

Biopharmaceuticals in transgenic plants: Has the time finally come?



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Presentation Overview

- How did we get here?
 - *The Situation ca 2000 & 2005*
 - *The Promise*
 - *So what happened?*
 - *Hurdles that were not overcome*
- Where's the room for optimism?
 - *Six reasons to be optimistic*
- Conclusions and Predictions

**Biopharmaceuticals made in transgenic plants
= plant-made pharmaceuticals (PMPs)**



The Situation

U.S.

■ *Pharmaceuticals*

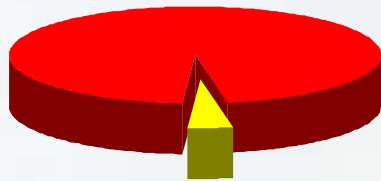
■ *Biopharmaceuticals*

1991
(\$45B)

1997
(\$70B)

2003
(\$216B)

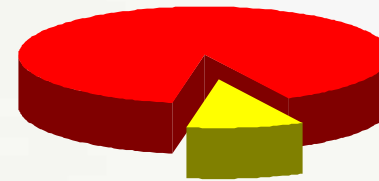
2010
(\$463B)



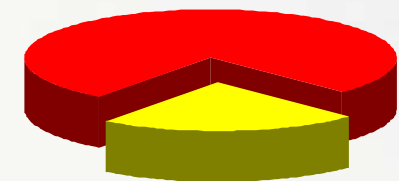
\$1.8B
(4%)



\$7.8B
(11%)



\$22B
(10%)



\$105B
(23%)

1700+ Products in Pipeline
400+ In Clinical Trials
94 new indications approved thru 2004

Manufacturing
COGs
~20% of Sales

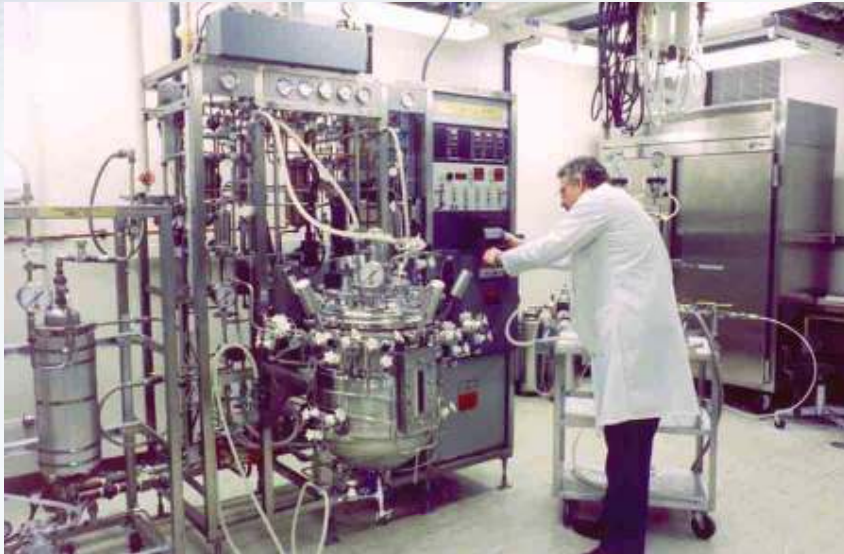


The Situation

- Monoclonal antibodies were “taking over” in biologics drug applications
 - *Potentially high volumes of drug needed*
- Manufacturing COGs exceeded US \$1,000/g
 - *Expensive manufacturing facilities (> US \$10,800/m²)*
 - *Low productivity of mammalian cell lines (100-500 mg/l)*
- Costs of biosafety testing were high
 - *Perhaps 20% of the manufacturing COGs*
 - *Viral testing (especially viral clearance)*
 - *Genzyme’s recent experience with Cerezyme (Gaucher’s) and Fabrazyme (Fabry’s)*



The Promise



The Promise



The Promise

- Huge reduction in manufacturing costs
- No viral testing (human viruses cannot replicate in plants)



Literature Review - 2009

- Published data – mostly from academic labs
- Plant nuclear genome (stable or transient/viral expression), chloroplast expression
- Food crops, seed crops, non-food crops, non-cultivated species
 - 24 human bacterial antigens and 66 human viral antigens have been expressed in 26 different plant systems
 - 51 biopharmaceuticals have been expressed in 13 different plant systems

H Daniell, ND Singh, H Mason, SJ Streatfield, Trends in Plant Science, Volume 14, Issue 12, Dec 2009, pp 669-79



On the industrial side ...

- Agragen
- ASU
- Bayer Innovation
- Biolex
- Chlorogen
- CIBG (Cuba)
- CropTech
- Cobento AS
- Dow AgroSciences
- Dow Chemical
- Epicyte
- ERA Biotech
- Farmacule
- Fraunhofer
- greenovation
- Guardian Biosciences
- Medicago
- Meristem
- Monsanto (IPT)
- NeoRx
- Nexgen Biotech
- Planet Biotech
- Prairie Plant Systems
- ProdiGene
- Protalix
- SemBioSys
- Syngenta
- Ventria



The Promise ~ 2005

U.S.

