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Promethius project
Highly confidential briefing

Purpose of briefing

- This briefing is intended to provide limited information of a highly confidential nature about this ongoing development project to facilitate regional and national consideration of the challenges and opportunities for registration and introduction of these novel paraquat formulations.
- Please do not make this information more widely available in the organisation at this time.

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Project objective

- A unique opportunity to improve key stakeholder (internal and external) perception of Gramoxone -an improved brand image- through the introduction of novel formulations delivering reduced toxicity and enhanced user acceptability.

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Stakeholder Benefits

- Candidate formulations are currently being assessed and we hope to identify user benefits.
- Herbicidal efficacy will be at least as good as the current formulations.
- The product will be as easy and reliable to use as the current formulations.
- The formulations are designed to confer enhanced user acceptability through either a change in the smell or a reduction in the current stenching agent to its minimum effective level.

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Stakeholder Benefits

- The formulations are also designed to confer a reduced toxicity hazard.
  - We hope to demonstrate an improvement in the acute dermal LD50.
  - We hope to demonstrate a reduction in the dermal adsorption of paraquat.
  - Dermal sensitisation, eye and skin irritancy and inhalation toxicity will likely be similar to current formulations and no worse.
  - There may be a marginal improvement in the acute oral LD50 as determined in guideline studies in rodents.
  - We hope to demonstrate a significant reduction (target = 10x) in the acute oral toxicity hazard to humans as determined by the systemic paraquat absorption and elimination pharmacokinetics in vomiting mammalian species.

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Limitations

- This significant reduction in acute oral toxicity hazard to humans will not prevent mortalities from the gross misuse of the product in suicide cases.
- Strictly no claims will be made to the effectiveness of these new formulations in reducing mortality rates following deliberate oral ingestion until reliable data have been collected several years after launch.
- Steps will be actively taken to manage exaggerated regulatory and other stakeholder expectations on this point.

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Limitations

- Modelling suggests that at best a hypothetical tenfold reduction in oral toxicity hazard to humans may result in an increase in the survival rate following intentional oral ingestion of paraquat formulations from 25% to 50%.
- In practice this level of improvement will likely not be evident in many countries.
- These formulations will likely offer no improvement in national product label classifications, where these are already correct according to the nationally operating classification schemes.

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Technology

- The novel formulations will be liquid and slightly more viscous than current Gramoxone (not as thick as Gramoxone Plus in France).
- The novel formulations will contain all three safening agents currently employed in existing paraquat formulations.
  - They will contain the same blue/green dye,
  - They will contain slightly more of the existing emetic
  - They will contain either the minimum effective level of the current stench or an alternative agent that is as effective as an olfactory alert but is more acceptable to users.

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Technology

- The reduction in oral toxicity hazard for man will be achieved by reducing the proportion of paraquat systemically adsorbed from the intestine following oral ingestion of the neat product.
  - The product will form a gel in the highly acidic conditions of the stomach, thus increasing the retention time in the stomach and consequently the opportunity to remove a greater proportion of the product by emesis.
  - Formulation components will also aid rapid purgation of the residual paraquat.

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Current status

- This project is still at a relatively early stage of development. Five candidate formulations containing 200g/l paraquat ion are currently undergoing efficacy field trials. Proof of concept studies to assess the probability of achieving the targets for improvement in toxicity hazard are yet to be conducted. Results from these toxicology studies are not expected before June 2002.
- The earliest date for freezing the formulation and commencing regulatory studies is July 2002.

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Current status

- Application of this formulation technology to higher concentration paraquat formulations, paraquat + diquat mixtures and other pre-mix formulations is currently being assessed.
- The maximum concentration of paraquat ion achievable with this formulation technology is <300g/l.
  - A 200g/l product is possible,
  - 300g/l is not,
  - work underway to assess 250g/l.

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Scope

- The current thinking is that this technology will be applied globally and in all paraquat formulations (where technically possible) replacing the currently marketed products.
- This will be discussed in a PLT with regional representation in November 2001.

