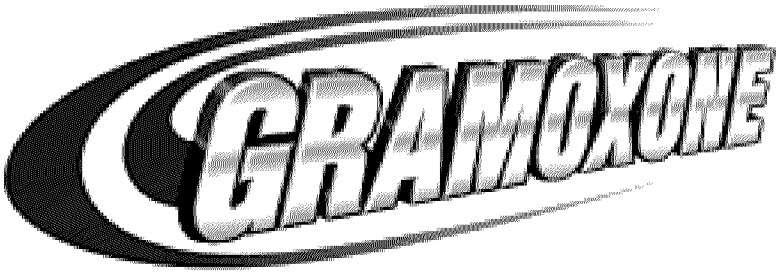

Alginate Wall technology

'Prometheus Project – GRAMOXONE T-Gel'

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Outline

- What we are seeking from the DeCo
- Intro to project- Change in focus / Business needs (DV)
- Does it Work? - Bio efficacy (DV)
- Is it Ours? - IP update (DV)
- Can we make it? - Supply chain strategy (DV)
- Is it Safe? - Dermal tox update, Alerting Agent change, Epidemiology Study (MC)
- Can we register it? - Regulatory Strategy (IW)
- Can we make money out of it? Business strategy (MV)
- What's next (DV)
- Wrap up

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What we are seeking from the DeCo:

- Approval on change in project focus from Oral to Dermal tox improvement
- Approval for Formulation Freeze upon successful completion of handlers tox, rat LD 50 tests, and initial dose of POC study (May 22).
- Approval of continued quest for 10x safening
- Approval for shifting resources to French formulations

GRAMOXONE: Strategic development plan

- Importance to Syngenta
  - Blockbuster: #1 brand, #2 a.i. in value
  - Continued growth: $430M in 01; $403M in 02; $425 Bud. 03, $486M in 07
- Business objective: Defend and grow AI market share, retain value.
- Key strategic activities / Critical Success Factors
  - Strong proactive defense against registration loss, regulatory and non-reg restrictions.
  - Improvment of product image
  - Differentiation / defense vs generics
  - Brand ladder management- how to grow AI share, and $/Kg AI overall
    - Development and introduction of improved formulations with Alginate Wall Technology
    - Rationalise formulations and reduce unproductive cost

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Alginate formulation

- We have discovered novel dermal safening benefits with the current alginate system
- The original project goal, 10x oral safening, will not be reached.
- The dermal benefits are so significant that the NSH Product Line has decided to proceed with the development of this technology for these benefits alone.
- We continue a major effort to characterize the benefits (oral and dermal) of other novel polymers.

What can we say?

Syngenta have a new patented paraquat alginate formulation technology that can deliver:

- **Reduced dermal irritancy of concentrate**
- **Reduced potential for operator exposure**
- ***Optimisation of emesis leading to reduced absorption from oral ingestion (POC study).***
- **More robust formulation in terms of weed efficacy**
- **An option of a new alerting agent (3-cis-hexanol: leaf alcohol) is compatible with the new formulation**

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With Alginate Wall Technology ....

- **.... We are in a position to offer a safer, easier to handle, more active product to the user,**
  - **Improved dermal irritation, less odour, higher efficacy**
- **....** *We can reduce the risk in case of accident by greater opportunity for medical intervention*
  - *Better emetic delivery aided by alginate technology*
- **.... We are better able to reposition the product, addressing new and already known benefits in a fresh way.**
- **.... We are able to differentiate vs generics on risk**
  - **Patented formulation, increased safety, new standard**

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Does it Work? Bio efficacy

- Trials conducted 2001-2003

2001 - Formulation Selection vs. internal standard

2002 – Formulation modifications vs. internal and local standards, w/wo tank-mix partners.

Yes – Lead formulation is as good or better than the internal standard, Gramoxone Tropics

2003 – Lead formulation(s) vs. local standards

Wider range of locations and local standards (19 countries, >100 trials)

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Is it Ours? Patents

- Freedom to Operate
  - We are aware of no FTO problems
- Patent Protection - Complicated
  - Our ability to obtain **broad** patent cover for the use of alginates in paraquat formulations is limited by the original magnoxone triggered gel application
  - **However we still expect to obtain useful protection**

Patent Property

- **PPD 50616 – Triggered Gel - filed March 2001**
  - The claims cover the use of an alginate **as a pH-triggered gelling agent** for a bipyridyl system containing an emetic and/or purgative.
  - The PCT application is currently undergoing prosecution
- **PPD 70214/5/6 – Dermal Protection - filed Jan 2003**
  - Three related cases filed on the same day to provide flexibility in our approach to claiming the use of alginates (and other polymers) for dermal protection in bipyridyl (and other) systems.
  - **Considerable work is underway in 2003 to substantiate these applications.**

Can we make it? Supply Chain Opportunities

- Reduction in the range, reduced supply complexity.
- Standardising range maximises purchasing leverage.
- Significant modification of existing facilities required to make new formulations (primarily around solids handling) will drive rationalisation of supply points, where appropriate.
- Opportunity to revisit and strengthen customer service criteria, product differentiation, planning frameworks, inventory criteria etc. – improved supply performance from a compressed, more efficient supply chain.