■ *Pharmaceuticals*

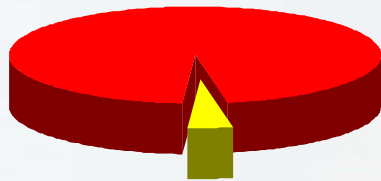
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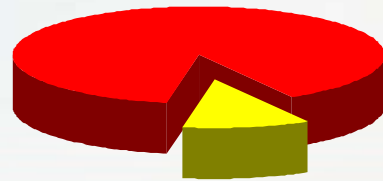
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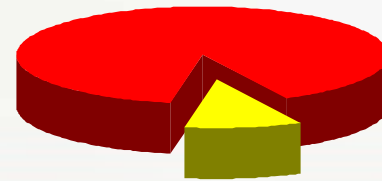
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(\$463B)



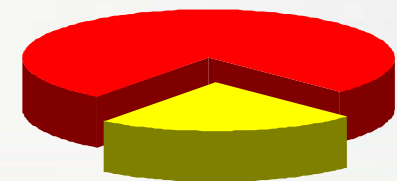
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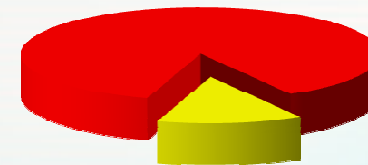


\$22B
(10%)



\$105B
(23%)

2009
(\$328B)



\$43B
(15%)



World's Top Selling Drugs - 2010

	<i>Drug</i>	<i>Indication</i>	<i>Company</i>	<i>Sales (\$Bn)</i>
1.	Lipitor	Cholesterol	Pfizer	\$11.7
2.	Plavix	Anticlotting	Sanofi/Bristol	\$ 9.6
3.	Advair	Asthma/COPD	GSK	\$ 9.0
4.	Remicade	Arthritis	Merck/J&J	\$ 7.4
5.	Enbrel	Arthritis	Pfizer/Amgen	\$ 7.1
6.	Humira	Arthritis	Abbott	\$ 6.8
7.	Avastin	Cancer	Roche	\$ 6.7
8.	Rituxan	Cancer	Roche	\$ 6.1
9.	Diovan	Hypertension	Novartis	\$ 6.0
10.	Crestor	Cholesterol	AstraZeneca	\$ 5.8

FACTBOX – World's top-selling drugs in 2014 vs 2010 - Reuters



So what happened?

- Not one plant-made vaccine has advanced beyond Phase I human clinical trials
 - *One veterinary vaccine has been USDA approved (Dow AgroSciences for Newcastle disease in poultry – 2006)*
- Only a few plant-made pharmaceuticals have advanced beyond Phase I human clinical trials
 - *SemBioSys (insulin for diabetes – Phase I/II results in June, 2009)*
 - *Biolex (ER IF α 2b for Hepatitis C – Phase IIb results in April, 2010)*
 - *Planet (Mab against *S. Mutans* – dental caries, Phase II in 2010)*
 - *Protalix (Enzyme for Gaucher's, Phase III 2009 – in registration)*



So what happened?

Transgenic plant “manufacturers” focused on their advantages, *vis-à-vis* mammalian cell culture ...

- Reduction in manufacturing costs
- Lack of human-infectious viral contaminants

... not the manufacturing, regulatory and perception hurdles. There were 4 such hurdles.



Hurdle #1 – Downstream Processing

*Manufacturing = Upstream Processing
(synthesizing the protein – USP)*

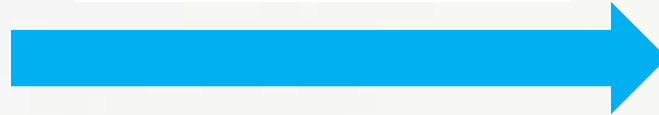
+

*Downstream Processing
(purifying the synthesized protein
to pharmaceutical grade – DSP)*

Also includes final fill and finish – but that is ignored here ...

