-regulate a new plant biotech trait-product and determine whether this time has increased over the past decade.

2) Methods

With the prior agreement of Crop Life, a questionnaire will be sent to the leading crop protection companies that have an active R&D programme.

This study will be carried out so that the results of each company remain strictly confidential. The individual company data will not be disclosed to CropLife International or any other party.

In order to achieve this, the results of each company questionnaire will be assigned a code. Each company result will subsequently be aggregated and mean values calculated. Only mean data will be presented.

Philips McDougal will delete/dispose of the data collected from individual companies once the summary report is established.

Philips McDougall will ensure that the exercise of collection and evaluating data is handled in full compliance with anti-trust regulations.

Philips McDougall will ensure that neither CropLife International nor the individual companies or other parties will be able to access the data.

The summary of findings will be released to CropLife International. The presentation of findings will be done in a way which doesn't allow any conclusions about market shares of individual companies.

(3) Study Results

The results of the study will be presented in the form of a written report which can be transmitted to Crop Life International in PDF format for subsequent viewing or printing.

(4) Timing

The study will commence during the week beginning March 7th and while the rate of company response will affect the timing, it is anticipated that the results will be available during May.

Appendix 2: Questionnaire on behalf of CropLife International

Part 1 – Cost

Breakdown of R&D Expenditure to bring a single New Plant Biotech Event to a major market

Instructions

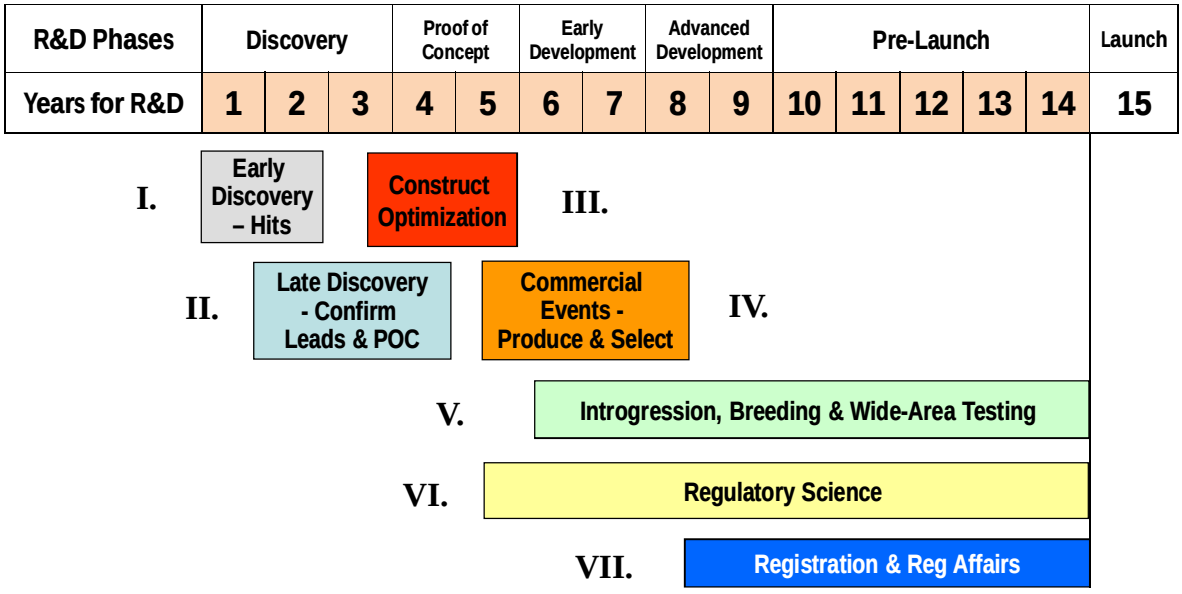
1. Use one of your company's Trait-Products introduced in 2008-12 to provide indicative data for total research and development costs, throughput and time required to discover, develop and deregulate a new event. The new event may have been or will be commercialized in a Trait-Product stack.
2. Provide the compiled total investment for all costs associated with the activities defined in each Activity Stage.
3. If the compiled investment information you have available spans two or more of the Activity Stages, please provide the value and indicate the relevant Actvity Stages represented by the value given.
4. If you are not able to provide a single value investment estimate, you may provide a range where the total range is no more than 10% of the median of the range.
5. Provide cost estimates on a fully-loaded basis to include as many of the following as possible:
    a. R&D staff
    b. general R&D operating costs
    c. external R&D collaboration, contract and testing costs
    d. capital depreciation for the R&D facilities required to execute the work
    e. R&D collaboration costs for any Activity Stages
    f. upfront payments and/or royalties for in-licensed events, technologies or components specific for the trait-event.
    g. costs to discover and develop promoters and selectable markers used to make the events (total if unique to the event or pro-rata if used for multiple events).
6. For e. and f. above please allocate the costs to the Activity Stage(s) in which the comparable in-house activity would normally take place.
7. Do <u>not</u> include the following costs
    a. Further discovery and development activities to generate back-up genes and events represented in this study until the "winner" reached the marketplace
    b. Breeding and development costs for stacks containing the event.
    c. Costs for biotech affairs, government affairs, industry affairs and public acceptance to enable the commercial launch of a product
    d. Direct capital expenditures (capital represented on a depreciated basis; see #5(d) above)
    e. Commercial seed production costs
    f. Amortization of merger or acquisition costs
    g. Post commercial launch development
    h. Product monitoring and stewardship
    i. Patent and litigation costs
    j. Sales and Marketing costs
8. Please indicate on the form the fully-loaded basis for the costs you are reporting.
9. Provide costs in your local currency. This will be converted during the process.

