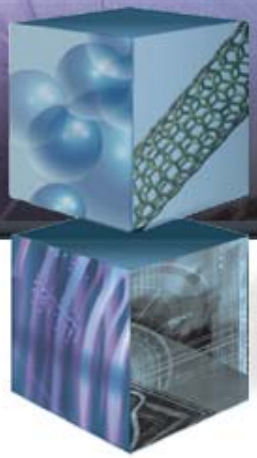
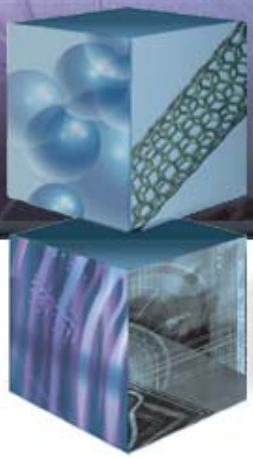


Advances in Synthetic Biology Conference

London, England
April 28, 2009



Synthetic Biology: The Challenge of Voluntary Containment vs. Governmental (EU, Federal, State and Local) Regulation

Could I Build Jurassic Park?

J. Mark Waxman, Partner

Foley & Lardner LLP

A Preamble

- Synthetic Biology: Nucleic acid molecules made solely by synthetic means.
- The US NIH Statement (March 4, 2009)
  - Nucleic acid synthesis technology...has galvanized aspects of the scientific community
  - Captured the attention of the general public and policy makers
  - The promise to accelerate discovery
  - But the same technology made lead to...pathogens with unexpected and potentially dangerous characteristics.
- What to do?

In The News

"I expect that this technology will be misapplied, actively misapplied and it would be irresponsible to have a conversation about the technology without acknowledging that fact." Drew Endy (MIT Soapbox Discussion, 2006).

"If a small group of synthetic biologists get their way, governance of extreme genetic engineering will be left entirely in their hands..." Extreme Genetic Engineering, An Introduction To Synthetic Biology (etc group, 2007).

"Constructing Life, The World of Synthetic Biology", *Technology Assessment*, Rathenau Institut, November, 2007.

"Researchers Take Step Toward Synthetic Life" *NY Times*, January 25, 2008.

"...nanotechnology is losing a public relations contest." NNAP, Second Assessment, April, 2008.

In The News

"Nanotechnology continues its rush into consumer products while nanotech legislation slowly percolates through Congress", Tech Talk, *http://blogs.spectrum.ieee.org/cgi-bin/mt/mt-t.fcgi/4632*, May, 2008.

"Scientists find bugs that eat waste and excrete petrol", *www.timesonline.co.uk*, June 14, 2008.

"Big questions on tiny, tiny technology" *The Boston Globe*, August 9, 2008.

"Army Slows Bioresearch At Maryland Laboratory" *The New York Times*, February 10, 2009.

