Working Group on Synthetic Genomics: Progress Report

Dr. David Relman, Chair NSABB Meeting March 30, 2006

Background

The Working Group on Synthetic Genomics was launched on November 22, 2005 to:

examine the potential biosecurity concerns raised by the laboratorysynthesis of Select Agents, and thebroader field of synthetic biology; and

recommend possible strategies to address these concerns.

Current Task

Consider the adequacy of the current regulatory framework in view of the ability to synthesize Select Agent genes and genomes

Issue

- Reverse genetics allows generation of viable virus from their published sequence.
- Traditionally, viruses are “rescued” from recombinant or cloned DNA, which requiresaccess to natural sources of the agent itself.
- The use, possession, and transfer of Select Agents are tightly controlled, but theavailability of DNA synthesis technologypresents new concerns, with respect to thelaboratory synthesis of Select Agent genomes.

Approach

To address this issue, the Working Group received briefings (Feb 15, 2006) on

- the extant legal framework for controlling Select Agents;
- current technological capabilities for synthesizing nucleic acids; and
- the state of the science, in a few key application areas, for deriving infectious agents from synthetic nucleic acids.
- The Select Agent Rules implement the

provisions of the USA PATRIOT Act andPublic Health Security and BioterrorismPreparedness and Response Act of 2002.

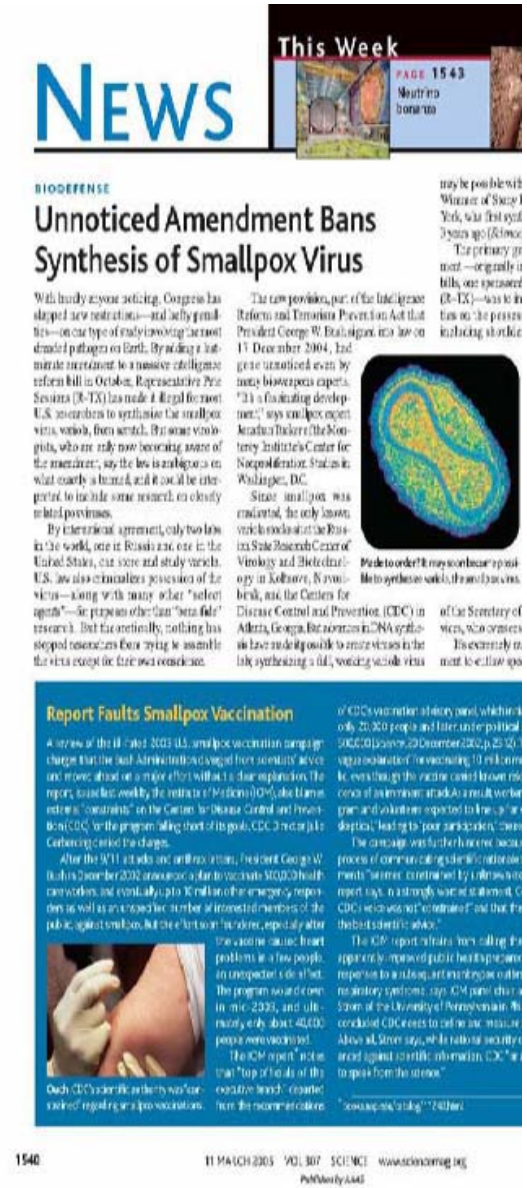
- • These regulations set requirements for possession, use, and transfer of SelectAgents and toxins. – define regulated agents by organism (name)and their genetic material
- • There are additional applicable laws and regulations.
  - • Makes it unlawful to knowingly produce,synthesize, or engineervariola virus
  - • Definition for variola virus includes “any derivative ofthe variola major virus thatcontains more than 85% of the gene sequence of

thevariola major virus or thevariola minor virus”

Summary of Findings

Legal Framework

18 U.S.C. 175c



NEWS

This Week

PAGE 1543
Neutrino bonanza

BIODEFENSE

Unnoticed Amendment Bans Synthesis of Smallpox Virus

With hardly anyone noticing, Congress has slapped new restrictions—and hefty penalties—on one type of study involving the most dreaded pathogens on Earth. By adding a last-minute amendment to a massive intelligence reform bill in October, Representative Pete Sessions (R-TX) has made it illegal for most U.S. researchers to synthesize the smallpox virus, variola, from scratch. But some virologists, who are only now becoming aware of the amendment, say the law is ambiguous on what exactly is banned, and it could be interpreted to include some research on closely related poxviruses.