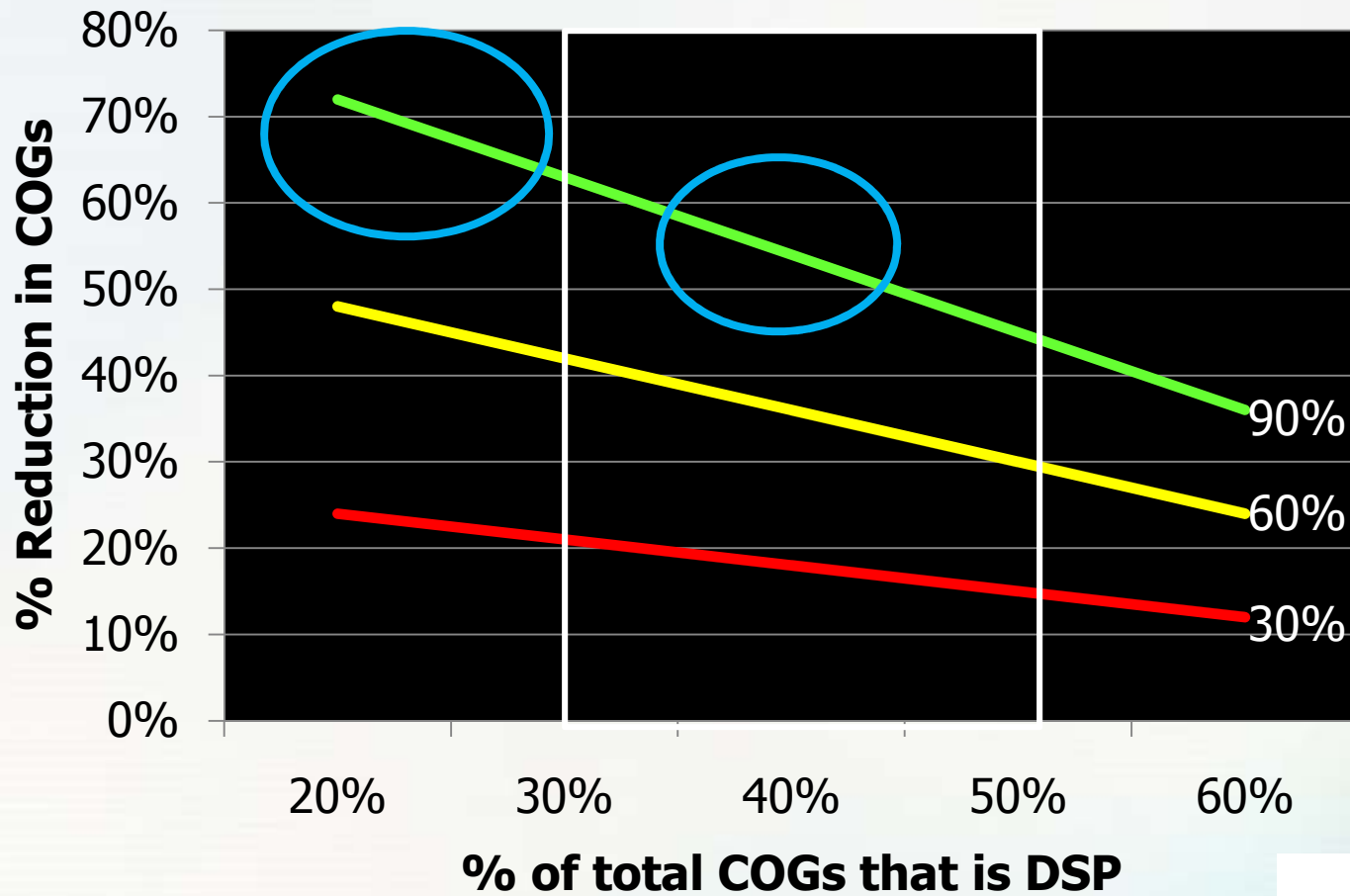


Hurdle #1 - Downstream Processing



Lowering USP Costs on Manufacturing COGs

For a typical biotherapeutic, 30-50% of USP+DSP Costs are DSP



An Egregious Example

Table 1

Cost of production of therapeutic proteins.

System	\$/g
Chinese hamster ovary (CHO) cells	300
Transgenic chickens/eggs	1-2
Transgenic goats/milk	1-2
Microbial fermentation	1.00
Plants*	0.10

*To derive the value for plants several assumptions were made: the expression level is 1% of the dry weight; each bushel of corn weighs 25 kg; at 150 bushels per acre, and 1% expression, 37.5 kg protein could be harvested per acre; growing costs are \$1000 per acre; 50% recovery during purification; final yield is 18.75 kg purified protein per acre.

