The Impact of Regulatory Changes on Sustainability of Products in Crop Protection

Black and Green?

Carbon Footprint and Sustainability for Formulations

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Regulators

- Never get fired for saying ‘NO!’
- Sometimes get fired for saying ‘YES!’

Content

- European Crop Protection Primary Legislation
  - Directive 91/414
  - NEW Regulation 1107/2009
- Other European Legislation
  - MRL Regulation 396/2005
  - Water Framework Directive 2000/60
  - Directive 67/548 Dangerous Substances
  - Directive 1999/45 Dangerous Preparations
  - NEW Classification, Labelling and Packaging Regulation
  - NEW Sustainable Use Directive 2009/128
  - NEW The REACH Regulation
- Formulation Development
- Conclusions

European Law

- Regulation
  - Legal in all Member States without changes to the original text from a fixed date
- Directive
  - Transposed into national law over a period of time

European Crop Protection Primary Legislation

Directive 91/414

Directive 91/414

- Harmonises the regulation of plant protection products in the European Union
- Establishes agreed criteria for the safety of the active substance and the safety and efficacy of the formulated product
- A two part process

Directive 91/414

- Part 1
  - Harmonises the process and ‘criteria’ for considering the safety of ACTIVE SUBSTANCES at the European level
  - Establishes a list of critical ‘end points’ for regulatory evaluation
  - Establishes a positive list of ACTIVE SUBSTANCES considered safe for use in plant protection products in Europe called Annex I

Directive 91/414

- Part 2
  - Allows FORMULATED PRODUCTS to be registered at national level using the harmonised ‘criteria’ and ‘end points’
  - This process allows plant protection products to be sold at Member State level and is the key to commercial success

Directive 91/414

- Implementation
  - Active substances in plant protection products on the market in Europe up to and including 25th July 1993 were considered ‘old’ or ‘existing’
  - Active substances in plant protection products submitted for evaluation for sale in Europe after 25th July 1993 were considered ‘new’
  - A review programme for ‘old’ active substances and their products based on risk assessment
  - An evaluation programme for ‘new’ active substances and their products based on risk assessment

Directive 91/414
Existing and New Active Substances

- **Existing Active Substances**
  - Active substances existing on the market in the EU prior to July 1993
  - Review completed March 2009
    - 26% approved (c.250)
    - 7% not approved after review (c.70)
    - 67% removed from market (c.680 no/incomplete dossier or withdrawn by industry)
  - ***Formulation reviews continue at Member State level***
- **New Active Substances**
  - Active substances not registered in the EU prior to July 1993
  - c.85 new active substances approved, 60 pending

NEW Regulation 1107/2009

- Legal on 14th June 2011
  - Across the whole European Union
  - Establishes a preliminary screen of 'cut-off' criteria for active substances – based on hazard
  - Establishes the principle of 'comparative risk assessment and substitution'
  - Establishes a positive list of safeners
  - Establishes a negative list of co-formulants

NEW Regulation 1107/2009

- Part 1
  - Harmonises, for a second time, the process and ‘criteria’ for considering the safety of ACTIVE SUBSTANCES at the European level
  - Establishes a list of critical ‘end points’ for regulatory evaluation
  - Establishes a positive list of ACTIVE SUBSTANCES considered safe for use in plant protection products in Europe

NEW Regulation 1107/2009

- Part 2
  - Allows FORMULATED PRODUCTS to be registered at national level using the harmonised ‘criteria’ and ‘end points’ with very strict and relatively short timelines
  - This process allows plant protection products to be sold at Member State level and is the key to commercial success

NEW Regulation 1107/2009

- Implementation
  - Active substances in plant protection products on the market in Europe under 91/414 are considered ‘old’ or ‘existing’ active substances
  - Active substances in plant protection products accepted for evaluation for sale in Europe after 14th June 2011 are considered ‘new’
  - A second review programme for ‘old’ active substances and their products also called Annex I Renewal (AIR) now based on hazard and risk assessment
  - An evaluation programme for ‘new’ active substances and their products now based on hazard and risk assessment

NEW Regulation 1107/2009

- Co-formulant Implementation
  - Co-formulants are included in the new regulation (Article 58) and these are to be authorised in accordance with procedures that have yet to be established in a separate Commission Regulation
  - There will be a negative list published of co-formulants that cannot be used in EU plant protection products
  - Co-formulants can be reviewed at any time using any information the EU Commission or Member States considers relevant