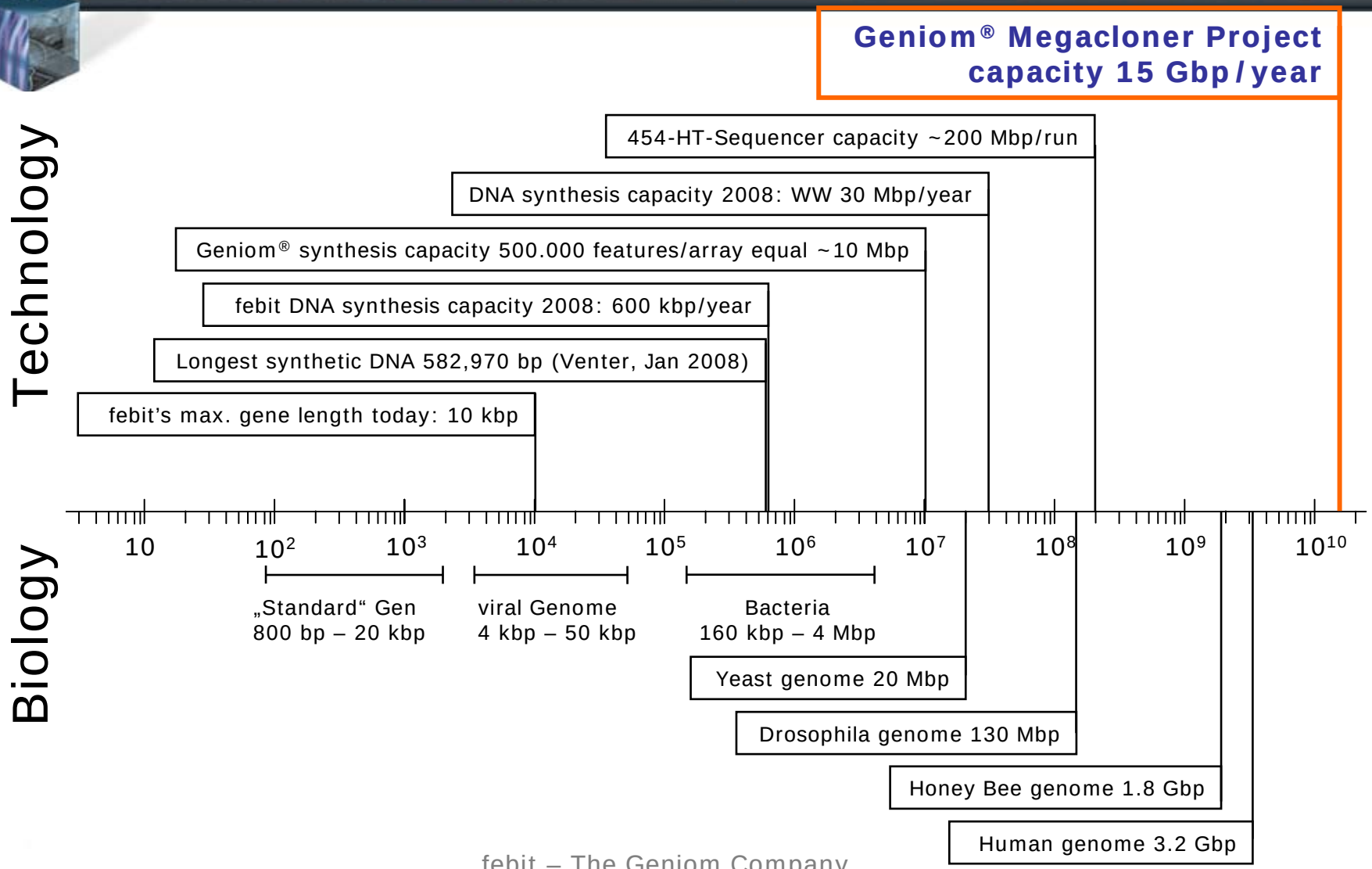
"Harvard fuels quest to create life from scratch," *The Boston Globe,* March, 18, 2009.

Are we one vial from disaster?

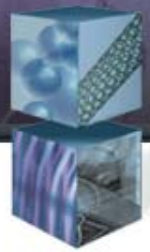
The Issue:

- DNA Synthesizer - $10,000
- Sequence or Synthesize - 10^{10} bases a day?
- 2020 – A single person can synthesize anyone (anything?) in a day?
- DY Bio
- Mail Order Oligonucleotides