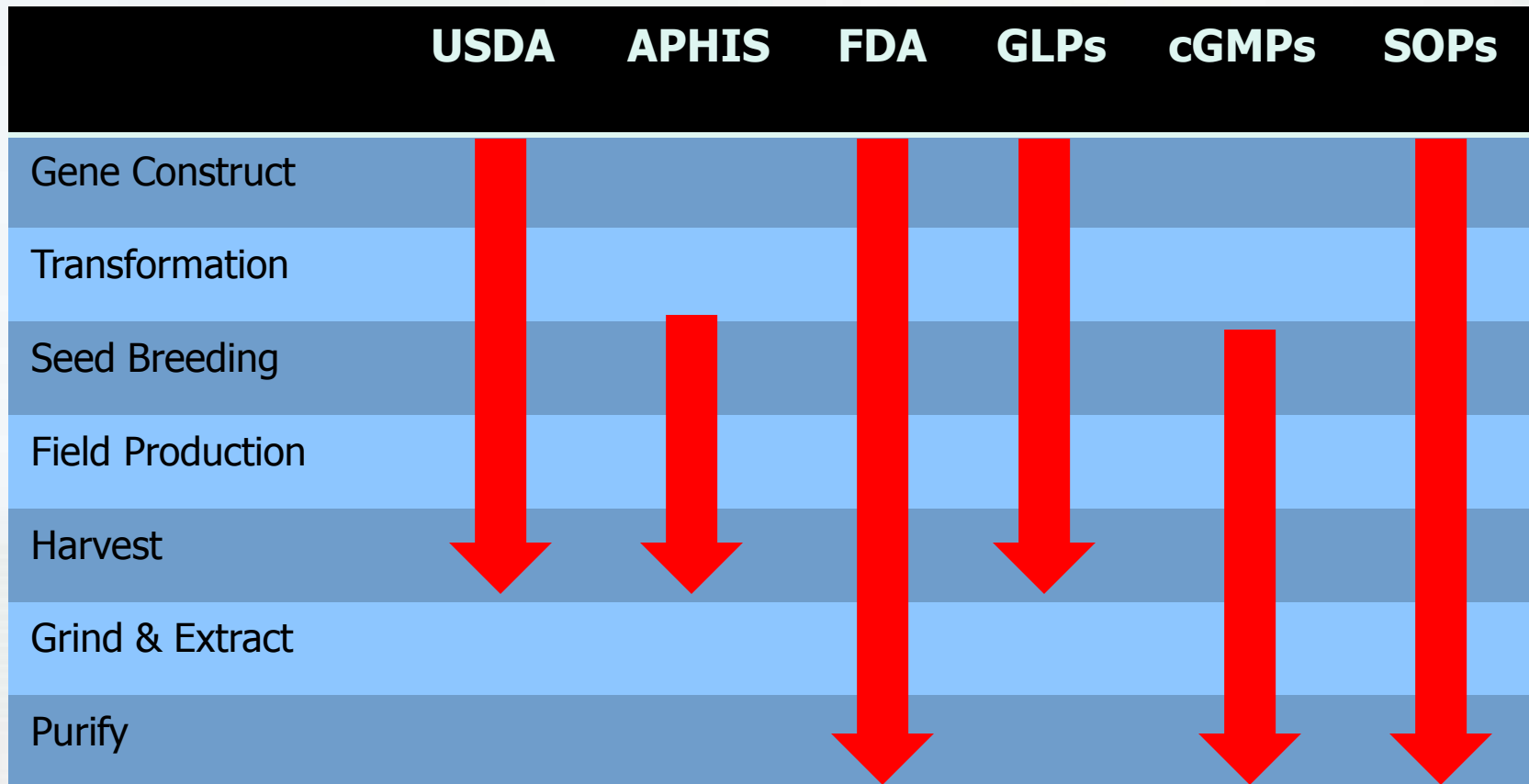


EE Hood, SL Woodward, ME Horn, Current Opinion in Biotechnology 2002, 13: 630-635



Hurdle #2 - The Regulatory Unknown

Significant Regulatory Oversight with Multiple, Overlapping Responsibilities



Hurdle #2 – The Regulatory Unknown

aka, “The Fear of Being First”

- 1999 “Gang of Four” proposed draft Guidance Notes to joint FDA/USDA committee (based upon existing Transgenic Animals Guidance)
- 2002 FDA proposes draft “Guidance for Industry: Drugs, Biologics, and Medical Devices Derived from Bioengineered Plants for Use in Humans and Animals”
- EMEA proposes “Points to Consider on Quality aspects on medicinal products containing active substances produced by stable transgene expression in Higher Plants”
- 2008 EMEA issues “Guideline on the Quality of Biological Active Substances Produced by Stable Transgene Expression in Higher Plants”



Hurdle #3 – Protein Expression Levels

- Amount of protein-expressing tissue
- Percentage (of FW) of that tissue that is the target protein

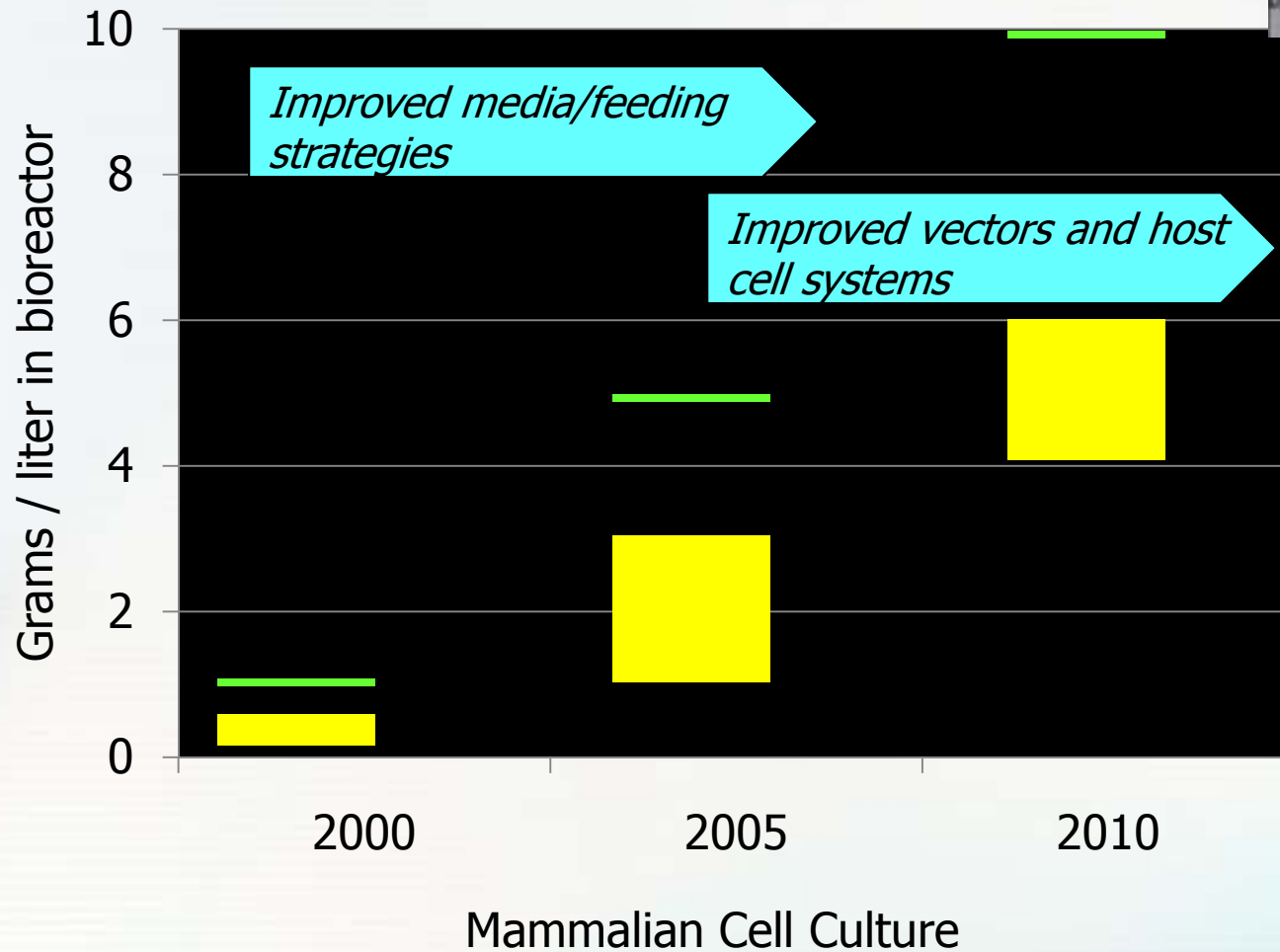
Why?