Hazard and Risk

- Hazard
  - A hazard exists where an object (or substance) or situation has an intrinsic (built-in) ability to cause an adverse effect
- Risk
  - Risk, on the other hand, is the chance that such effects will occur: the risk can be high or negligible

Hazard and Risk

- Risk = hazard + exposure
- For harm to occur in practice - in other words, for there to be a risk - there must be BOTH the hazard AND the exposure to that hazard; without both these at the same time, there is no risk
- Under 91/414 risk assessment was the guiding principle but under the new regulation 1107/2009 in certain cases hazard will be used without reference to risk assessment

Other European Legislation

Other European Legislation

- EU Maximum Residue Limit (MRL) Regulation 396/2005
  - The amount of plant protection product residue in food and feed commodities following safe use of the product
  - Update of data required for EU MRLs
  - Re evaluation of data or requirement for new data

Other European Legislation

- Water Framework Directive 2000/60
  - Water in rivers, estuaries, coasts and aquifers will improve under measures set out in River Basin Management Plans, drawn up for river basin districts across Europe under the Water Framework Directive
  - River Basin Management Plans are plans for protecting and improving the water environment and have been developed in consultation with organisations and individuals

Other European Legislation

- Classification and Labelling
  - Directive 67/548 Dangerous Substances
  - Directive 1999/45 Dangerous Preparations
  - NEW Classification, Labelling and Packaging Regulation
    - The European Union's classification and labelling process is designed to indicate the hazard of chemical substances, not the statistical risk they may pose through normal, or even extreme, use. The hazard's 'critical end-point' is determined from the effects obtained in high dose animal studies which are designed to give conservative results so as to afford protection to all sectors of the population, rather than an assessment of realistic exposure levels from everyday handling or use of the product

Other European Legislation

- EU Classification and Labelling
  - Consequences
    - Various solvents and co-formulants have been lost to the plant protection product industry through classification and labelling restrictions
    - This has consequences for global product lines where one regulatory area can effectively dictate product availability
    - Enormous cost and complexity to make formulation changes

Other European Legislation

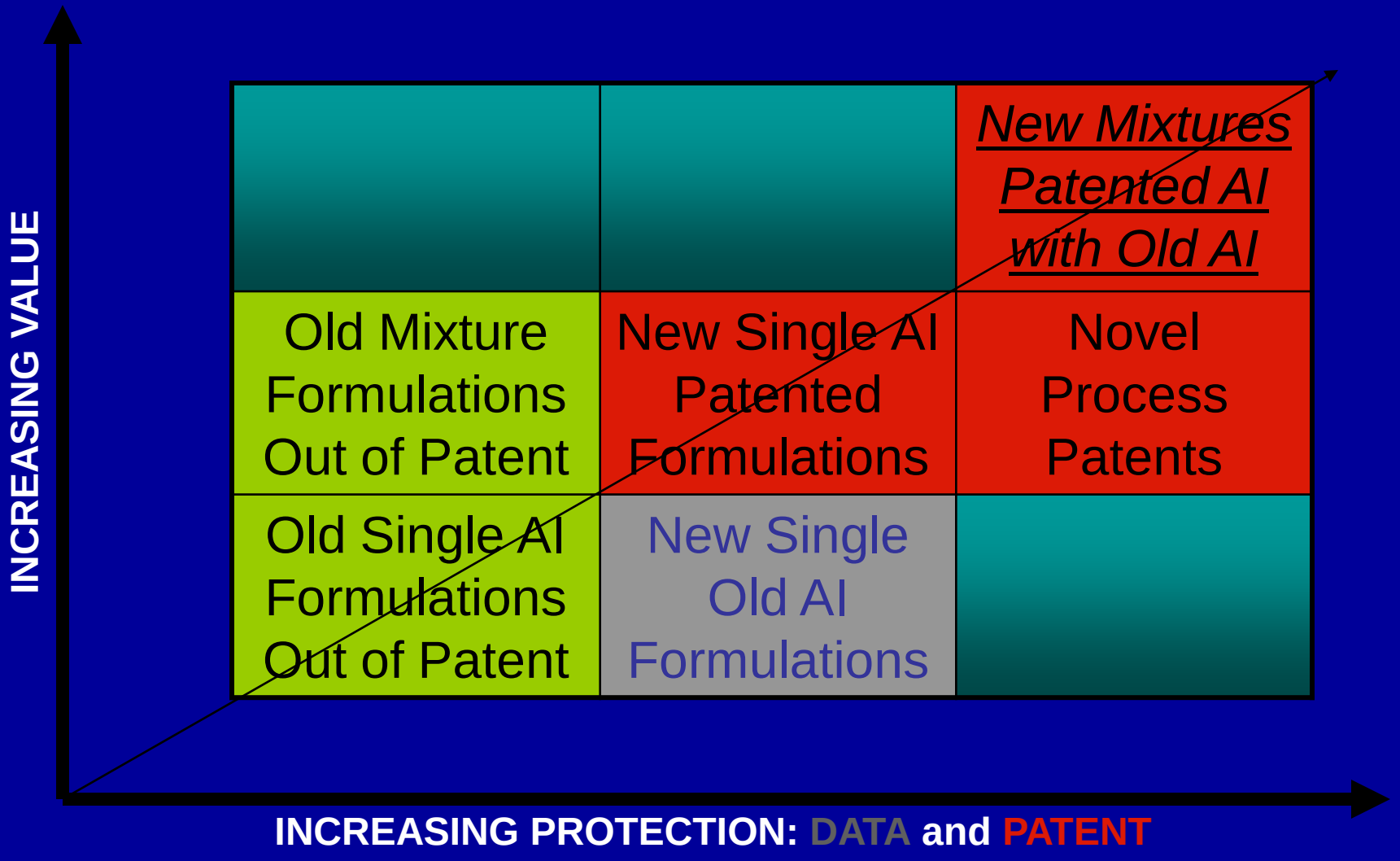
- NEW Sustainable Use Directive 2009/128
  - Member States to implement by 14th December 2011
  - A framework to achieve a sustainable use of pesticides by reducing the risks and impacts of pesticide use on human health and the environment and promoting the use of Integrated Pest Management and of alternative approaches or techniques such as non-chemical alternatives to pesticides

