

SYNGENTA CROP PROTECTION

BASEL, SWITZERLAND

PARAQUAT DICHLORIDE

**REGULATORY STATUS, OUTLOOK AND
STRATEGY**

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1. EXECUTIVE SUMMARY

The recent EU decision to include paraquat on the list of approved active substances supports the international scientific consensus of the human and environmental safety of paraquat and is consistent with the conclusions of the US EPA's re-registration eligibility decision and the recent WHO/JMPR toxicological evaluation. However, the EU decision, and to some extent the political nature in which it was necessarily achieved, has for the time being heightened NGO activity against the product and stimulated regulatory and governmental opposition or scrutiny in some countries.

It is considered that paraquat will continue to attract significant regulatory and NGO scrutiny, often as a result of the –

- Perceived risks in occupational knapsack use, particularly in developing countries,
- Frequency of abuse by intentional ingestion and the associated low survival rate,
- Perceived environmental persistence,
- Perceived ecological risk to birds and wild mammals,

Paraquat registrations will remain insecure and will require considerable proactive defence. Global, regional and country Critical Success Factors are proposed and it is strongly recommended that these become objectives for the business and regulatory managers concerned during 2004 and beyond. Overall, the global regulatory situation is considered likely to remain generally under control in the period until 2008. The situation between 2008-2013 and beyond will be determined by a combination of factors –

- Stewardship programmes successfully ensuring, demonstrating and communicating the safety of Gramoxone under typical use in developed and developing countries.
- Success in demonstrating and communicating the economic, environmental and social benefits of paraquat and its importance for the sustainable use of glyphosate products.
- Success of the AWT product roll-out globally, the impact of AWT on the survival rate following ingestion and the adoption of AWT as the standard by national and international authorities.
- The outcome of the EU's 2008 interim review, and the EU's 2013 periodic review, as to whether the requirements for Annex I inclusion continue to be satisfied.
- The level of generic entry potentially limiting Syngenta's influence over paraquat regulatory strategy.
- Success in keeping paraquat out of the Rotterdam Convention on Prior Informed Consent (PIC).
- Success in containing the perceived association between paraquat and Parkinson's Disease as an academic rather than a regulatory human safety issue.
- Success in managing the development and implementation of hazard based, precautionary and comparative regulatory policies.
- Success in managing the impact of food industry protocols on paraquat use.
- The lack of emergence of a replacement active ingredient, perceived to be of lower risk.

The key regulatory strategy elements are to:

- Defend all registrations.
- Continue to expand stewardship and toxicovigilance programmes on a global basis.
- Gain and consolidate international consensus of the human and environmental safety of paraquat.
- Provide regulatory support to marketing within Syngenta to manage sustainable agriculture & food industry activities to ensure Syngenta has freedom to sell paraquat as well as registrations.
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- Ensure that high safety and stewardship standards are maintained by regulators through adoption of FAO specifications and protection of intellectual property.
- Successfully introduce the new AWT formulations, making these the new safety standard.
- Promote the environmental, societal and economic benefits of paraquat in world agriculture.
- Build capability to defend both the license to sell and freedom to sell paraquat in potential future risk assessment (e.g. neurotoxicity) and hazard paradigms.
- Understand and negate the influence of NGOs on paraquat regulatory decision making.

- Manage the development of international conventions and treaties (e.g. PIC, POPs, ATP).and ensure these do not result in regulation restricting paraquat use.

2. BUSINESS OBJECTIVES/STRATEGY

Paraquat, as the dichloride salt, is a non-selective contact herbicide for total vegetation control in a wide variety of uses, predominantly in terrestrial weed control outlets. Paraquat is one of the world's number two herbicide in sales terms and a "blockbuster" product for Syngenta.

The top 10 markets accounted for 67% of the Gramoxone business in 2002,

- USA, China, Mexico, Thailand, Malaysia, Australia, Brazil, Japan, South Korea and Indonesia

The top 32 markets accounted for 95% of the Gramoxone business in 2002,

- Taiwan, Colombia, Guatemala, Spain, France, Honduras, Italy, UK, India, El Salvador, Ecuador, English Caribbean, Venezuela, Portugal, South Africa, Nigeria, Dominican Republic, Greece, Costa Rica, Ivory Coast, Iran, Nicaragua

The business objective for 2004, is to achieve global Gramoxone sales of ~\$388M, which without AWT formulation development is forecast to decline to \$334M in 2008. This assumes an unfavourable interim review in 2008 in the EU and knock on impact in other markets. With the successful introduction of AWT formulation technology, there is forecast to be an upside of \$68M in 2008, and \$100M by 2013 compared to this base case.

With the positive adoption of AWT formulations by regulators and the food industry, there is an expectation that sales will be maintained in developed EU and NAFTA markets, and sales will grow in developing markets (principally China, Philippines, Indonesia, and Vietnam) through progression from hand weeding and adoption of minimum tillage techniques. The development of glyphosate resistance in Australia and the USA, is forecast to increase the rotational use of paraquat in sustainable agriculture practices.

In both the developed markets, and those subject to strong generic pressure (low compliance to FAO standards) it is critical that registrations and share are held in the coming years. The major competitive threats in priority are from generic paraquat, glyphosate and glufosinate.