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Supply Chain Challenges

- Minimising impact on variable and fixed product costs:
  - Additional additives
  - Capital investment
  - Distribution implications (lower strength tech/formulations)
- Developing robust formulations for the full range with maximum range of pack size and ambient conditions.
- A supply strategy that allows engagement with third party manufacturers without jeopardising I.P. position or product integrity – „core component“ strategy.
- Managing huge operational complexity of the transition.

Is it Safe?

Alerting Agent, Dermal Tox, Oral Tox

HA conclusion on alerting agent

- Demonstrated that Cis-3-hexen-1-ol (2g/l) and pyridine base (0.1g/l) are both alerting and showed some dislike in human volunteer sniffing trials
- Anecdotal evidence indicates smell induces nuisance health effects (e.g. nausea and headaches)
- Both Cis-3-hexen-1-ol and pyridine base have been shown to be less objectionable than Gramoxone products following application and suggest a reduction in nuisance health effects
- Possible associations with food, drink and household products are no worse than with existing Gramoxone products.
- Package of toxicology to register Cis-3-hexen-1-ol as an inert in the US is planned to commence mid year.

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HA conclusion on alerting agent

- It is recognised that:
  - There are regional differences in detection and acceptability of the proposed alerting agents
  - There is a large inter-individual variation
- Therefore there is no guarantee of alerting in all regional sub groups noting cultural, ethnic and dietary variations, however
- The alerting agent in only one of a number of stewardship measures to discourage abuse of Gramoxone.

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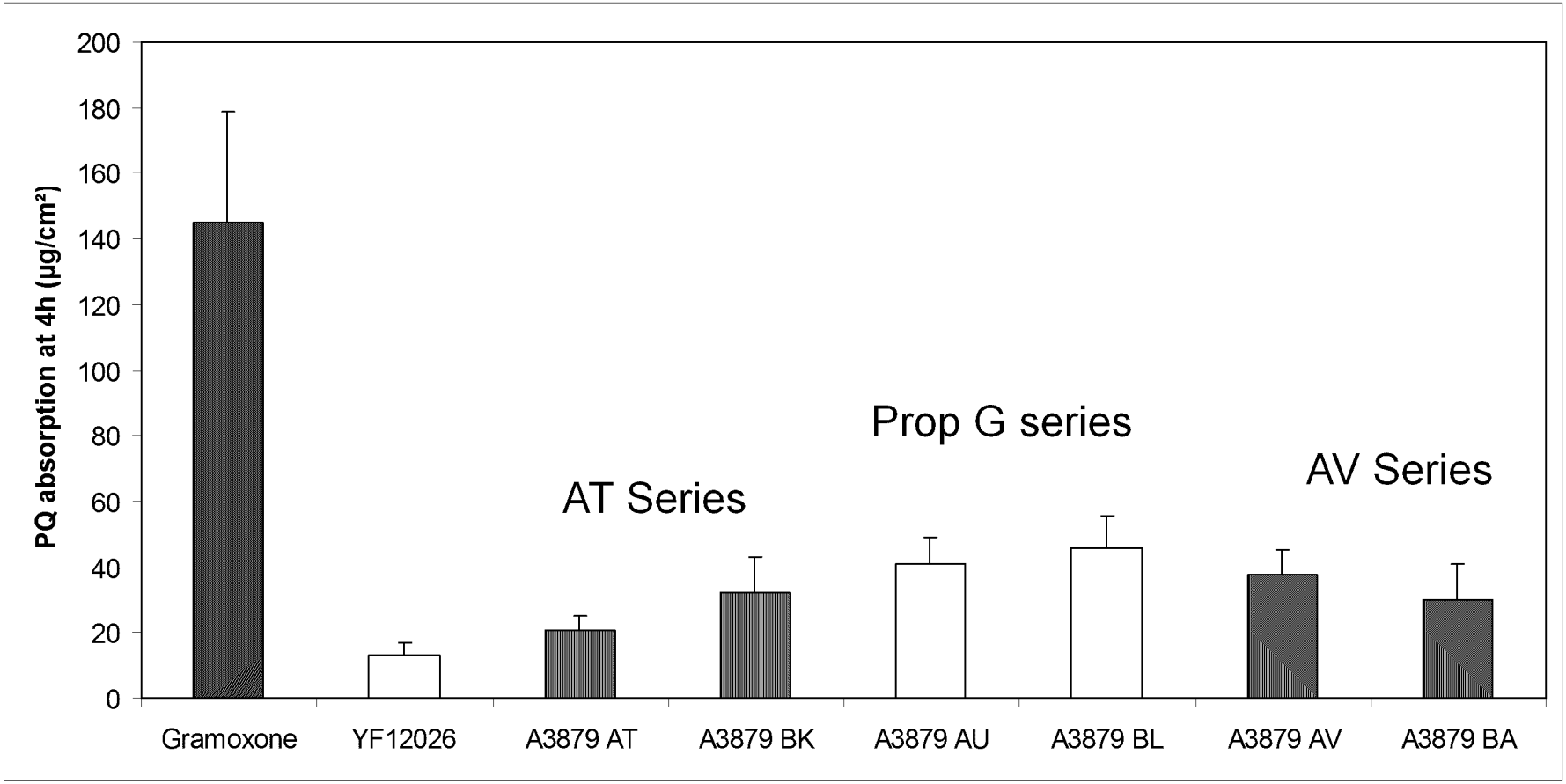
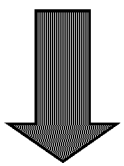
Dermal absorption of paraquat in mouse whole skin model at 4 hours