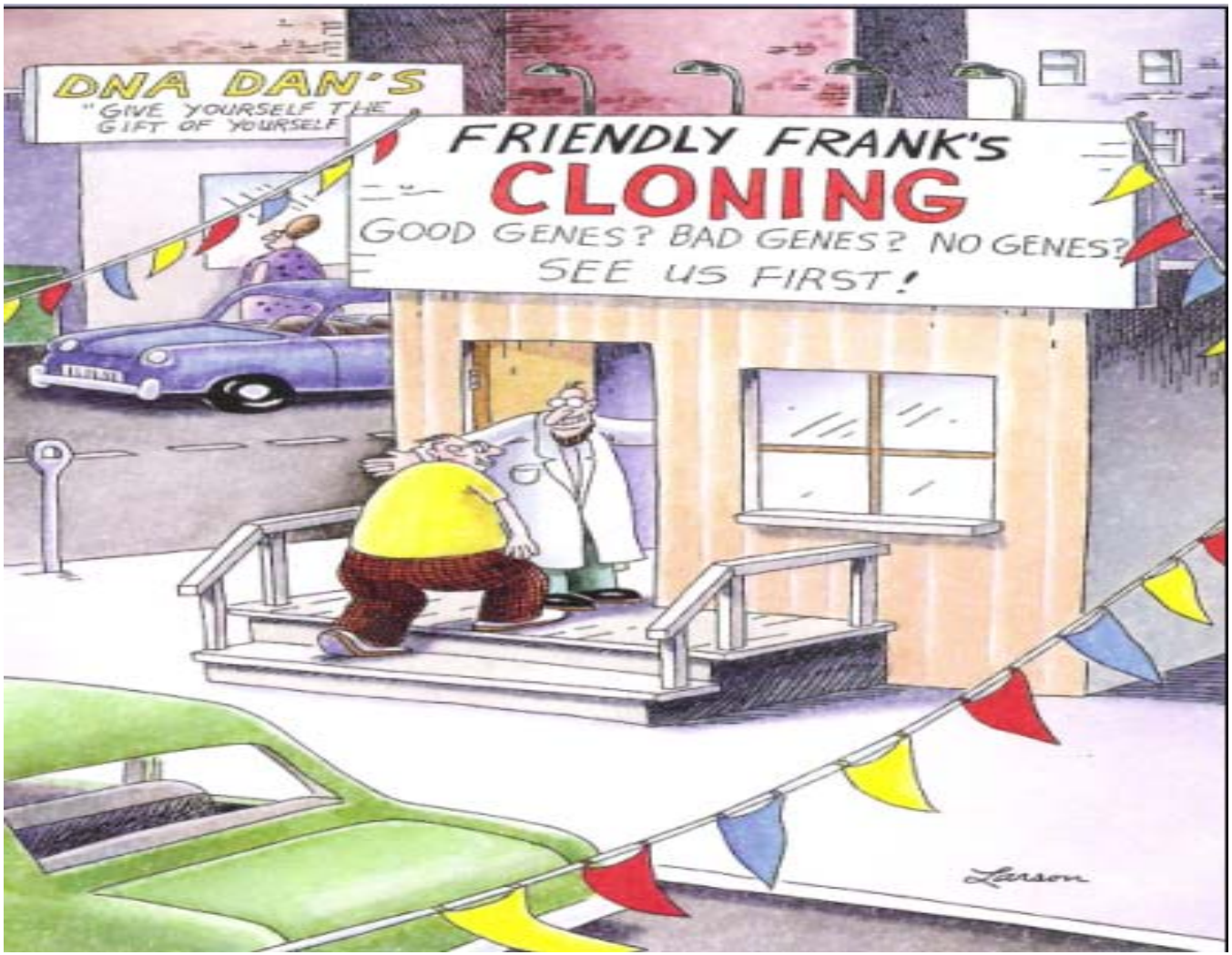
Next Disruptive Wave



Synthetic Biology: Key Markets



Life Science Research	AgBio	Renewable Energy	Industrial	Pharma
New Reagent Development	Crop Improvement	Cellulase Development	Enzyme Optimization	Antibody Engineering
Custom Genes	Host for Heterologous Expression	Metabolic Engineering	Strain Improvement	Enzyme Replacement Therapy
				Biocatalysts for Drug Synthesis
				Assay Development



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The Issues Before Us

- Biosecurity and the Dual Use Problem
  - Clear value vs. clear threat
  - The Issue – prevention vs. development
  - People are paying attention – e.g. National Science Advisory Board on Biosecurity (NSABB)
    - Transmissibility
    - Detectability
    - Pathogenicity
      - How do we know it when we see it beyond “Select Agents”?

