BLUEHERON®

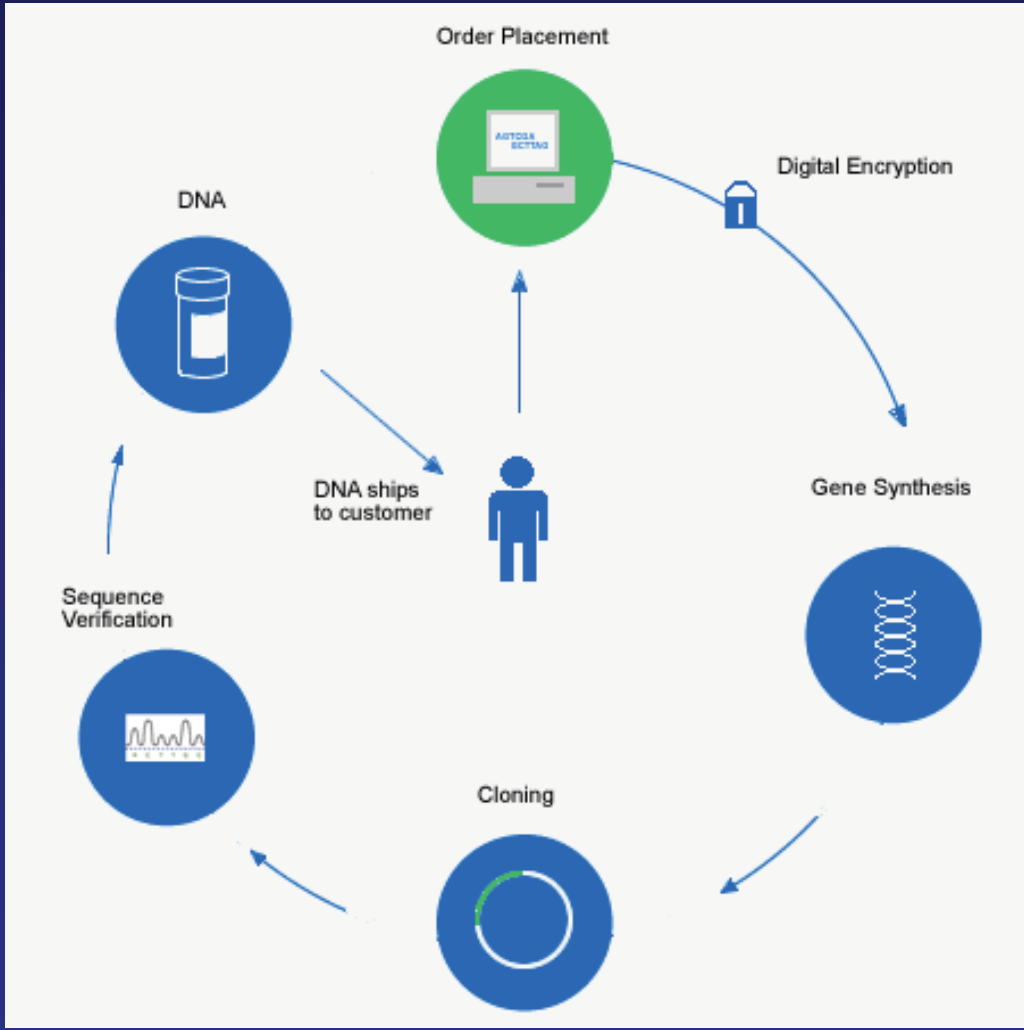
BIOTECHNOLOGY

NSABB July 1, 2005

Regulation of DNA Synthesis

- **DNA manipulations are at the heart of modern biology**
- **Current regulations need improvement**
  - Lack clarity and specificity
- **Good choices in regulation can enhance our ability to respond to new diseases**
  - Strengthen our ability to respond rapidly with R&D
  - Good regulations are more likely to be adopted internationally

What is Gene Synthesis?



GeneMaker®
Gene Synthesis

1. **Customer orders via secure website**
2. **Blue Heron manufactures and ships DNA molecule(s)**
3. **About 2 to 4 weeks later, customer receives <u>exactly</u> the DNA they want**
   - Customers use DNA molecules for research

Gene Synthesis Improves Research Productivity

- **Saves researchers time and money**
  - Cost continues to decline rapidly
- Complete control of sequence allows improved experimental design and new experimental approaches
- Gene synthesis can help to speed the response to new diseases

Why is Regulation of the Technology Important?