The key strategy elements are -

- - Vigorously defend all registrations and uses
 - Use economies of scale, quality and brand strength to defend molecular share
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 - Drive out non value adding complexity and cost from the supply chain
 - Develop markets and product positioning to achieve "technical share" in key markets and gain new users in developing markets
 - Continued investment in Gramoxone to ensure that brand awareness is obtained or sustained to support market share goals
 - Proactive communications / targeted collaborations with key influencers to improve product image / raise purchase consideration
- Introduce improved Alginate Wall Technology formulations to substantially changing the product image

3. REGULATORY TARGETS FOR 2004

- Raise the level of proactive regulatory defence of paraquat globally. Improve our understanding of the social, economic and political environment in each major market, the regulators attitudes, the influence of NGOs (both locally and in other countries) and develop and implement plans to improve the position of paraquat.

- Put in place the global stewardship and other activities necessary to ensure and demonstrate the safety of Gramoxone under typical use in both developed and developing countries.
- Agree and implement the programme of activities to deliver on the requirements set following Annex I listing of paraquat in the EU.
- Achieve the successful development and registration of AWT in “early” markets in accordance with the business objectives.
- Achieve re-registration under the Australian ECRP review without major new restrictions.
- Promote national enforcement of the revised FAO specifications for paraquat dichloride.
- Consolidate the international consensus on the dietary safety of paraquat via the CCPR/JMPR review in 2004.
- Maintain and enhance the activities in Malaysia to create a political and scientific environment in which the re-registration of paraquat products can be achieved.

- Implement stewardship programmes in developed and developing countries, teaching farmers and their families how to handle agricultural chemicals safely with particular emphasis on the measures that will preclude topical irritation and local symptoms.
- Ensure Syngenta meet the FAO specification that stipulates all paraquat product must include a dye and an effective emetic and may contain a stench or thickening agent.
- Discourage decanting, offer a range of pack sizes and closed transfer systems so that the product purchased is as close to the quantity needed, delivered with the minimum amount of rehandling.
- Actively support projects run by internationally renowned experts and non-governmental organisations working in the field of suicide prevention.
- Introduce improved formulations employing the AWT technology designed specifically to reduce oral toxicity and be less irritant to skin and eyes.

7.3. AWT project

Alginate Wall Technology (AWT) offers the prospect of a significant further reduction in the toxicological hazards associated with existing paraquat formulations. Pharmacokinetic studies in laboratory animals have demonstrated a significant reduction in the oral toxicity hazard via the combination of a pH triggered gel, boosted emetic and purgative. It is anticipated that AWT technology will eliminate fatalities from accidental ingestion and significantly increase the survival rate following intentional ingestion. AWT formulations have also demonstrated a much improved topical and eye irritation profile. The formulation technology is patented and represents a new barrier to generic entry. The AWT project is considered a unique opportunity to improve key internal and external stakeholder perceptions and rejuvenate the brand image of Gramoxone. It is Syngenta's intention that AWT formulations be introduced globally in a phased approach. This will of course take time to achieve and will be dependent upon the successful resolution of the practical difficulties associated with the manufacture, supply, marketing and sale of a new formulation of paraquat in the different market conditions that exist around the world. Not least of these is complying with local regulatory procedures for product approval. The strategy is to -

- Use the formulation improvements as an anchor for the launch of a new range of products, to :
 - Achieve a solid regulatory base, moving from a defensive to strong proactive approach to both the Regulators and Food Industry.
 - Revitalise and differentiate the product on improved safety and performance characteristics, to repositioning the product on new and forgotten grower benefits, growing AI share, and achieving higher \$/Kg AI margin:
 - Reposition generic competition on the basis of technology advances and safety.
 - Rationalise Formulations and simplify the supply chain.
- Seek early introduction in the countries where either a significant regulatory threat exists or where a new product standard can be achieved (EU, Central America and selected APAC).
- Build formulation capability to respond to demand in a sequential manner, starting with Seneffe and then upgrading sites according to progress of demand
- Conduct an early assessment of the impact of the AWT formulations on the survival rate following ingestion, in an epidemiology study in Sri Lanka.
- Establish AWT formulations as the new standard for paraquat products nationally and via FAO.

7.4. Neurotoxicity

In 1999 EPA began a phased data call-in (DCI) of acute, subchronic, and developmental neurotoxicity studies. Paraquat was not a high priority but is included in later phases of the DCI. New studies pose risk of unexpected findings at doses below current reference doses. Paraquat has some structural similarity to MPTP which has been shown to induce Parkinson's Disease (PD) like symptoms in humans. Publications exist citing correlation between incidence of PD and herbicide use, including paraquat. Paraquat has markedly different properties from MPTP such that it does not readily cross the blood-brain barrier. Recent studies have focussed on the cumulative effects of pesticides, including paraquat; different developmental stages of the animal models; and development of PD hazard models, using high levels of pesticides to demonstrate changes. A high level of funding will ensure PD research will increase and focus on environmental factors such as exposure to pesticides. There are a number of well known PD sufferers and these will ensure PD receives high media attention. Future publications may show misleading results or interpretation & it is highly likely that paraquat will continue to be drawn into the debate. The strategy is to -

- Monitor publications and presentations.
- Develop links with key researchers to gain forward visibility and influence of further work.

- Develop capability for Syngenta to challenge key findings.
- Implement an influencing strategy to -
 - ensure that a rational risk assessment will prevail.
 - contain any potential impact on Gramoxone.
 - shift the focus of serious PD research to other environmental factors with an exposure profile more consistent with being a PD risk factor.
- Consider appropriate timing for generation of paraquat neurotoxicity studies.