The Issues Before Us

- The Challenge Is International
  - Movement
    - The pulonium analogy?
    - Easily portable - Biobricks
  - Procurement
    - Mail order
    - Carriers
  - Use
    - Unlimited experimentation
    - DNA cut and paste
  - The Challenge of Unilateral Regulation

The Issues Before Us

- Beyond Biosecurity
  - Environmental and Health Concerns
    - Food, Livestock and Agriculture
    - The Workplace
    - The Environment

The Issues Before Us

- The Patchwork Challenge and the "Control Dilemma"
  - Too many or too few regulators?
  - The Stem cell development and oversight process and automobile pollution analogies

The Issues Before Us

- Regulation as something else (e.g. nanotech)
  - Industrial pollution
  - Fungicide and plant contaminants
- Or, can we define what really needs regulation?
  - Gene synthesis activity with select virus/agents?
  - Experimentation
  - Remember – not all risks are intentional and foreseen!

The EU Approach

- A Summary: From Genetically Modified Organisms To Synthetic Biology: Legislation in the EU, in Six Member Countries and in Switzerland
  - Franco Furger and Fernfachhochschule Schweiz
- Synbio is not a distinct discipline
- The scientists do not believe synbio creates any fundamental new challenge – rules and regulations in place are adequate
- Focus
  - Safety of personnel in contained facilities
  - Release of GMOs into the environment

The EU Approach

- Laws dealing with:
  - Deliberate release of GMOs into the environment
  - Contained use of pathogenic and/or genetically modified organisms
  - Protection of workers exposed to biological agents at work
  - Biosafety Advisory Council (e.g. Belgium)

The EU Approach

- Deliberate Release –
  - Decisions and regulations
    - E.g. February 2004 – arrangements for the operation of the registers for recording information on genetic modifications in GMOs provided for in Directive 2001/181 EC of the European Parliament and of the Council
  - Contained use of Pathogenic and/or Genetically Modified Organisms
    - E.g. Directive 90/219/EEC (April 23, 1990) addressing use, risks, etc, including a series of subsequent decisions
  - Protection of Workers Exposed To Biological Agents At Work
    - E.g. Directive 2000/54/EC

In the U.S.

- With respect to biotechnology generally, the US uses health and safety laws written prior to the advent of modern biotech.
  - The current system was delineated under 1986 Coordinated Framework for Regulation of Biotechnology
    - Reliant on:
      - Plant Protection Act
      - Federal Food, Drug & Cosmetic Act
      - Insecticide, Fungicide and Rodenticide Act
      - Toxic Substances Control Act

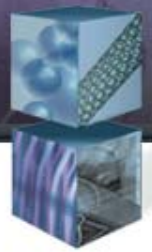
The Current Framework...Is Inadequate

- And More Generally –
  - FDA, Department of Agriculture, EPA
  - Laboratory Licensing

The Current Framework...Is Inadequate

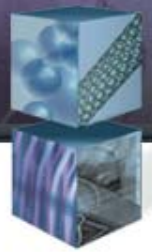
- Select Agents
  - “nucleic acids that can produce infections forms of any of the select agent viruses.”
  - Regulation of the possession, use and transference of select agents.
  - Classical swine fever, foot & mouth disease, equine encephalitis, Ebola, hemorrhagic fever viruses.

The Current Framework...Is Inadequate



- Export/Import Administration Regulations (19 CFR Part 12)
  - E.g. Germany – BAFA (Bundesamt für Ausfuhrkontrolle) (evaluation of ordered sequence as well as the ordering party for a permit)
- Criminal Code Prohibitions: Variola Virus (18 U.S.C §175c)
  - "knowingly develop, produce, stockpile...any biological agent, toxin, or delivery system for use as a weapon"
  - Possession of biological agent, toxin, or delivery system that is not reasonably justified by a prophylactic, protective bona fide research or other peaceful purpose
- NIH Guidelines for Research Involving Recombinant DNA – 2009 Proposed Update

And More Recently, State and Local Activity



- State Laws: Nanotechnology – 29 States have considered; 22 States have laws with some impact
  - Colorado – Office of Preparedness, Security and Fire Safety responsible for protocols for security at biotechnology labs and facilities.
  - Florida – Permit required for the release of exotic organisms, which include genetically modified organisms; biotechnology considered a potential weapon of mass destruction.
  - Hawaii – Notification of applications related to genetically modified organisms.
  - Michigan – Forbids importation of genetically engineered organisms or species that have potential to endanger health and safety of humans, crops, livestock, wildlife and property.
  - California – DTSC Inquiry (January 22, 2009) – Nanotube inquiry.