By international agreement, only two labs in the world, one in Russia and one in the United States, can store and study variola. U.S. law also criminalizes possession of the virus—along with many other "select agents"—for purposes other than "bona fide" research. But theoretically, nothing has stopped researchers from trying to assemble the virus except for their own consciences.

The new provision, part of the Intelligence Reform and Terrorism Prevention Act that President George W. Bush signed into law on 17 December 2004, had gone unnoticed even by many biowarfare experts. "It's a frightening development," says smallpox expert Jonathan Tucker of the Monterey Institute's Center for Nonproliferation Studies in Washington, D.C.

Since smallpox was eradicated, the only known variola stocks exist at the Russian State Research Center of Virology and Biotechnology in Koltsovo, Novosibirsk, and the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. But advances in DNA synthesis have made it possible to create viruses in the lab by synthesizing a full, working variola virus

Made to order? It may soon become possible to synthesize variola, the smallpox virus.

Report Faults Smallpox Vaccination

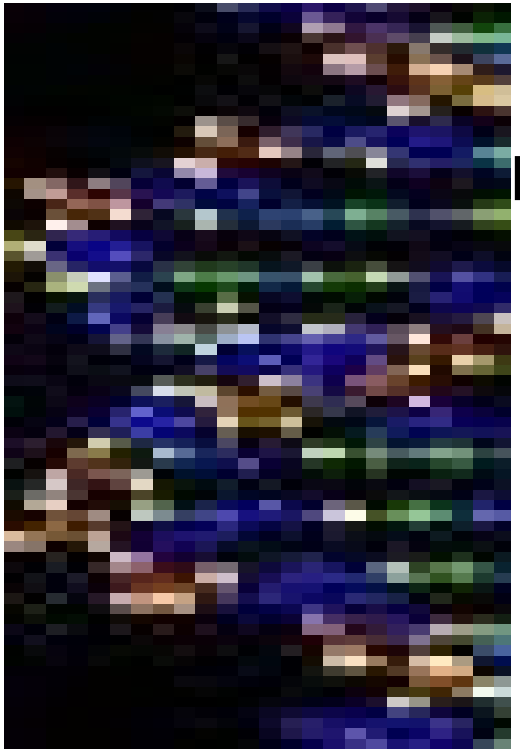
Ouch. CDC's scientific authority was harmed regarding smallpox vaccinations.

Key Controls for Select Agent Genetic Material

Possession, Use and Transfer within U.S.

Export Controls

Import into the U.S.



Export from the U.S.

Synthesis Technology

- Reagents and equipment for synthesizing DNA are readily available, around the globe.
- Synthesizing oligonucleotides up to 120 inlength is routine and common; beyond 180 issomewhat of an art.
- Some complete viral genomes can be synthesized at the present time, but not allDNA synthesis companies have thiscapability.

DNA Synthesis: Do It Yourself

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8 items found for **DNA synthesizer** — Add to Favorite Searches

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Compare	Item Title	PayPal	Bids	Price*	Shipping to USA (edit)	Time Left
	ALF Express II DNA Synthesizer Sequencer no reserve		-	$9.86	Calculate	6d 19h 58m