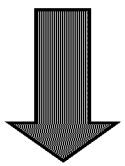
Dermal irritation general effects on skin

- Worst case evidence of necrosis, study terminated or incomplete recovery
- Scabbing
- Shiny skin / no hair
- Skin re- growth with or without fur
- Recovery 43 days



- Gramoxone and French formulations

- Desquamation
- New skin growth with normal hair growth
- Full recovery in 35 days



- New alginate wall products:
  - A 3879BU and A3879BV
- Technical material

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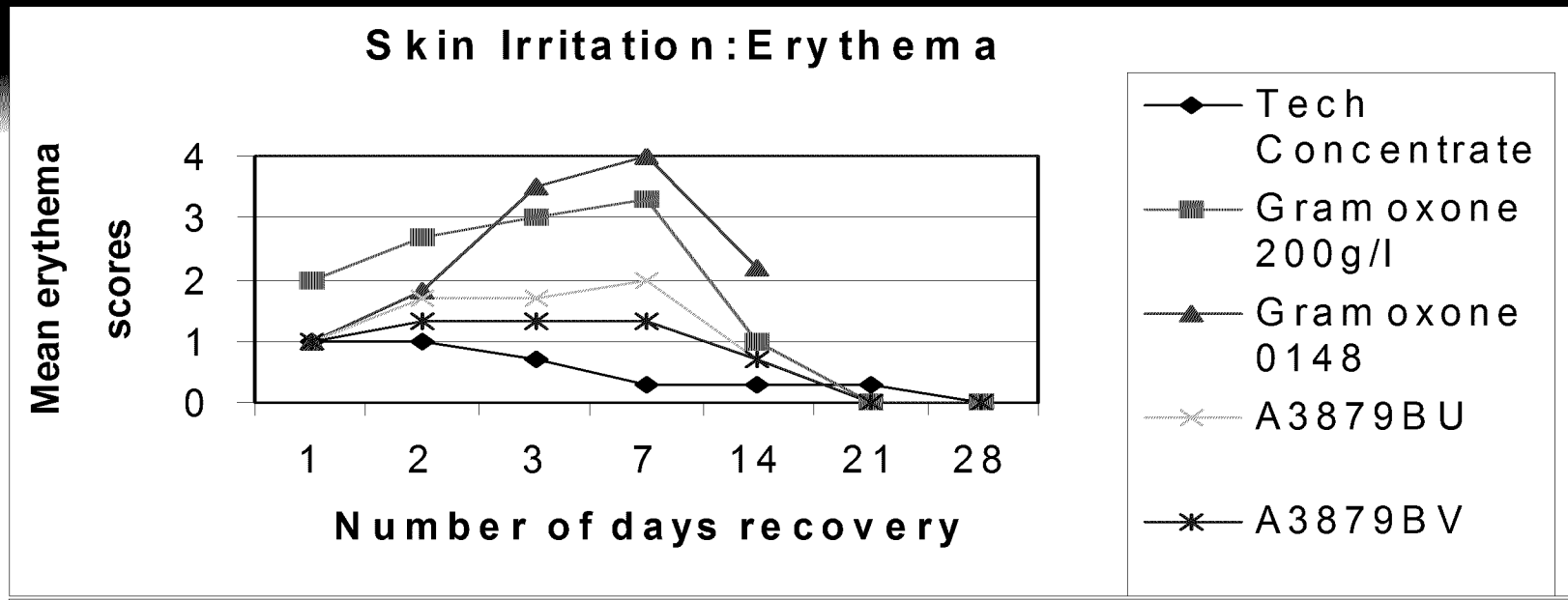
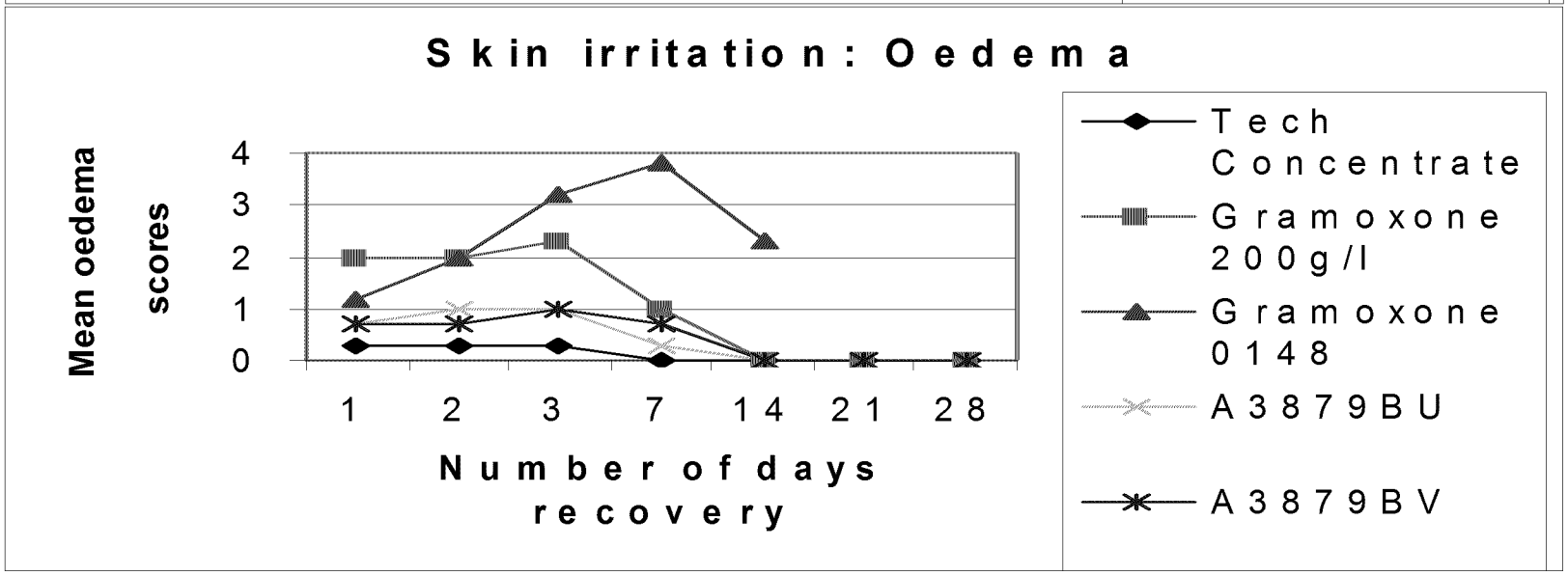