Municipalities

- Berkeley: Municipal Code –
  - Requires manufacturers, researchers, other businesses to file written disclosure plans that identify their production or use of nanoparticles, disclose toxicity data and provide plans for safe-handling.
  - A “Model Ordinance”

The Calls For Action

- IASB – 2004 (George Church Proposal)
- Department of Energy (Biological and Environmental Research Advisory Committee, 2004)
- ETC Group
- International Consortium For Polynucleotide Synthesis (ICPS)

The Calls For Action

- Synbio 2.0
- Biologic and Toxins Weapons Convention (BWC)
- Synthetic Genomics: Options For Governance (J. Craig, Venter Institute; MIT; CSIS)(October, 2007)

But There Has Not Been A Sustained And Focused Effort

What's Next – The Call For Oversight

- Is There A Best Model – Guidance From The EU?
  - REACH
  - IPPC

REACH

- Registration, Evaluation, Authorization and Restriction of Chemicals
  - SCOPE – All substances whether manufactured, imported, used as intermediates or placed on the market
  - Registration – Substances on their own or in preparation
  - Data Sharing
  - Information in the supply chain
  - Downstream users
  - Evaluation
  - Authorization – Substances of high concern
  - Restrictions

Integrated Pollution Prevention And Control

- Permitting – Installation operators must demonstrate a “forward plan” demonstrating:
  - Satisfactory Environmental Management Systems (EMS)
  - Justification of Best Available Technologies (BAT)
    - Site specific criteria
    - Cost benefit analysis
  - Full understanding of pollutant releases
  - Energy, water and waste minimalization audits and recommendations

The Voluntary Effort

- NIH Guidelines
- CDC/NIH Laboratory Biosafety Guidance
- Coordinated Framework Guidance
- The NSABB Proposed Framework
- The IASB Recommendations – An International View

The NIH 2009 Proposed Guidelines

- Published March 4, 2009: Comments Due May 4, 2009
- Reasons of the Recombinant DNA Guidelines to include “synthetic experiments involving more than half but less than two thirds of the genome of certain viruses in tissue culture”
- Specific coverage of nucleic acids molecules made solely by synthetic means (e.g. synthesized chemically or by other means without use of recombinant technology)

The Proposal

- Oversight of recombinant experiments involving introduction of drug resistant traits
- Change the level of review for defined (2/3 standard) synthetic experiments
- Organisms and viruses containing such molecules

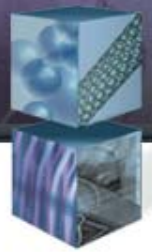
Exempt Experiments (Section IIIF)

- A balance between safety and overregulation
- Exemption where NA molecules are not expected to have
  - A biosafety risk
  - Or introduction into biological systems would be akin to processes that already occur in nature

Exempt Experiments (Section IIIF)

- IIIF1
  - Synthetic nucleic acids that cannot replicate unless they are used in human gene transfer (consistent with recombinant DNA research)
  - Exempts basic non-clinical research
- IIIF2
  - Replicating NAs that are not in cells
    - Not in a biological system that will permit replication
    - Have not been modified to enable improved penetration of cell membranes
- IIIF3
  - Exempt molecules must have exact NA sequence of an organism that currently exists in nature
- IIIF8
  - A mechanism to allow expansion of exemptions to molecules not covered elsewhere in IIIF

What Does It Take To have A Successful Voluntary Effort?



- An Identified Scope
- Defined Standards and Protocols
- Meaning Processes To Benchmark Against Standards
  - Accreditation or Certification
  - Oversight
  - Enforcement
- Government Acceptance
- Public Education

Where Do You Start?

- Commercial Gene Synthesis Companies?
- Laboratories?
- Environment Disposal Issues?
- A Convenor?

Questions?

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