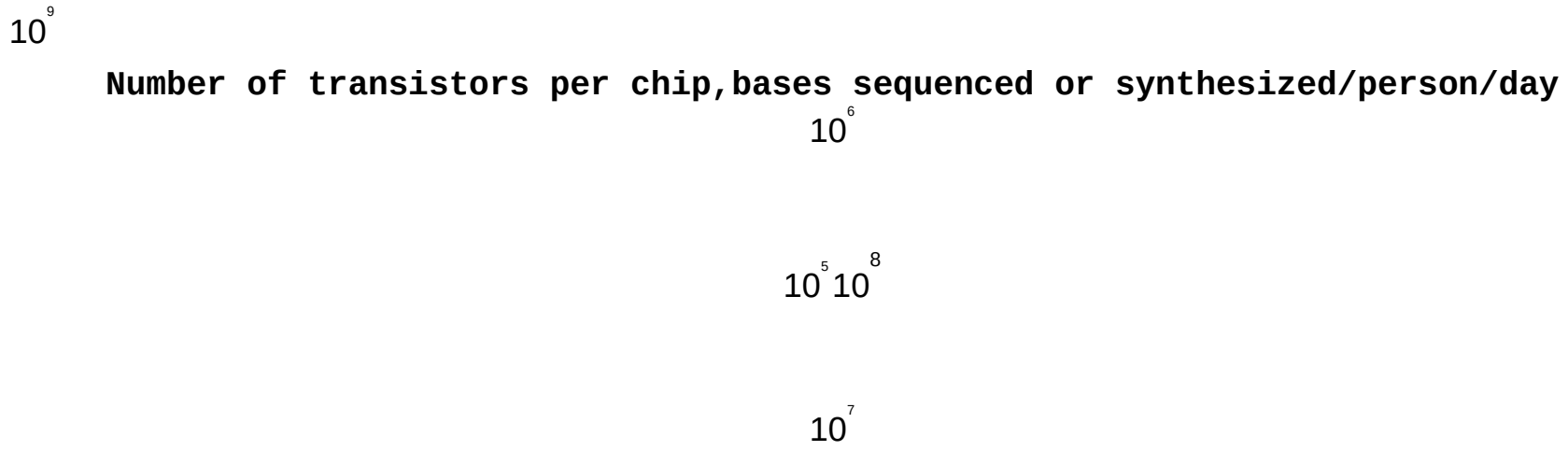
Additional Buy It Now items from eBay Store sellers