Skin Irritation:Erythema
Mean erythema scores
0
1
2
3
4
1
2
3
7
14
21
28
Number of days recovery
Tech Concentrate
Gramoxone 200g/l
Gramoxone 0148
A3879BU
A3879BV


Skin irritation: Oedema
Mean oedema scores
0
1
2
3
4
1
2
3
7
14
21
28
Number of days recovery
Tech Concentrate
Gramoxone 200g/l
Gramoxone 0148
A3879BU
A3879BV

Comparison of handlers toxicology package

Test	Gramoxone	AT based products A3879BU and BV
Oral MLD mg/kg	612 (f), 707 (m)	550 - 2000
Dermal MLD mg/kg	590 (m), 735 (f)	>1000<2000
Dermal irritation	Moderate to severe R38, recovery 43d	Reduced irritation, recovery 35d
Eye irritation	Moderate R36	In progress
Sensitisation	Not a sensitiser (x3)	In progress (x9)
Inhalation	(T+)	(T+)

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Next steps

- Completion of handlers toxicology package – end April
- In vitro human dermal absorption balance study – 2Q'03
- Demonstrated that A3879BU and BV are no worse than Gramoxone orally
- Proceed to the dog
  - Select either A3879BU or BV
  - Demonstrate this is no worse than Gramoxone
  - Effective emesis occurs at low doses
  - Demonstrate how much safening is achieved