Please indicate your
Company:_____ **Currency Used:**_____

Appendix 2 Continued: Questionnaire on behalf of CropLife International

Part 1 – Cost

Timeline and Activity Stages
for Biotech Crop Discovery and Development
Used for this Study



This figure is included to illustrate the various Activity Stages
in the biotech trait R&D process being used for this questionnaire.

Appendix 2 Continued: Questionnaire on behalf of CropLife International

Activity Stage	Definition	Cost (X.XM) [1]
I. **Early Discovery "Hits"**	**Activity**: Preliminary screening and identification of genetic sequences with the potential to deliver the trait of interest. May involve screening genetic libraries, knowledge-based *in silico* genome searches, random activation tagging, gene sequence shuffling, etc. **Output to the next Activity Stage**: genetic sequence "hits".	
II. **Late Discovery "Leads"**	**Input**: genetic sequences **Activity**: Use one or more surrogate model plant system assays (e.g, Arabidopsis, micro-crop), normally with one or two utility promoter cassettes, to evaluate the hits in order to determine which hits may be capable to deliver the trait of interest. This is considered to represent "proof of concept". **Output**: Genetic sequence "leads"	
III. **Construct Optimization**	**Activity**: Lead genetic sequences are combined with different promoter sequences selected for their pattern of constitutive, temporal or tissue-specific expression required to optimize gene expression and gene product accumulation in order to achieve the trait of interest. The target crop is transformed and evaluated under greenhouse and/or field conditions. To evaluate each construct conclusively in plants may be characterized per construct for the trait of interest and no negative agronomic effects. **Output**: Genetic constructs (coding sequence(s) and markers) "leads"	
IV. **Commercial Event Production & Selection**	**Activity**: The Lead genetic constructs are used to product commercial-quality events which are pre-screened using various forms of molecular characterization to eliminate complex or multiple insertions. These events may go through a preliminary evaluation in the greenhouse or nursery as T0 or T1 plants for the trait of interest depending on the complexity of the trait. The numbers may vary depending on the transformation methodology used. **Output**: Commercial-quality events "leads"	
V. **Introgression, Breeding & Wide-Area Testing**	**Activity**: The lead commercial quality events are introgressed into the most elite germplasm to produce sufficient quantities of seed for product-quality hybrids or varieties for evaluation under normal and/or managed field conditions to confirm the trait of interest, to ensure no negative impact of the trait on key performance attributes, yield or grain quality, and to evaluate potential interactions of the event and trait in key product germplasm in multiple environments both alone and with other events. These field evaluations will likely happen over 3-5 years. **Output**: Commercial quality event(s) to regulatory science	
VI. **Regulatory Science**	**Activity**: Conduct all regulatory science studies and data generation in the field, greenhouse, growth chambers and laboratories (internal and external contract research organizations) to fully characterize the event insertion and to confirm the food, feed and environmental safety of products containing the event and representing the trait. The field evaluations may require two seasons to produce the data and prepare the comprehensive data package required for submissions to obtain cultivation and import approvals. **Output**: Regulatory packages to submit for commercial event(s)	
VII. **Registration & Regulatory Affairs**	**Activity**: The staffing resources required to prepare, submit and manage to approval the submissions in 1-2 countries/jurisdictions for cultivation approval and in 5-7 countries/jurisdictions for import approval. Normally 12-15 different agencies. **Output**: Submissions made and approvals obtained for commercial sale and grain production.	