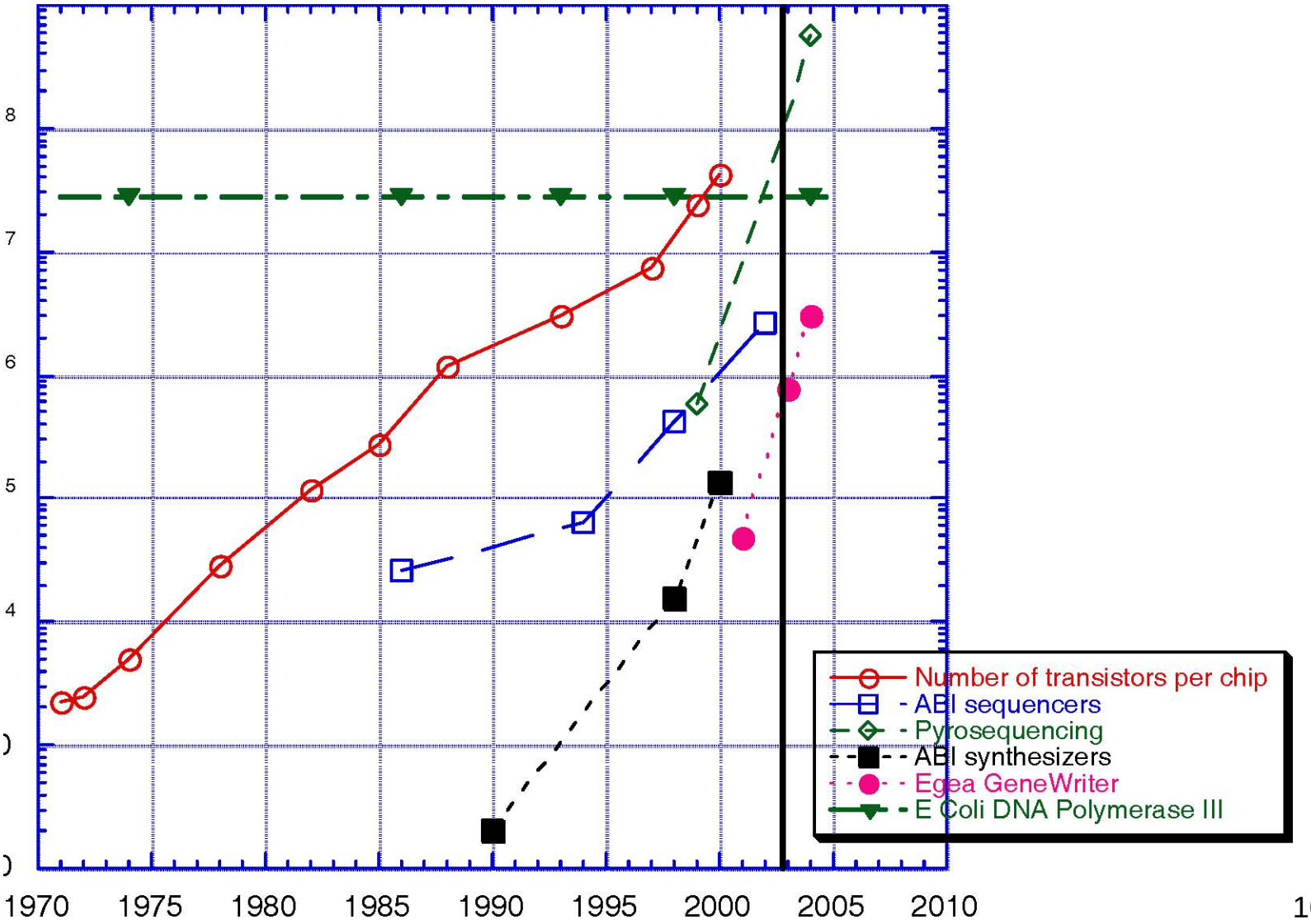
AUTOGEN 540 DNA PURIFICATION SYNTHESIZER ISS		Buy It Now	$450.00	Not specified	7d 03h 53m
MILLIGEN/BIOSEARCH CYCLONE 8400 DNA SYNTHESIZER		Buy It Now	$99.00	Not specified From Canada	10d 06h 13m
Dynatech Laboratory Inc. ML1000 DNA synthesizer		Buy It Now or Best Offer	$799.00	Not specified	11d 13h 05m
QIAGEN AUTOWORK BIO ROBOT 9604 DNA ANALYZER SYNTHESIZER		Buy It Now or Best Offer	$34,999.99	$249.95	15d 13h 32m
ABI Applied Biosystems 3948 DNA Synthesizer $5995		Buy It Now or Best Offer	$3,800.00	Not specified	16d 08h 50m
MilliGen / Biosearch 8700 DNA SYNTHESIZER, Lab Bio-Tech		Buy It Now or Best Offer	$495.00	Not specified	18d 15h 03m
DNA oligonucleotide synthesizer PCOS		Buy It Now or Best Offer	$1,999.00	Not specified	26d 09h 37m

Compare — To compare items side-by-side, select the check boxes and click the **Compare** button.

Search: 29 March 2006 11:20P

Comparing the pace of biological technologiesand Moore’s Law (Robert Carlson, 2003)





Biosecurity and Bioterrorism: Biodefense, Strategy, Practice and Science Vol. 1 No. 3, 2003

Commercial DNA Synthesis Foundries

Rob Carlson, University of Washington; Gerald Epstein and Anne Yu, CSIS

18 July 05. Method: Rough Google search. Thus not a thorough survey. No academic facilities.

Data Source: Rob Carlson, U of W, Seattle
www.synthesis.cc, rob@synthesis.cc

How 12 companies answered when asked if they screen orders for sequences that bioterrorists could turn into weapons

BaseClear, Leiden, The Netherlands	**Not Routinely**
Bio Basic, Markham, Canada	**No**
Bionexus, Oakland, California	**Not Routinely**
Bio S&T, Montreal, Canada	**No**
Blue Heron Biotechnology, Bothell, Washington State	**Yes**
DNA 2.0, Menlo Park, California	**Yes**
Entelechon, Regensburg, Germany	**Yes**
GeneArt, Regensburg, Germany	**Yes**
Genemed Synthesis, South San Francisco, California	**No**
GenScript, Piscataway, New Jersey	**Usually**
Integrated DNA Technologies, Coralville, Iowa	**Yes**
Picoscript, Houston, Texas	**Not Routinely**

- It is possible to recover/reconstruct infectious virus from DNA for certain Select Agents (and routine insome laboratories). – Successful use of such reverse genetic systems currently requires that one be “skilled in the art”.
- Vaccine researchers have created infectious

GENE SCREENS

Adapted from Aldhous, P. “The bioweapon is in the post” *The New Scientist* Issue 2525, 2005.