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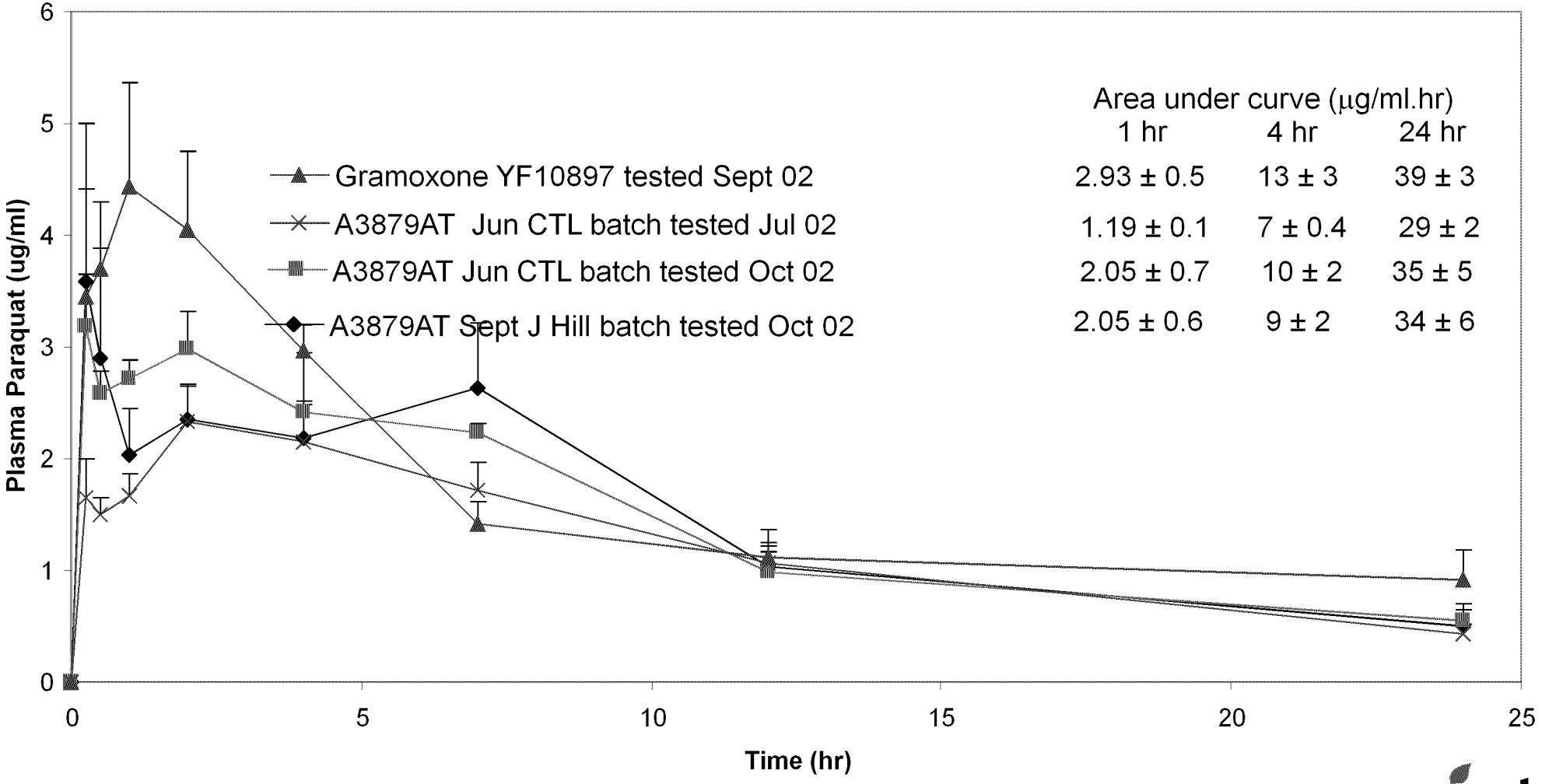
Plasma Paraquat following an oral dose of 40 mg/kg PQ ion (n=4) in the rabbit

3 REPEATS OF A3879AT (PYRIDINE STENCH)



Area under curve (μg/ml.hr)

	1 hr	4 hr	24 hr
Gramoxone YF10897 tested Sept 02	2.93 ± 0.5	13 ± 3	39 ± 3
A3879AT Jun CTL batch tested Jul 02	1.19 ± 0.1	7 ± 0.4	29 ± 2
A3879AT Jun CTL batch tested Oct 02	2.05 ± 0.7	10 ± 2	35 ± 5
A3879AT Sept J Hill batch tested Oct 02	2.05 ± 0.6	9 ± 2	34 ± 6