- **Molecular biology and genetics are integral to life science research**
  - Techniques are ubiquitous regardless of discipline
- **Billions of dollars are spent globally to obtain and modify DNA each year**
  - NIH direct costs are >$1B
- **Tools that improve the speed of R&D could be critical in the response to new diseases**
  - Serious new infectious diseases likely to arise from nature
  - Threat of “bio-terror”

Infectious Disease

- **Scientists need DNA from pathogens to study the basic biology of the pathogen and to develop new therapeutics**
- **Some pathogens can be synthesized**
  - Most viral genomes can be made with today's gene synthesis technology
  - One or more bacterial genomes are likely to be synthesized within the next year
- **Nefarious uses of synthesis are possible**
  - However, direct isolation is less expensive and less technologically complex than gene synthesis

Current Select Agent Regulations

- Government approval required to possess or **distribute certain pathogens and pathogen genes**
  - "Select Agents"
- **Compliance with select agent regulations**
  - Blue Heron screens all orders against a database of genes from select agents
  - We review every sequence that resembles a select agent genes
  - We do a detailed analysis of the genes from select agents to determine if they are covered

Current Regulations Require Interpretation

- **Many genes from select agents are not dangerous and are not controlled**
- **Many genes from select agents resemble harmless genes**
- **Many scientists use non-functional parts of genes from select agents in their research**
  - Viral coat proteins for vaccine development
  - Enzymes for testing anti-microbial and anti-viral drugs
  - DNA fragments or proteins for development of diagnostics

Recent Examples

- **100% identity with a part of a toxin protein**
  - Matches ~ 30% of the toxin protein
  - Literature scan revealed that this is a domain that is a well-known target for vaccine development
  - The domain alone is not functional
- **85% identical to a pathogen gene**
  - Common metabolic pathway
  - 95% identical to a non-pathogenic sequence
- **90% identical to sequences from a virus**
  - Regulatory sequence
  - Commonly used in many expression vectors
- **Each example required input from a PhD biologist to decide if we should provide the gene**

Regulatory Clarity is Needed

- **Goals**
  - Restrain/monitor access to dangerous DNA fragments
  - Retain ability to carry out rapid biomedical and other life science R&D
- **However, no national regulatory scheme can completely block the arrival of new pathogens**
- **Moreover, poorly-conceived regulation could impede our ability to respond to the emergence of new pathogens**

Our Perspective on Regulations

- **Regulations should define the DNA sequences that are covered**
  - Current select agent rules require interpretation
- **Regulations should define the action to be taken when targeted sequences are requested**
  - What needs to be reported? To whom? What is the involvement of our customer in the process?

Solution: Select DNA Sequence Database

- **A list of Select DNA Sequences**
  - DNA sequences that could be used to build pathogens or to enhance pathogenicity
- **Select sequences defined in terms of a reference sequence and a percentage identity to the reference sequence**
- **Active maintenance by an oversight panel and a set of organism-specific experts**
  - Updated on a regular basis (e.g., monthly)

Select Sequences

- **Three classes of sequences**
  - Specific genes from select agents — Require a permit
  - Related Genes — Require reporting
  - All other genes — No reporting required
- **Control of high-threat sequences**
- **Tracking of sequences that could be incorporated into new pathogens**
  - Fragments of genes from select agents
  - Other pathogenic genes
  - Other sequences?
- **No reporting requirement for most sequences**

Operational Considerations

- **Positive requirement to check orders against the Select Sequence database**
  - Current rules make it illegal to provide certain sequences but do not require providers to check for those sequences
- **Clear procedures for identifying organizations and individuals which are authorized to possess molecules encoding Select Sequences**
- **Centralized database to collate information on reportable sequences**
  - It is currently possible to buy the parts of a virus from several different providers and without violating any regulations until the parts are assembled

Gene Synthesis is an International Industry

- **Researchers are located all over the world**
- **Gene synthesis companies exist all over the world**
  - Dozen or more in US
  - Similar number in Europe
  - Several in Asia
- **Ad hoc (non-commercial) gene synthesis occurs regularly in labs all over the world**
- **US regulations cannot block nefarious access to this technology**
  - US regulations can impact the efficiency of our response to pathogens

Regulations Can Impact Technology

- **Pharmaceutical researchers will not outsource gene synthesis if regulations require disclosure of all sequence orders**
  - Sequence data is confidential
- **Such regulation would drive demand for gene synthesis instruments**
  - “Gene synthesis in a box”
- **The development and dispersion of gene synthesis instruments would make the technology harder to control**

Rapid, Effective R&D is the Solution

- **Our response to new pathogens depends on decades of basic research AND the immediate application of today's best technology**
  - Gene synthesis could play an important role in rapid responses to new diseases
- **Regulations that significantly restrict access to the best technology will be counter-productive**
  - Such regulations will increase the risk from pathogens by limiting legitimate researchers and reducing our ability to respond effectively
  - Moreover, they will not significantly restrict nefarious access to the technology

Regulatory and Policy Choices

- Scientists working for the good of society have an extremely large advantage in resources
- Balanced regulations that discourage nefarious projects without chilling the R&D enterprise will preserve this advantage
- We have the opportunity to make regulatory and policy decisions that will improve lives by reducing the danger of infectious disease

Summary

- **Gene synthesis and molecular biology are central to modern biological research**
- **The technology is ubiquitous and international, thus control from within the USA is not possible**
- **Current regulations need improvement**
  - Clear definition of Select Sequences
  - Tracking of related sequences
- **Poor regulatory choices today could significantly reduce our ability to respond to new pandemics, whether natural or man-made**
  - Good choices are more likely to have a global impact