State of Science

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- It is possible to recover/reconstruct infectious virus from DNA for certain Select Agents (and routine insome laboratories). – Successful use of such reverse genetic systems currently requires that one be “skilled in the art”.
- Vaccine researchers have created infectious chimeric viruses using combinations of genomicmaterial from different Select Agents. – These novel organisms do not fit into traditional classification schemes

Preliminary Conclusions

Genetic/Genomic Material Synthesized *De Novo*

The Select Agent Rules (SAR) regulate:

- **genetic material** that encodes Select Agenttoxins, and
- Select Agent **genomic material** that is inherently infectious and capable of producinga Select Agent virus;

regardless of whether this material isobtained via *de novo* synthesis ortraditional methods.

42 CFR Sections 73.3, 73.4 Final Rule

(c) Genetic Elements, Recombinant Nucleic Acids, and Recombinant Organisms:

(1) Nucleic acids that can produce infectious forms of any of the select agent viruses listed in paragraph (b) of this section.

(2) Recombinant nucleic acids that encode for the functional form(s) of any of the toxins listed in paragraph (b) of this section if the nucleic acids:

(i) Can be expressed *in vivo* or *in vitro*, or

(ii) Are in a vector or recombinant host genome and can be expressed *in vivo* or *in vitro*.

(3) HHS select agents and toxins listed in paragraph (b) of this section that have been genetically modified.

Biosecurity Concerns

- The basic concern is that synthetic genomics may enable acquisition of a Select Agent (SA), outside of the SAR.
- • This concern emerges from issues pertaining to
  - scientific advances
  - industry practices
- Individuals versed in, and equipped for routine methods in molecular biology can use readilyavailable starting materials and procedures toexpress some SA

de novo.

- This kind of work may not have received adequate attention.
- Synthetic genomics allows the expression of agents that resemble and behave like SA, yetmight not be defined as SA based on genomesequence similarity, confounding traditionaldefinitions of agent identity.
- Screening of synthesis orders is not a standard practice among vendorsof synthetic genes/genomes.
- There is no widely-accepted, optimized methodology forscreening ordered sequences.

Biosecurity Concerns: Science

Biosecurity Concerns: Practices

42 CFR Sections 73.3, 73.4 Discussion of Changes (Federal Register 70:13298, 2005)

Commenters asserted that ''the government should require that service providers test for Select Agent sequences'' before they are made and transferred. The commenters argued that ''Although the Select Agent program covers transfer and possession of Select Agents, if DNA synthesis companies do not check the sequences they could inadvertently synthesize and transfer a Select Agent.'' We made no changes based on these comments. It is incumbent upon the entities that manufacture substances to know what they are manufacturing and to ensure that they comply with the provisions of the regulations in part 73 and 9 CFR part 121.

Adequacy of Regulations

Science and technology are rapidly evolving,such that there is a need to

- clarify the legal scope and interpretation of the SAR as they pertain to synthetic genomics;
- deliberate further on the adequacy of the current legal framework controlling selectagents; &
- explore a variety of strategies for addressing biosecurity concerns related to syntheticgenomics.

Next Steps

Points for Further Deliberation

The WG will consider the need for
• criteria that provide for identification of SA; • outreach and education to the scientific and business communities, including guidance on their responsibilities under the SAR;
• best practices for DNA synthesis providers; &

• other measures for addressing biosecurity concerns related to synthetic genomics.