- Growing costs are mostly labor and, for a particular crop, are fixed
- The higher the mass of FW and percentage of target protein per gram of FW, the higher is the protein output for those costs
- Generally accepted target for “commercial production” of a biopharmaceutical is target protein:
 - *0.1% of FW*
 - *1 g target protein / 1 kg of FW*



Hurdle #3 - Protein Expression Levels

The Competition has not been sleeping!



Hurdle #4 – Public Perception on Containment

Issue: Gene Flow

*Genetically
Modified
Plants*

*Genetically
Unmodified
Plants*



Hurdle #4 – Public Perception on Containment

Incidents

Starlink Corn (2000)

- EPA approved Aventis CropScience SA Starlink corn (containing an insecticidal protein, Cry9C) for use as an animal feed)
- In late 2000, StarLink corn was found in 300+ corn products
 - *Legal damage settlement of \$100 million*
 - *Estimated losses to US corn producers between \$25 - \$290 million*



Hurdle #4 – Public Perception on Containment

Incidents

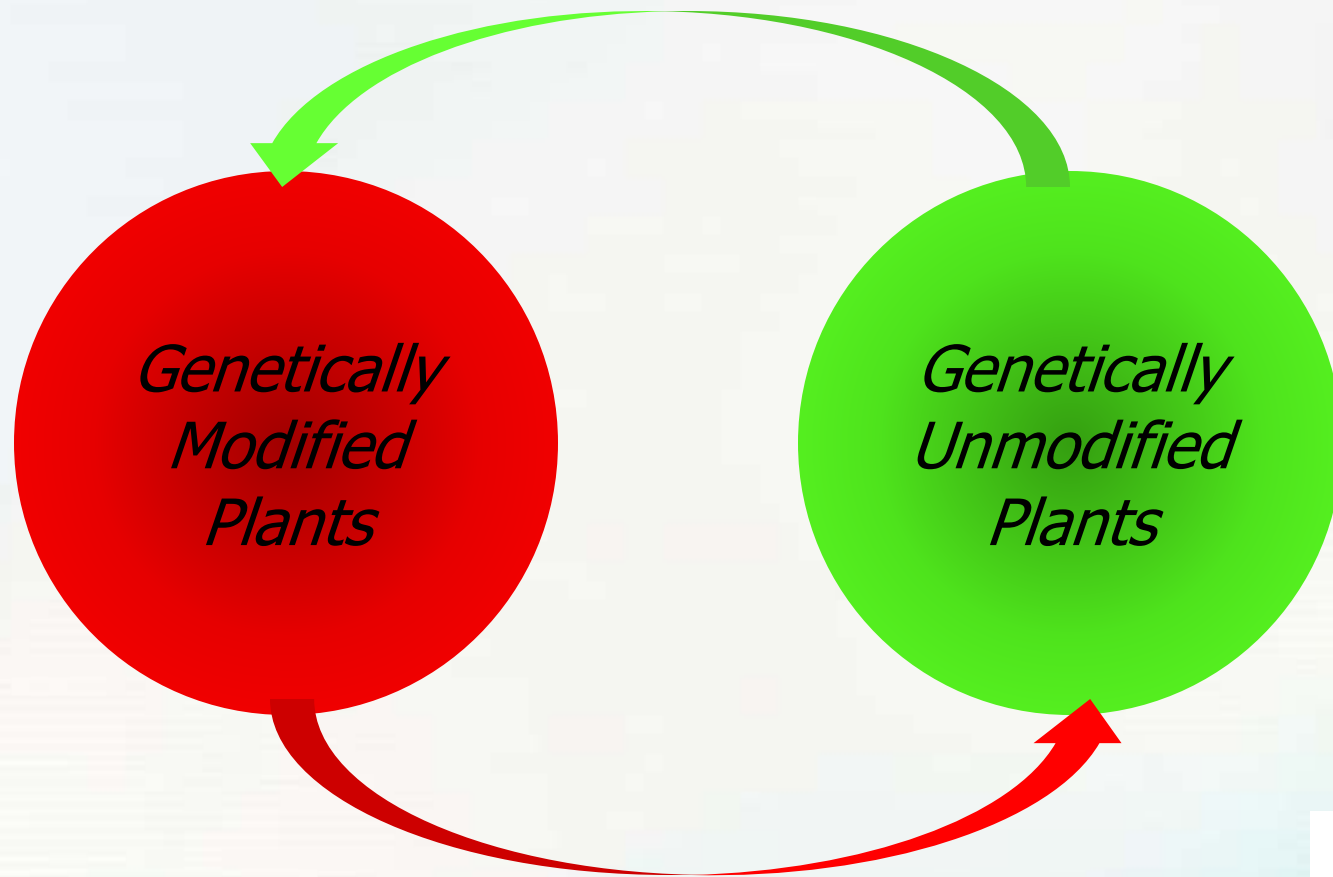
ProdiGene corn (2002)