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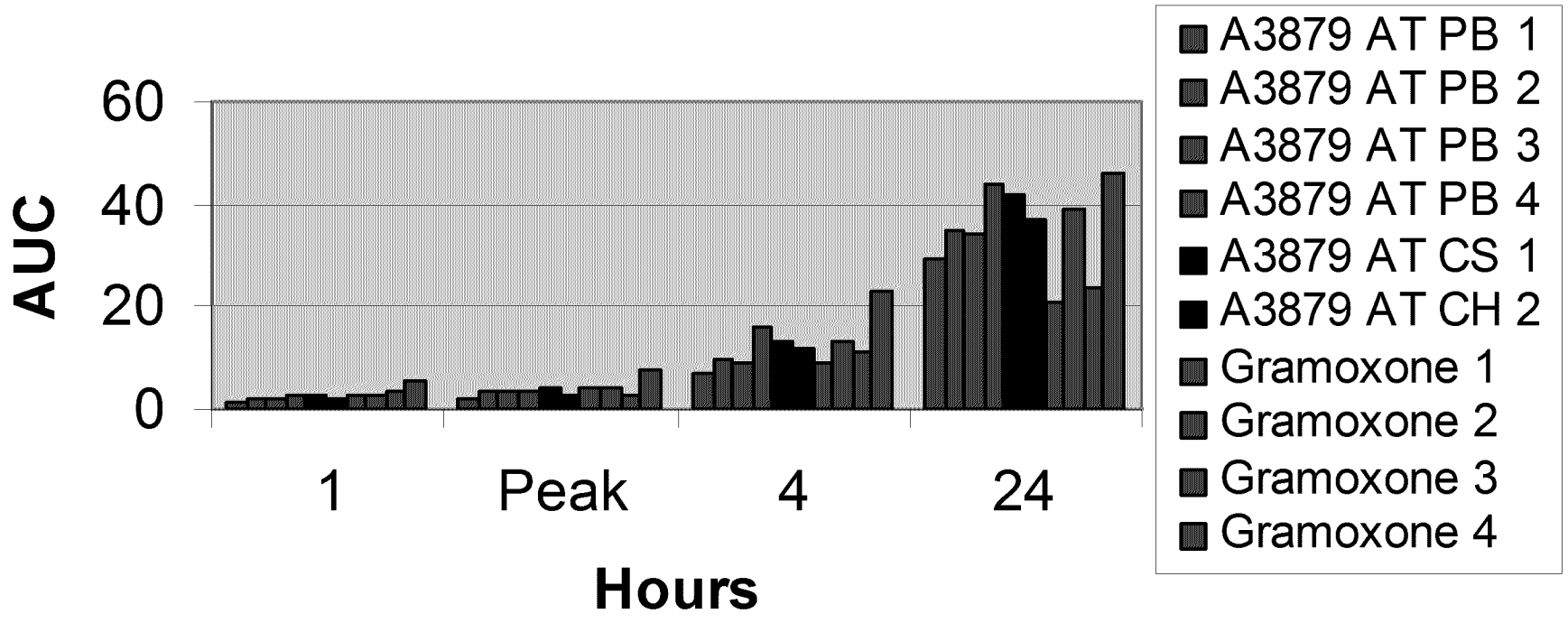
DeCo Prometheus Vitolo 26303

Comparison Gramoxone and lead dermal formulations

Paraquat absorption in the rabbit following a dose of 40mg/kg



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What are the messages to the Regulators

Syngenta have a new patented alginate formulation technology that can deliver

- *(Less toxic product?)*
- **Reduced dermal irritancy of concentrate**
- **Reduced potential for operator exposure**
- *(Effective emesis at low doses?)*
- **More robust formulation in terms of weed efficacy**
- **An option of a new alerting agent (cis-3-hexen-1-ol, leaf alcohol) that is compatible with the new formulation.**

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Can we register it?

Registration Strategy

Can we register it? Regulatory Considerations

- Yes it is registerable
- The timelines for registration will vary by country and are largely driven by the need for official efficacy trials
- Upsides on standard registration timelines and competitive opportunities will depend on the extent to which regulators perceive the formulation change to be significant
- This is a great opportunity to do what the regulators have been asking for
  - Demonstrate that we are listening to them by improving the toxicity of the formulation.