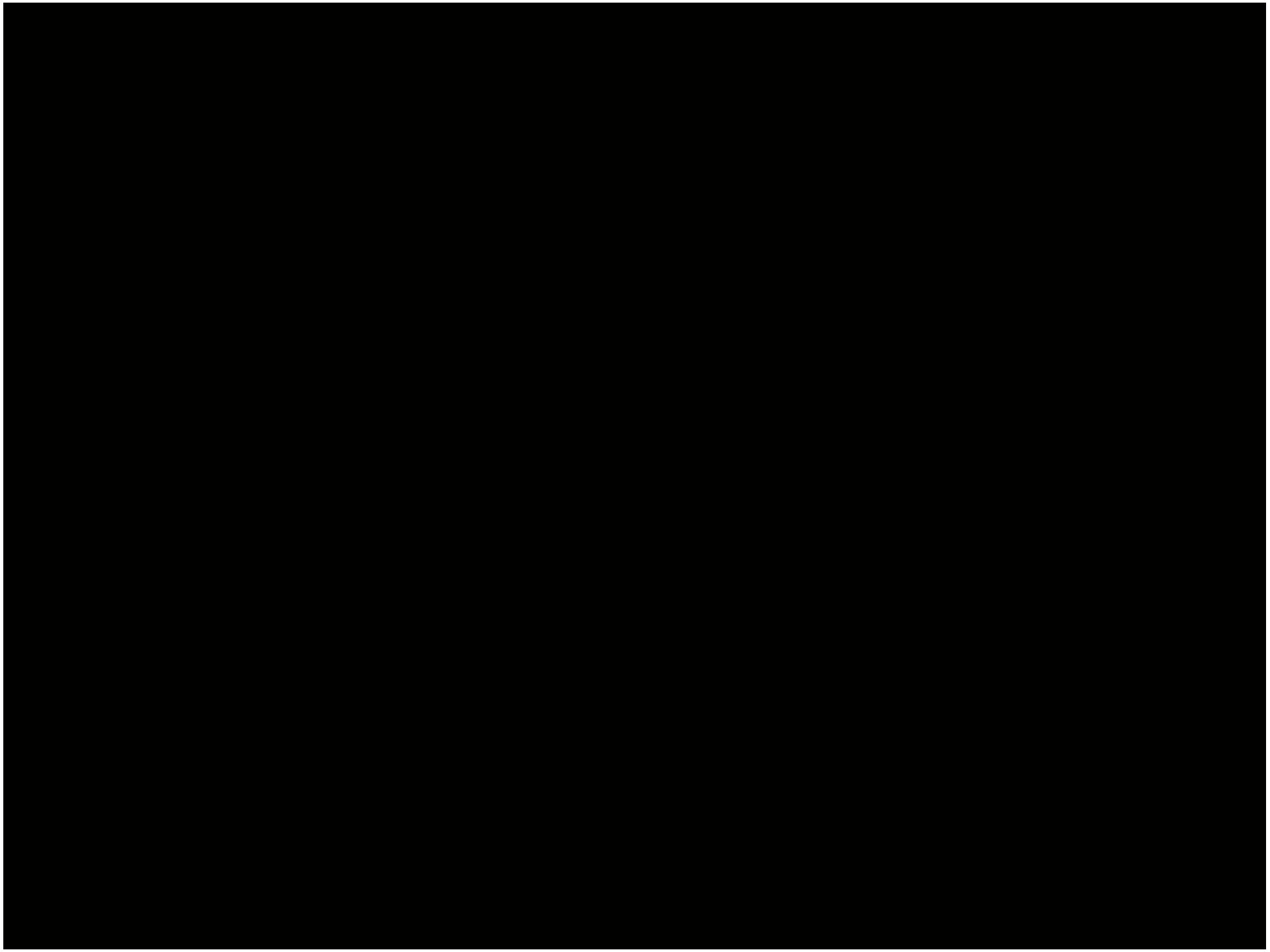
Action Items

- Collect additional information regarding the biosecurity concerns raised by thesynthesis of SA, by engaging
  - additional scientific experts; – other groups working on related issues; &
  - relevant international communities.
- Refine preliminary conclusions and develop recommendations to the Board.
- Given the international nature of this field, what are the most appropriate international

parties with whom the WG might engage?