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Cost

- The new formulations will cost more than the current ones although there is potential for savings resulting from range rationalisation.
  - Both points are being considered further.

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IP

- Syngenta filed a new patent application 27 March 2001 (PPD 50616) for this specific formulation technology.
- Syngenta have existing IP on the uses of triggered gel technology in paraquat formulations (EP 0467529).
  - This original patent will continue to provide broad protection for only a limited further period
  - It represents prior art that limits the scope of the March 2001 and any future patent applications.
- The strategy is to continue to research alternative formulation technologies and file further patent applications for these alternative triggered gel formulations.

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Regulatory strategy

- The plan is to draft a first cut global regulatory strategy by November 2001,
- Then at the RDT meeting in February 2002,
  - further develop this global regulatory strategy and national implementation plans
  - check that the regulatory study plan meets all countries needs

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Business objective - assumptions

- Seek the earliest possible registration approvals of these novel formulations globally.
- Use this opportunity for range rationalisation
  - e.g. move from country specific low concentration formulations in France, Germany and Japan to global formulations.
- Seek legitimate advantage with respect to generic paraquat products.

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Regulatory assumptions

- If unrealistic expectations are held by regulatory or other stakeholders about the impact of this formulation change on either the number of incidents of deliberate oral ingestion of paraquat formulations or their outcome, the regulatory & non-regulatory climate for Gramoxone will likely deteriorate considerably, not improve.

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Regulatory assumptions

- This technology will not provide a panacea to generic paraquat product threats.
  - The likelihood of this technology being adopted as an international standard will be very low at the time of first registration but may increase once data are available to evaluate the practical impact of the technology in man.
  - The impact on the regulatory climate for new generic registrations will likely be greater than where generic registrations already exist.
  - In practice, the IP position will not be rigorously policed or defended by regulatory agencies because it relates to human safety of the formulated product.

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Regulatory challenges

- Present rationale for fast-track approval, minimising bureaucratic registration processes that does not use (or overplay) the reduction in oral toxicity.
- Develop a regulatory study plan that facilitates fast-track registrations
  - Use bridging arguments to avoid studies of longer duration (e.g. dietary residues and efficacy) or seek to make these a condition of approval to be conducted post registration, to facilitate earliest registration submission.
  - Conduct all short-term studies (e.g. handlers tox, ecotoxicology) to avoid delays incurred by regulatory debate of technical arguments for extrapolation of data.

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Regulatory challenges

- Develop a strategy to maximise the impact on the situation of generic product approvals at the earliest opportunity after introduction.
  - Seek to de-register our existing products.
  - Maximise protected data associated with these novel formulations.
  - Seek to establish an oral toxicity standard for paraquat formulations (e.g. FAO specification) achievable either by this technology or significant dilution of products not employing this technology.
  - Seek to achieve legitimate advantage over generic products not employing this technology in terms of regulatory and non-regulatory restrictions.
  - Conduct studies to monitor the practical impact of the formulation change and seek to leverage legitimate advantage from the results, as they become available.

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Formulation change

Current Gramoxone formulation

- ai
  - 200 g/L paraquat ion
- stench
  - 10 g/l pyridine bases
- emetic
  - 0.5 g/L PP796
- surfactants
  - 43 g/L Synprolam 35 x 15
  - 86 g/L Nansa 1169A
- antifoam
  - 0.25g/l Silcolapse 5020
- dye
  - 5 g/l Sulfacide Blue 5J
- pH adjuster
  - Acetic acid (to pH 6.5-7.5)
- water (up to 1 litre)

New candidate formulation

- ai
  - 200 g/L paraquat ion
- emetic
  - 0.5 g/L PP796
- surfactants
  - 43 g/L Synprolam 35 x 15
  - + (30 g/L Nansa HS90/S)
  - or (22.4 g/L Aerosol OT-B)
- alginate
  - 15 g/L Manutex RM
- purgative
  - 74 g/L $MgSO_4.1.5H_2O$
- water (up to 1 litre)

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