- September – ProdiGene ordered by USDA to destroy 155 acres of Iowa corn contaminated with genes coding for two difference medicines
- October – USDA inspectors find that 550,000 bushels of Nebraska soybeans have been contaminated with leaves and stalks from corn plants containing a pig vaccine
- December – company agrees to pay a \$250,000 fine plus an estimated \$2.8 million to dispose of the soybeans



Hurdle #4 – Public Perception on Containment

Issue: Gene Flow



Best solution – complete containment



Courtesy of Prairie Plant Systems, Inc., Saskatoon, SK Canada



So, where are we today

And

Where's the room for optimism ??



Where's the room for optimism?

- The pharma world is moving towards protein products



World's Top Selling Drugs - 2010

<i>Drug</i>	<i>Indication</i>	<i>Company</i>	<i>Sales (\$Bn)</i>
1. Lipitor	Cholesterol	Pfizer	\$11.7
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	<i>Drug</i>	<i>Indication</i>	<i>Company</i>	<i>Sales (\$Bn)</i>
1.	Lipitor	Cholesterol	Pfizer	\$ 6.3
2.	Nexium	GERD	AstraZeneca	\$ 3.4
3.	Prevacid	GERD	Takeda	\$ 3.3
4.	Zocor	Cholesterol	Merck	\$ 3.1
5.	Advair Diskus	Asthma/COPD	GSK	\$ 2.8
6.	Zoloft	Depression	Pfizer	\$ 2.6
7.	Plavix	Anticlotting	Sanofi/Bristol	\$ 2.6
8.	Effexor SR	Depression	Wyeth	\$ 2.2
9.	Singulair	Asthma	Merck	\$ 2.1
10.	Norvasc	High BP	Pfizer	\$ 2.1

www.drugs.com/top200_2005.html



World's Top Selling Drugs - 2014

<i>Drug</i>	<i>Indication</i>	<i>Company</i>	<i>Sales (\$Bn)</i>
1. Avastin	Cancer	Roche	\$ 8.9
2. Humira	Arthritis	Abbott	\$ 8.5
3. Enbrel	Arthritis	Pfizer/Amgen	\$ 8.0
4. Crestor	Cholesterol	AstraZeneca	\$ 7.7
5. Remicade	Arthritis	Merck/J&J	\$ 7.6
6. Rituxan	Cancer	Roche	\$ 7.4
7. Lantus	Diabetes	sanofi-aventis	\$ 7.1
8. Advair	Asthma/COPD	GSK	\$ 6.8
9. Herceptin	Cancer	Roche	\$ 6.4
10. NovoLog	Diabetes	Novo Nordisk	\$ 5.7

FACTBOX – World's top-selling drugs in 2014 vs 2010 - Reuters



Where's the room for optimism?

- The pharma world is moving towards protein products
- The pharma world is moving, *stealthily*, to plant manufacturing methods



Partnerships & Acquisitions

- Product development companies are partnering with PMP technology companies
 - *Protalix: Pfizer, Teva*
 - *Biolex: Merial*
 - *Dow AgroSciences: acquires technical assets of Chlorogen*
 - *Meristem: Quintiles*
 - *Medicago: Phillip Morris International*
 - *SymBioSys: Arcadia Biosciences*
 - *Bayer Innovation: Icon Genetics*
- There are far more un-announced collaborations than announced collaborations