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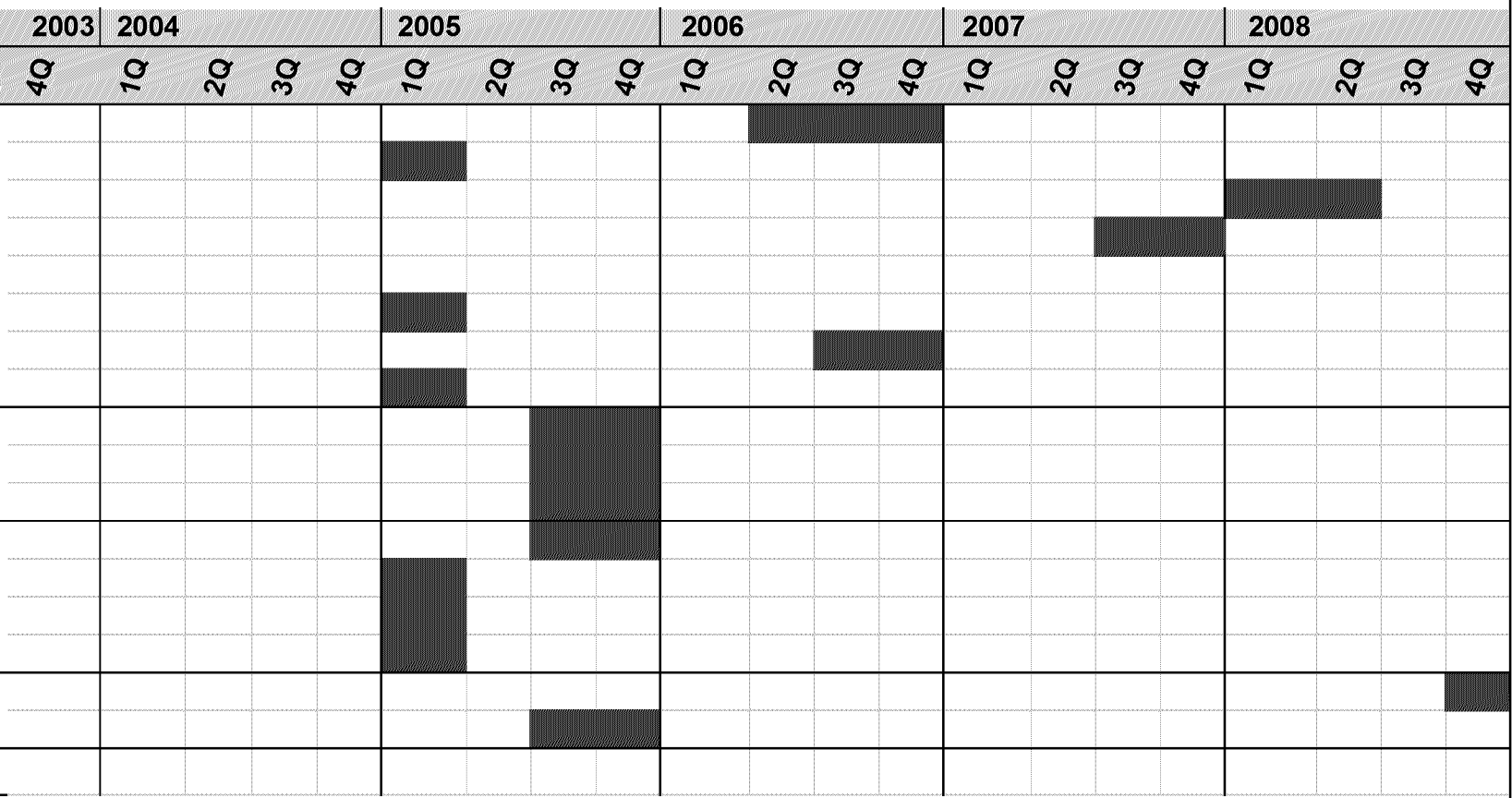
Registration timeline estimates

Region	COUNTRY	B2003
APAC	China	50.2
	Thailand	27.8
	Japan	25.3
	Australia	23.4
	Malaysia	21.0
	Indonesia	17.6
	South Korea	16.9
	Taiwan	9.8
EAME	France	9.5
	Spain	9.5
	UK	5.6
LATAM	Brazil	20.0
	Guatemala	11.9
	Colombia	10.3
	Honduras	7.1
NAFTA	USA	58.4
	Mexico	28.8
	TOTAL	**353.3**



Discussion with regulators

- Seek a meeting with each national registration authority to present the new formulation as
  - a significantly lower irritancy formulation
  - enhanced operator safety (reduced dermal adsorption)
  - (where relevant) enhanced user acceptability (new effective alerting smell to address anecdotal reports of nausea related to the current stench)
- Use the opportunity of the meeting to
  - remind the authorities of the key benefits of the product
  - explain the re-registrations in EU & US
  - listen to and seek to address any concerns
  - reinforce Syngenta's commitment to stewardship
  - seek commitment to make compliance with new FAO specification mandatory
- Standard registration timelines for a major formulation change

Can we make money with it?

Economic case

GRAMOXONE T Gel: Market Objectives

Target

- Launch a "NEW" industry standard (reduced tox profile) early '05, in all countries ASAP.
- Establish a new regulatory / stewardship standard that will make it difficult for generics to compete in.
- Improve user acceptability with new "Alerting Agent" in selected markets.
- Phase out old formulation registrations ASAP after GMX T Gel reg.
- Minimum 24T AI at $500M , GM 50%+ in 2007

Benefit:

- A new lease of life to possible limitation on license to sell, and freedom to operate. Reposition – New product launch GMX T Gel : Address key stakeholders on user acceptability, and establishing new regulatory standard.
- Create a new brand ladder platform from which to continue to grow the business, if not in AI potential, then in share of AI.
- Formulation rationalization and standardization by 2006
- Sales upside, (volume and value) based on market share gain, recover legacy numbers