Other European Legislation

- NEW The REACH Regulation
  - Registration, Evaluation, Authorisation and Restriction of Chemicals Regulation
  - REACH is a new European Union regulation concerning the Registration, Evaluation, Authorisation and restriction of Chemicals. It came into force on 1st June 2007 and replaces a number of European Directives and Regulations with a single system
  - REACH applies to substances manufactured or imported into the EU in quantities of 1 tonne per year or more
  - Reduced requirements for plant protection products as they are covered by 91/414 and 1107/2009
  - Co-formulants, safeners and intermediates require notification under REACH

Formulation Development

Valuable Protected Formulations



Definitions

- Patents
  - To protect inventions e.g. a new chemical
  - Do not protect the cost of proving safety i.e. the registration dossier
- Regulatory Data Protection
  - To protect the cost of proving to the satisfaction of the regulators that new plant protection products are safe and efficacious

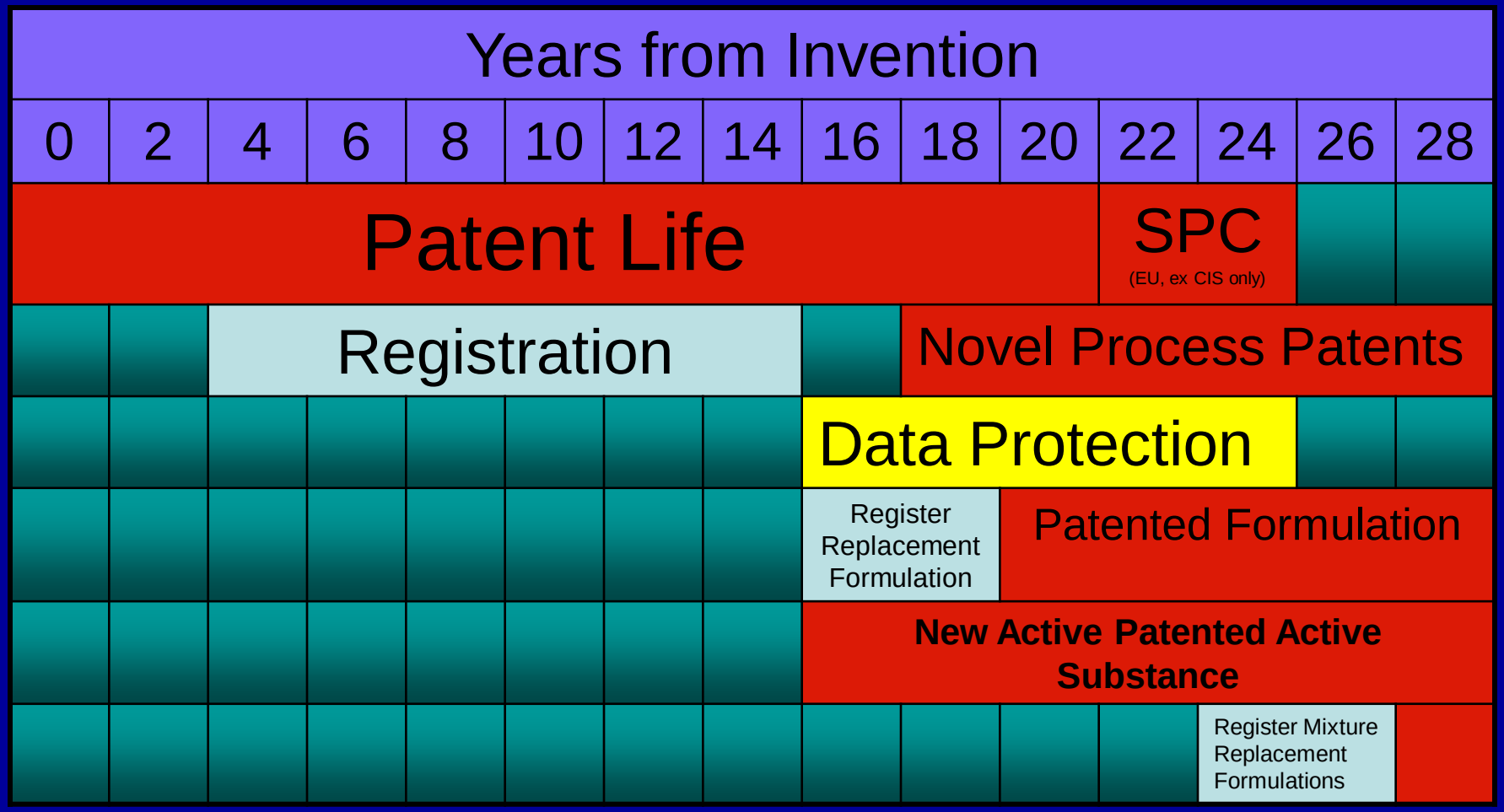
Definitions

- Proprietary Product
  - Patented
- Proprietary Generic Product
  - Out of patent with some regulatory data protection
- Generic Product
  - Out of patent with no regulatory data protection