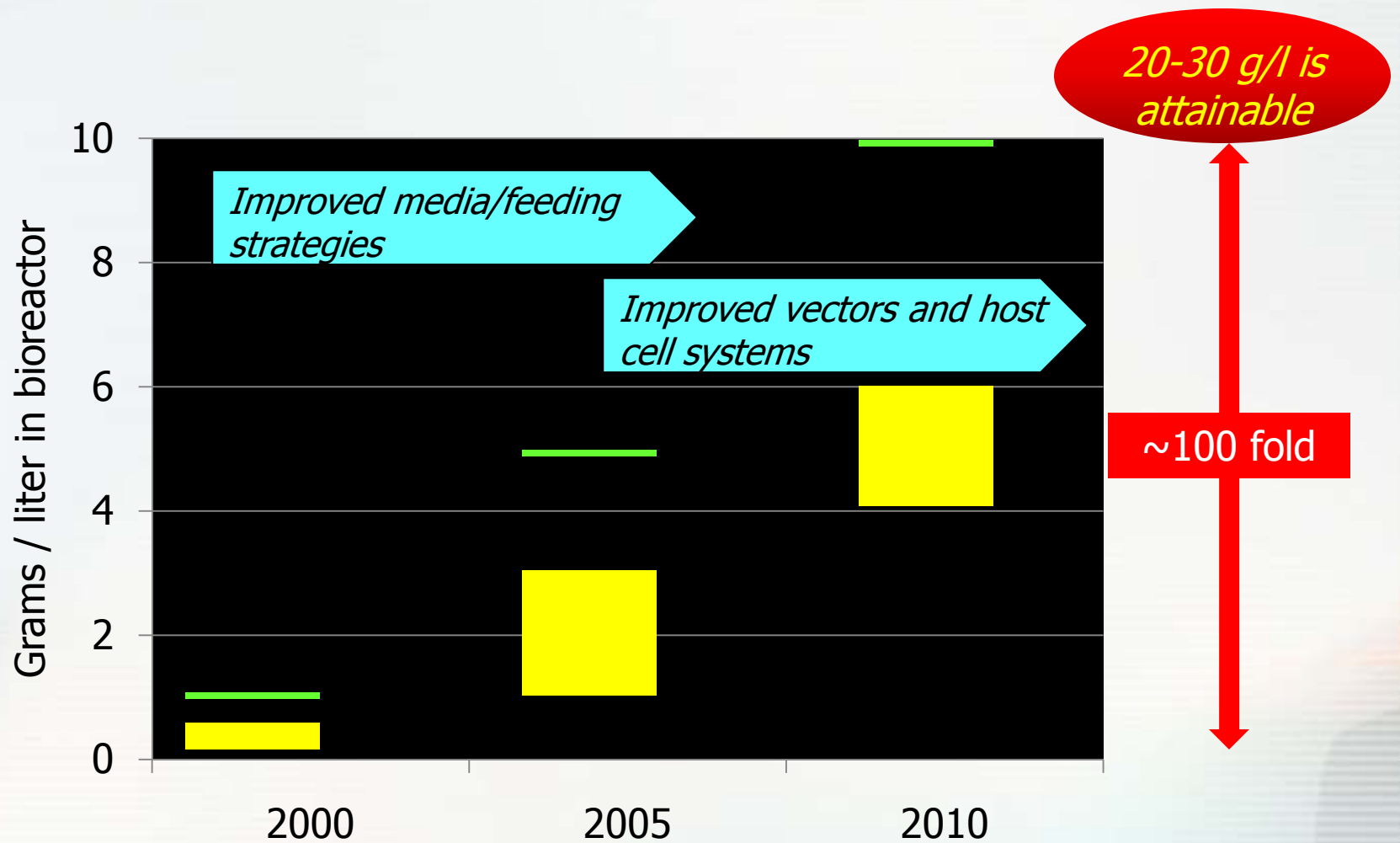


Where's the room for optimism?

- The pharma world is moving towards protein products
- The pharma world is moving, stealthily, to plant manufacturing methods
- Mammalian cell culture expression levels will probably top out at ~20-25 g/L



Hurdle #3 - Protein Expression Levels



Where's the room for optimism?

- The pharma world is moving towards protein products
- The pharma world is moving, stealthily, to plant manufacturing methods
- Mammalian cell culture expression levels will probably top out at ~20-25 g/L
- Contamination issues continue to plague cell culture manufacturers



Genzyme – The Poster Child

2009

- Mar 2 FDA Warning letter on manufacturing deficiencies
- Jun 16 Discloses viral contamination → plant shut down
- Aug 25 FDA grants fast-track review to Protalix



2010

- Feb 26 FDA Approves competitor Gaucher drug from Shire
- Mar 24 Company announces FDA to take enforcement action
- May 24 Consent decree: \$175M penalty, filling/packaging moved from Allston, manufacturing oversight by 3rd party
- Aug 10 Company announces it will take 3-4 years to rectify manufacturing issues

Cost in stock price, lost revenues, fines, addressing the problems?

Likely well north of \$1 billion



Where's the room for optimism?

- The pharma world is moving towards protein products
- The pharma world is moving, stealthily, to plant manufacturing methods
- Mammalian cell culture expression levels will probably top out at ~20-25 g/L
- Contamination issues continue to plague cell culture manufacturers
- A transgenic pharmaceutical has already been approved in the US and EU



GTC Biotherapeutics' Atryn®

- Anticoagulant human antithrombin manufactured in the milk of transgenic goats
- Approved by EMEA in 2006 and FDA in 2009 for treatment of patients with hereditary antithrombin deficiency who are undergoing surgical or childbirth procedures
- First preclinical work done in the mid-1990s – initially rejected by EMEA and a “tough slog” through the FDA

So, why is this relevant?

- *Many “trailblazing” issues overcome*
 - *Regulatory pathway established (fear of being first)*
 - *Use of animals for production (PETA)*
 - *Potential for mammalian virus contamination*



Significantly lower capital expenditures



78,125 – 156,250 L Cell Culture Facility*



1,500 Goat Milk Production Facility*
(Annual Output 3,750 – 7,500 Kg)

Mean CapEx = \$550M – \$1,100M (includes DSP)

Cell Culture CapEx @ 35% = **\$200M – \$400M**

Actual Investment to date = **\$25M**

* Assumes 2 g/L productivity

* Based on actual productivity (5 g/L and 10g/L)



Where's the room for optimism?

- The pharma world is moving towards protein products
- The pharma world is moving, stealthily, to plant manufacturing methods
- Mammalian cell culture expression levels will probably top out at ~20-25 g/L
- Contamination issues continue to plague cell culture manufacturers
- A transgenic pharmaceutical has already been approved in the US and EU
- Genetic manipulation will make it possible to control important post-translational modifications (such as glycosylation)



Glycosylation

The bad news ...