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Assumptions : Economic Case

- **Repositioning: Leverage formulation change to redress existing perceptions presents a unique opportunity to challenge AI share decline**
- **Do Nothing: Decline of value and volume**
  - ***Lack of product differentiation:*** Emetic access, and quality not a sustainable advantage
  - ***Credibility ?:***Declining regulatory / political support in select markets
  - ***Quality without a premium:*** Limited opportunity to reduce VPC cost base in short term.
- **AI Defense case**: **Break even 12% loss of sales, year 4**
  - ***Price premium justification:*** Recovery of incremental VPC in price
  - ***Lower Cost base*** : Improve TPC base by increasing AI production volume throughput.
  - ***Raise Barrier to entry:*** Increase competitor cost of conformance by raising regulatory and food industry barriers to entry
  - ***Slow generic AI market share growth rate:*** Differential offer based on improved safety with formulators

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Cost impact (estimates)
Negotiations continuing

- PLT allowed $0.21/l increase (incl novel AA) in 2001 $.
- G-Tropics is $0.98, APE-free version YF10987 is $1.06
- We have assumed the 21 cents is on top of the YF10987 price - thus max allowed = $1.27 (excl Pack, and fill)
- A3879 BU – Alginate Wall + reduced PB alert $1.18 (+ $0.12)
- A3879 BV – Alginate Wall + cis-3-hexanol alert $1.28 (+ $0.22)

Exchange rate $1=£1.57, APAC VPC

Key issues

- Role out for each region , Country implementation plans Key Regional dialogues : Q1/03
- Misperceptions within / of Syngenta: Over-promising and under-delivering.
- Subtle and sophisticated messages to various Stakeholders need to be developed:
  - Users Growers, Channel
  - Non–users, Regulatory Authorities, Medical Community, NGO`s,
- Incorporation of assumptions into Sympact 2003.

What's next?

Sub-projects/Wrap up

Projects within Prometheus

2nd Priority

Pq/Dq formulations
Preglox;120+80; Sprayseed

Straight Pq Formulations
USA 240g/l;China 250g/l

1st Priority

Dermal Tox
Patenting Exercise

200 g/l Alginate
+/- novel AA

French Formulations
R-Bix;Plus

Research

BiPAS
R&T adjuvant Project

10x oral tox improvement
research project

Rhodia collaboration
external collaborator
polymer modifications

PQ-Polymer Research

The original project goal, 10x oral safening, will not be reached.

The PLT has determined that we should continue to work towards the 10x goal.

We clearly need to deliver significant oral tox improvements in activity of our polymer formulations

This will be done through discovery and optimisation of polymer/adjuvant combinations.

Paraquat - polymer technology will be the basis of our life cycle management strategies for GRAMOXONE.

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Alginate French formulation development

- Paraquat has been the subject of intense regulatory scrutiny.
- The loss of registration of paraquat in France would have a significant negative impact on existing paraquat registrations globally.
- On the 24th February 2003 the French Commission des toxiques (CET) notified Syngenta that it has six months to propose modifications to the formulation to improve safety
- In order to credibly meet the CET requirement by September 2003, and thus maintain CET support for continued approval of at least some paraquat uses in France, we have initiated development of:
- 100g/l paraquat formulation (R-Bix)
- 100g/l paraquat + 50 g/l diquat formulation (Plus)
- These projects were not included in PIT, and resources have been transferred from the 120/80 PQ/DQ project (with a shortfall of $600k).

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Next Steps

- Finalize Oral Tox position (April)
- Assumptions , implications review with key countries (Mid March)
  - Impact on new technology on each Stakeholder
  - Assessment vs 2002 Sympact numbers
  - Agreement on provisional Sympact 2003 position (End April)
- Compilation of Business case (May)
- Formulation freeze (May)
- Business case review (June)
- Internal Region and country launch meetings (Q4 ’03)

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To get the most out of this technology:

- **Identify and understand key stakeholder issues to manage both license and freedom to sell.**
- **Engage all stakeholders**
  - **Improved Tox / risk profile (clear and consistent)**
  - **Unique benign environmental impact**
  - **Unique mode of action, and role in sustainable agriculture.**
  - ***In tandem with our stewardship initiatives***
- **Define the strategy to establish higher regulatory standards (raise the barriers)**
- **Leverage new formulation safety features with formulators to defend and grow molecular market share vs generics.**

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Six Questions

- Does it Work? Yes
- Is It Ours? Yes
- Is it Safe? Dermal Yes, Oral TBD
- Can we register it? Yes
- Can We Make it? Yes
- Is it Worth it? Yes, This is a unique opportunity for stewardship, regulatory, and commercial reasons.

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