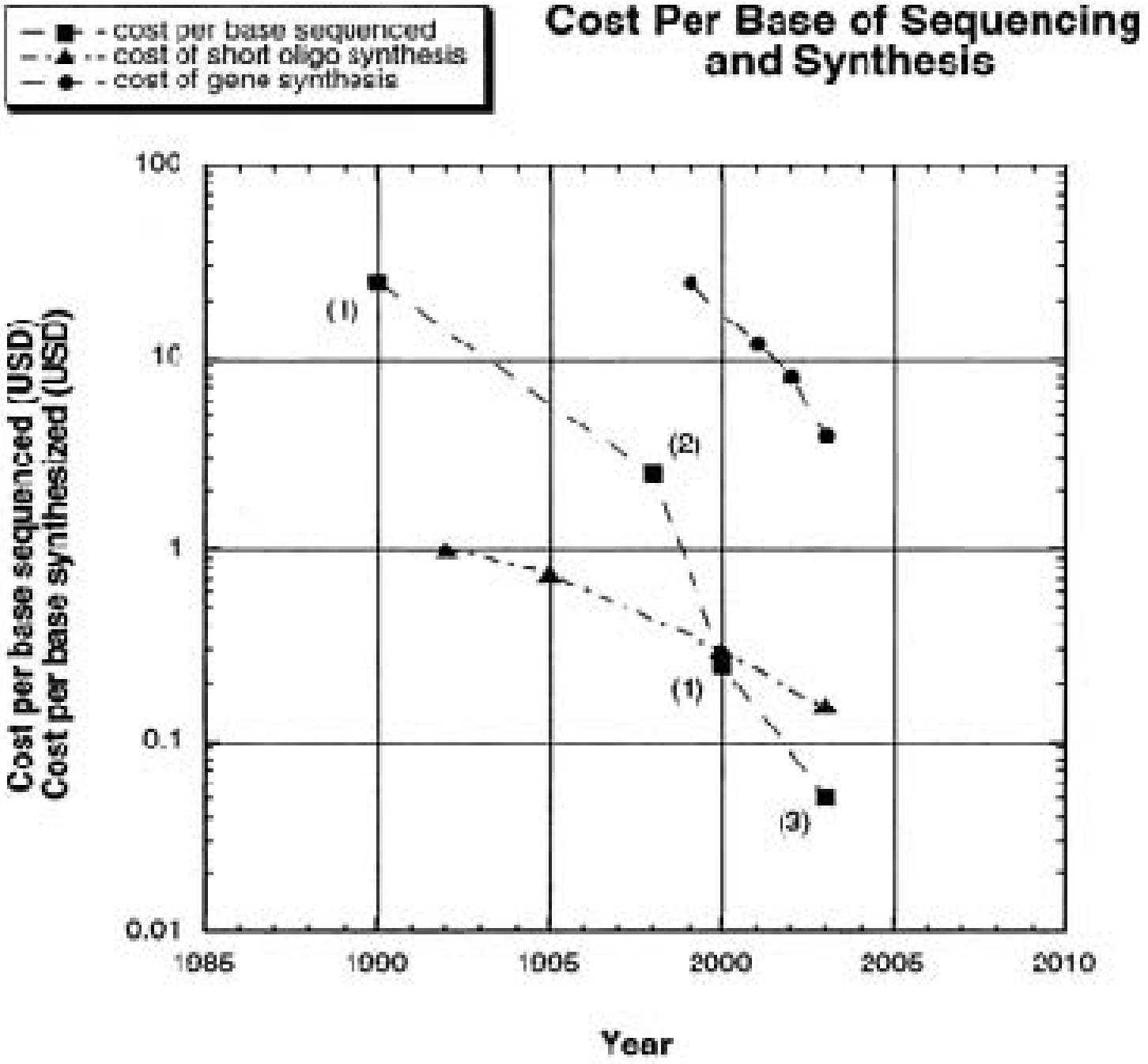
- How do the WG's findings impact the deliberation of other WGs, and vice versa?
- Are there other issues that the Board would like the Working Group to address?