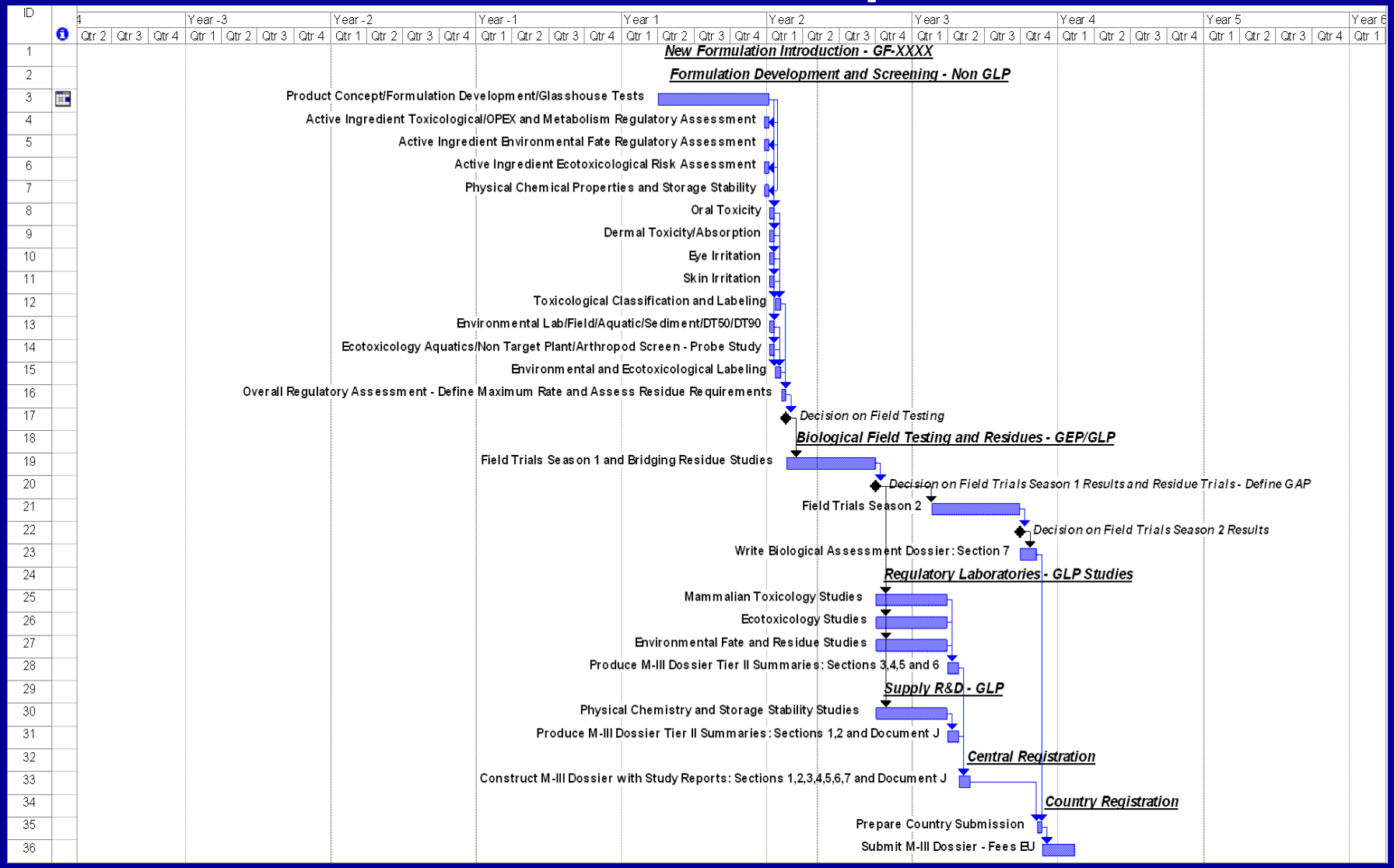
Definitions

- Patents
  - Protect against unlawful copying
  - Patent life is 20 years from filing plus the possibility in the EU and former CIS of 5 further years – SPC: Supplementary Protection Certificate
  - Globally enforceable
- Regulatory Data Protection
  - Protect against unlawful use of originator data when applying for a product registration
  - Can be zero but usually 5 to 10 years duration depending on country and circumstances…perpetual in Japan
  - Difficult to enforce and sometimes non-existent

Product Life Cycle



Formulation Development Plan



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Formulation Development Plan