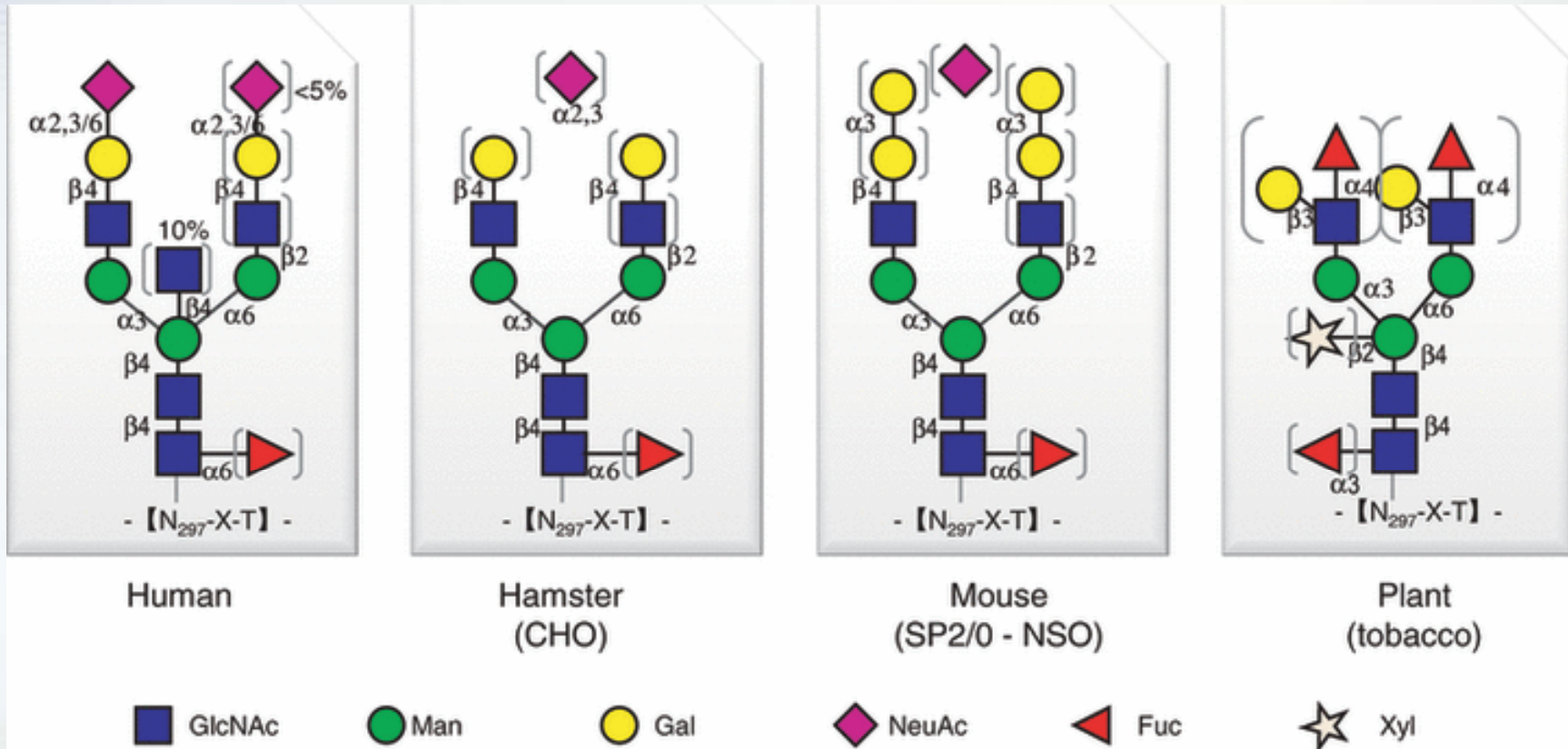
- ~50% of all proteins in eukaryotes, and ~33% of all approved biopharmaceuticals (2006) are glycoproteins
- The biological activity of many therapeutic glycoproteins (notably monoclonal antibodies, blood factors and interferons) is dependent on their glycosylation status
- Plant glycosylation patterns can be different among species and among vegetative portions of the plant (leaves, roots) vs. non-vegetative parts of the plant
- Plant glycans are immunogenic

The good news ...

- Plants can perform N-linked and O-linked glycosylation similarly to human



N-linked Glycosylation



V Gomord, A-C Fichette, L Menu-Bouaouiche, C Saint-Jore-Dupas, C Plasson, D Michaud and Loic Faye, *Plant Biotechnology Journal* (2010) 8,, pp. 564-587



Some Conclusions

- The pharma world is moving towards protein products → transgenic systems represent one means of reducing manufacturing costs and reducing virus contamination issues (opportunity)
- Regulatory acceptance is ever-so-slowly coming – approval of a transgenic animal biotherapeutic has helped
- Mammalian cell culture expression levels will probably top out at ~20-25 g/L (competition is slowing)
- Gene flow is no issue at all if the plants are grown within contained facilities



Some Predictions

- **Within 1 year**, the first PMP will be approved by the FDA and EMEA (Protalix enzyme replacement therapy)
- **Within 3 years**, most biopharmaceutical companies (= most pharmaceutical companies) will have PMP manufacturing development programs in place – likely in conjunction with outside contractors (growers, DSP CMO's, etc.)
- **Within 5 years**, there will be 1-2 more approved PMP's
- **Within 10 years**, many approved biopharmaceutical products will be produced *in planta* (reduced costs → generic forms of the drug)
- **Within 15 years**, PMPs will be preferred for manufacture of glycosylated proteins because pharmacologic properties of such proteins will be tailored by controlling post-translational modifications such as glycosylation



*Thank you for your
attention!*



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