[1] See the Instructions (Section #1, item #5) for the costs to include.

Company:_____ Currency Used:_____

Appendix 2 Continued: Questionnaire on behalf of CropLife International

Part 2 - Throughput

Purpose: This information will be analyzed to understand the number of units typically being handled and evaluated in each Activity Stage to obtain a commercial event and to determine what kind of dynamic changes have occurred in the past decade.

Instructions: For the biotech event used to complete Part 1 of this Questionnaire (2008-2012) please provide an estimate of the number of units for each Activity Stage. If your company commercialized an event before 2002, please provide comparable unit-throughput information for each Activity Stage for that event.

		# of Units	
Activity Stage	**Definition**	**An event sold before 2002**	**Event used in Part 1 (2008-12)**
I. Early Discovery - Hits	**Activity**: Preliminary screening and identification of genetic sequences with the potential to deliver the trait of interest. May involve screening microbial libraries, knowledge-based *in silico* genome searches, random activation tagging, gene sequence shuffling, etc. **Unit**: genetic sequence opportunities		
II. Late Discovery - Leads	**Activity**: Use one or more surrogate model plant system assays (e.g, Arabidopsis, micro-crop), normally with one or two utility promoter cassettes, to evaluate the hits in order to determine which hits may be capable to deliver the trait of interest. This is considered to represent "proof of concept". **Unit**: genetic sequences		
III. Construct Optimization	**Activity**: Combine each lead genetic sequence with different promoter sequences selected for their pattern of constitutive, temporal or tissue-specific expression required to optimize gene expression and gene product accumulation in order to achieve the trait of interest. The target crop is transformed and evaluated under greenhouse and/or field conditions. To evaluate each construct conclusively plants may be characterized per construct for the trait of interest and no negative agronomic effects. **Unit**: genetic constructs (all construct configurations)		
IV. Commercial Event Production & Selection	**Activity**: Commercial-quality events are produced and pre-screened using various forms of molecular characterization to eliminate complex or multiple insertions. These may go through a preliminary evaluation in the greenhouse or nursery as T0 or T1 plants for the trait of interest. Number may vary depending on the transformation methodology used. **Unit**: commercial quality events produced		
V. Introgression, Breeding & Wide-Area Testing	**Activity**: Events are introgressed into the most elite germplasm to produce sufficient quantities of seed for product-quality hybrids or varieties for evaluation under normal and/or managed field conditions to confirm the trait of interest, to ensure no negative impact on key performance attributes or grain quality, and to measure yield. These field evaluations will likely happen over 3-5 years. **Unit**: commercial quality events evaluated in the field		
VI. Regulatory Science	**Activity**: Conduct regulatory science studies and data generation in the field, greenhouse, growth chambers and laboratories (internal and external contract research organizations) to fully characterize the event insertion and to confirm the food, feed and environmental safety of products containing the event and representing the trait. The field evaluations may require two seasons to produce the data and prepare the comprehensive data package required for submissions to obtain cultivation and import approvals. **Unit**: commercial quality events used to develop regulatory science data packages		
VII. Registration & Regulatory Affairs	**Activity**: The staffing resources required to prepare, submit and manage to approval the submissions in 1-2 countries/jurisdictions for cultivation approval and in 5-7 countries/jurisdictions for import approval. Normally 12-15 different agencies. **Unit**: events included in regulatory submissions		

Appendix 2 Continued: Questionnaire on behalf of CropLife International

Part 3 (a) – Time

Purpose: This information will be analyzed to determine how long it now takes and how long it has taken in the past to conduct each Activity Stage in plant biotech trait-product R&D and to determine whether the length of time required to complete certain Activity Stages has increased significantly in the past decade.