ID	Task Name	Duration	Start	Finish	RWUS	OCRFS
1	**New Formulation Introduction - GF-XXXX**	**150.8 wks**	**4/1/05**	**2/20/08**	**761.7 days**	**$0**
2	**Formulation Development and Screening - Non GLP**	**47.2 wks**	**4/1/05**	**2/24/06**	**85.7 days**	**$0**
3	Product Concept/Formulation Development/Glasshouse Tests	40 wks	4/1/05	1/5/06	30 days	$25,000
4	Active Ingredient Toxicological/OPEX and Metabolism Regulatory Assessment	2 wks	1/2/06	1/13/06	5 days	$0
5	Active Ingredient Environmental Fate Regulatory Assessment	2 wks	1/2/06	1/13/06	15 days	$0
6	Active Ingredient Ecotoxicological Risk Assessment	2 wks	1/2/06	1/13/06	3 days	$0
7	Physical Chemical Properties and Storage Stability	2 wks	1/2/06	1/13/06	2 days	$2,000
8	Oral Toxicity	2 wks	1/6/06	1/19/06	2 days	$2,000
9	Dermal Toxicity/Absorption	2 wks	1/6/06	1/19/06	2 days	$2,000
10	Eye Irritation	2 wks	1/6/06	1/19/06	2 days	$2,000
11	Skin Irritation	2 wks	1/6/06	1/19/06	2 days	$2,000
12	Toxicological Classification and Labeling	2 wks	1/20/06	2/2/06	1 day	$0
13	Environmental Lab/Field/Aquatic/Sediment/DT50/DT90	2 wks	1/16/06	1/27/06	0 days	$10,000
14	Ecotoxicology Aquatics/Non Target Plant/Arthropod Screen - Probe Study	2 wks	1/6/06	1/19/06	1 day	$25,000
15	Environmental and Ecotoxicological Labeling	2 wks	1/30/06	2/10/06	1 day	$0
16	Overall Regulatory Assessment - Define Maximum Rate and Assess Residue Req	2 wks	2/13/06	2/24/06	2 days	$0
17	Decision on Field Testing	0 wks	2/24/06	2/24/06	0 days	$0
18	**Biological Field Testing and Residues - GEP/GLP**	**90 wks**	**2/27/06**	**11/16/07**	**210 days**	**$0**
19	Field Trials Season 1 and Bridging Residue Studies	32 wks	2/27/06	10/6/06	100 days	$200,000
20	Decision on Field Trials Season 1 Results and Residue Trials - Define GAP	0 wks	10/6/06	10/6/06	0 days	$0
21	Field Trials Season 2	32 wks	2/26/07	10/5/07	90 days	$100,000
22	Decision on Field Trials Season 2 Results	0 wks	10/5/07	10/5/07	0 days	$0
23	Write Biological Assessment Dossier: Section 7	6 wks	10/8/07	11/16/07	20 days	$0
24	**Regulatory Laboratories - GLP Studies**	**30 wks**	**10/9/06**	**5/4/07**	**86 days**	**$0**
25	Mammalian Toxicology Studies	26 wks	10/9/06	4/6/07	40 days	$60,000
26	Ecotoxicology Studies including Non Target Plant Studies	26 wks	10/9/06	4/6/07	5 days	$250,000
27	Environmental Fate and Residue Studies	26 wks	10/9/06	4/6/07	15 days	$70,000
28	Produce M-III Dossier Tier II Summaries: Sections 3, 4, 5 and 6	4 wks	4/9/07	5/4/07	26 days	$0
29	**Supply R&D - GLP**	**30 wks**	**10/9/06**	**5/4/07**	**20 days**	**$0**
30	Physical Chemistry and Storage Stability Studies	26 wks	10/9/06	4/6/07	10 days	$28,000
31	Produce M-III Dossier Tier II Summaries: Sections 1, 2 and Document J	4 wks	4/9/07	5/4/07	10 days	$0
32	**Central Registration**	**4 wks**	**5/7/07**	**6/1/07**	**10 days**	**$0**
33	Construct M-III Dossier with Study Reports: Sections 1, 2, 3, 4, 5, 6, 7 and Docum	4 wks	5/7/07	6/1/07	10 days	$0
34	**Country Registration**	**13.6 wks**	**11/19/07**	**2/20/08**	**350 days**	**$0**
35	Prepare Country Submission	2 wks	11/19/07	11/30/07	300 days	$0
36	Submit M-III Dossier - Fees EU one formulation in 27 Member States	11.6 wks	12/3/07	2/20/08	50 days	$300,000

Conclusions

Conclusions

- Plant Protection Product 91/414 Review
  - 74% of existing active substances and their associated formulated products off the market over a 15 year period 1995-2010
  - New active substances and their associated formulated products are not being registered quickly to compensate for the loss

Conclusions

- Classification and Labelling Legislation
  - Many co-formulants have either been lost to the plant protection industry or put under severe regulatory pressure that has required their removal from formulated products
  - Re formulating existing products is complex and expensive
  - The regulatory process does not handle formulation changes efficiently

Conclusions

- Research and Development Costs
  - New Active Substance
    - The cost of developing a new active substance and associated formulated products for the USA and EU rose from $152million in 1995 to 256million in 2008
    - The time to market in the USA and EU has increased from 8 years in 1995 to 10 years in 2008 which erodes patent life
    - In the EU the new regulation 1107/2009 may well lead to up to 14 years of the patent being eroded

Current Emphasis

Conclusions

- Research and Development Costs
  - New Formulation
    - The cost of developing a new formulated product for the USA and EU is currently $5million
    - The time to market in the USA and EU is currently 4-6 years

New Emphasis

Conclusions

- Novel Formulation Development
  - More cost effective
  - Ability to patent
  - Less uncertainty
  - Quicker time to market
  - Less complexity
  - More chance of success

Thank you!