Questions for Board / Points for Discussion



Optional Slides

Carlson, R. “Pace and Proliferation of Biological Technologies”, *Biosecurity and Bioterrorism* Vol. 1 No. 3, 2003


- cost per base sequenced
- cost of short oligo synthesis
- cost of gene synthesis
Cost Per Base of Sequencing and Synthesis
100
10
1
0.1
0.01
1985
1990
1995
2000
2005
2010
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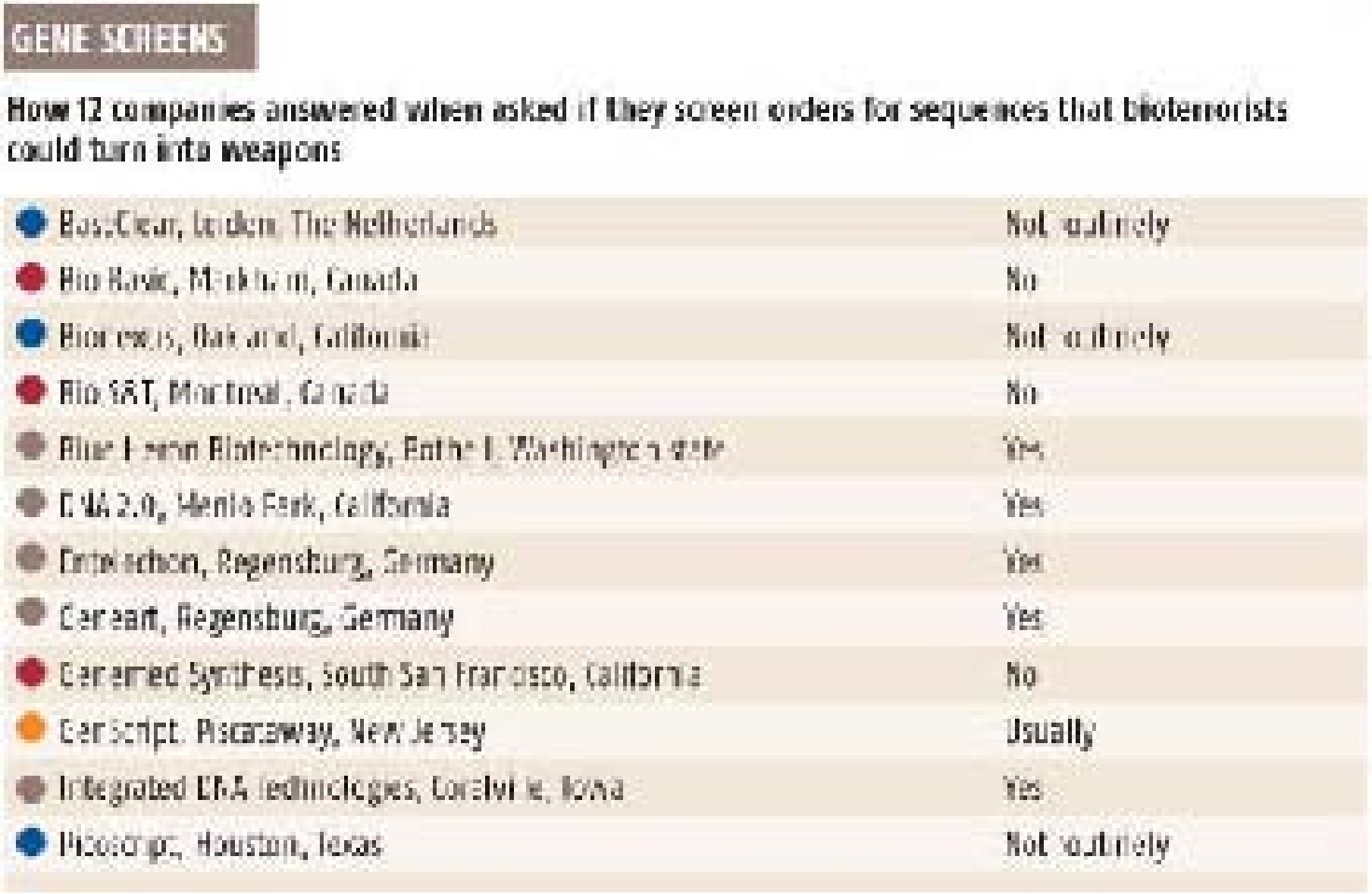
Cost per base sequenced (USD)
Cost per base synthesized (USD)
Year



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