Instructions:

- If you commercialized an event before 2002, provide comparable duration for the Activity Stages for that event.
- For the biotech event used to complete Part 1 of this Questionnaire please provide an estimate for the length of time it took for each Activity Stage of R&D process.
- Please provide a best-estimate for the duration of each Activity Stage now.

The Definitions for each Activity Stage are the same as in the prior tables. Please use the **number of months** to complete this section.

Activity Stage	Duration [1] for an Event sold before 2002	Duration for the Event used in Part 1 (2008-2012)	Current Duration – the time it takes now to complete the Activity Stage
I. Early Discovery - Hits			
II. Late Discovery - Leads			
III. Construct Optimization			
IV. Commercial Event Production & Selection			
V. Introgression, Breeding & Wide-Area Testing			
VI. Regulatory Science			
VII. Registration & Regulatory Affairs			
TOTAL			

Appendix 2 Continued: Questionnaire on behalf of CropLife International

Part 3 (b) – Time

Number of years required to bring a successful product to the market.

Purpose: This information will be analyzed to determine what is the total calendar time required to discover, develop and de-regulate a new plant biotech trait-product and whether this time has increased over the past decade.

Instructions:

Due to the overlapping nature of the Activity Stages in the total R&D process *(see chart on page 2)*, the total development time cannot be calculated from the data in Part 3(a). Therefore, we are asking you to represent the approximate (actual) or estimated (future) total calendar time in # of months from the start of Early Discovery research (Activity Stage I) until the biotech event was or will be fully deregulated (required cultivation and import approvals) and a commercial hybrid or variety with the event was or will be (best estimate) offered for sale.

For each proprietary biotech event your company has commercialized or expects to commercialize in 2010-2014, please indicate the year when Early Discovery research first began and the year for first commercial sale. The discovery and early development work may have been done by another company which licensed the hit or lead or event to your company for further development and commercialization.

Please indicate with an asterisk any biotech events that were co-developed and the resulting event has been or is expected to be commercialized by another CropLife International (CLI) member company.

For events that were developed by one CLI member company and licensed to one or more other CLI member companies, only the principal developer of the event should include that event in this table.

	Month & Year when Early Discovery (Activity Stage 1) started	Month & Year of 1st Commercial Sale	Crop Species	Country of 1st Sale
A				
B				
C				
D				
E				
F				
G				
H				
I				
J				
K				

Appendix 3: Cost of New Biotech Plant Trait: Survey Variance

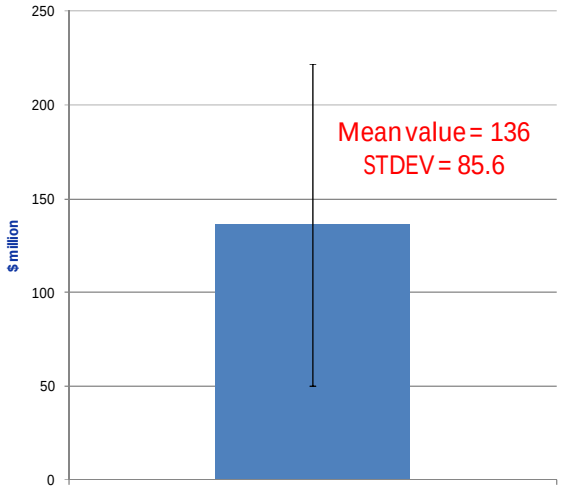
As outlined in the section of methods, one of the main aims of this study was to determine the value of expenditure that is required to discover, develop and register a new biotechnology derived crop trait product introduced in a key international market between 2008-2012..

The companies chosen to participate in the survey were those that are considered to be the leading companies in terms of new trait development. This is exemplified by the fact that these companies were responsible for over 95% of all new biotechnology derived crop traits introduced in EU and the USA in the last ten years. (Source Phillips McDougall SeedService).

The following figure shows the mean value and variance (as measured by standard deviation) within the results of the survey.

Cost of New crop trait Product Discovery, Development and Authorisation – 2008-2012

Survey Results (Mean and Standard Deviation)



The figure above highlights the considerable variation between company responses, however this is not unexpected particularly as the extent and crop focus to which research is conducted within these companies varies significantly.