FDA Oversight of Synthetic Biology

Frank F. Weichold, M.D., Ph.D.
Office of the Chief Scientist/Commissioner

Carolyn Wilson, Ph.D.
CBER

Jason Dietz, Ph.D.
CFSAN

Larisa Rudenko, Ph.D., DABT
CVM

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Disclaimer

This presentation reflects the views of the authors and should not be construed to represent FDA's views or policies.

Overview

- Describe how FDA regulates various products
  - Administrative units
  - Legal authorities
  - Regulatory triggers: Product vs Process

- Brief description of regulatory processes for different products
  - Implications of FDA's regulatory approaches for the products of synthetic biology
- Challenges, anticipations

What does FDA do?

- Mission: Protect *and promote* public health
- Protect:
  - Assure safety, effectiveness and security of human and veterinary drugs, vaccines, other biological products, medical devices, food, cosmetics, radiation-emitting devices
- Promote:
  - Help speed innovations that make needed products available, and where possible, more effective, safer and affordable
  - Provide accurate, science based information to maximize product benefits and reduce risks
  - Enhance preparedness by facilitating the development and availability of Public Health Emergency Medical Countermeasures
- Regulate tobacco products

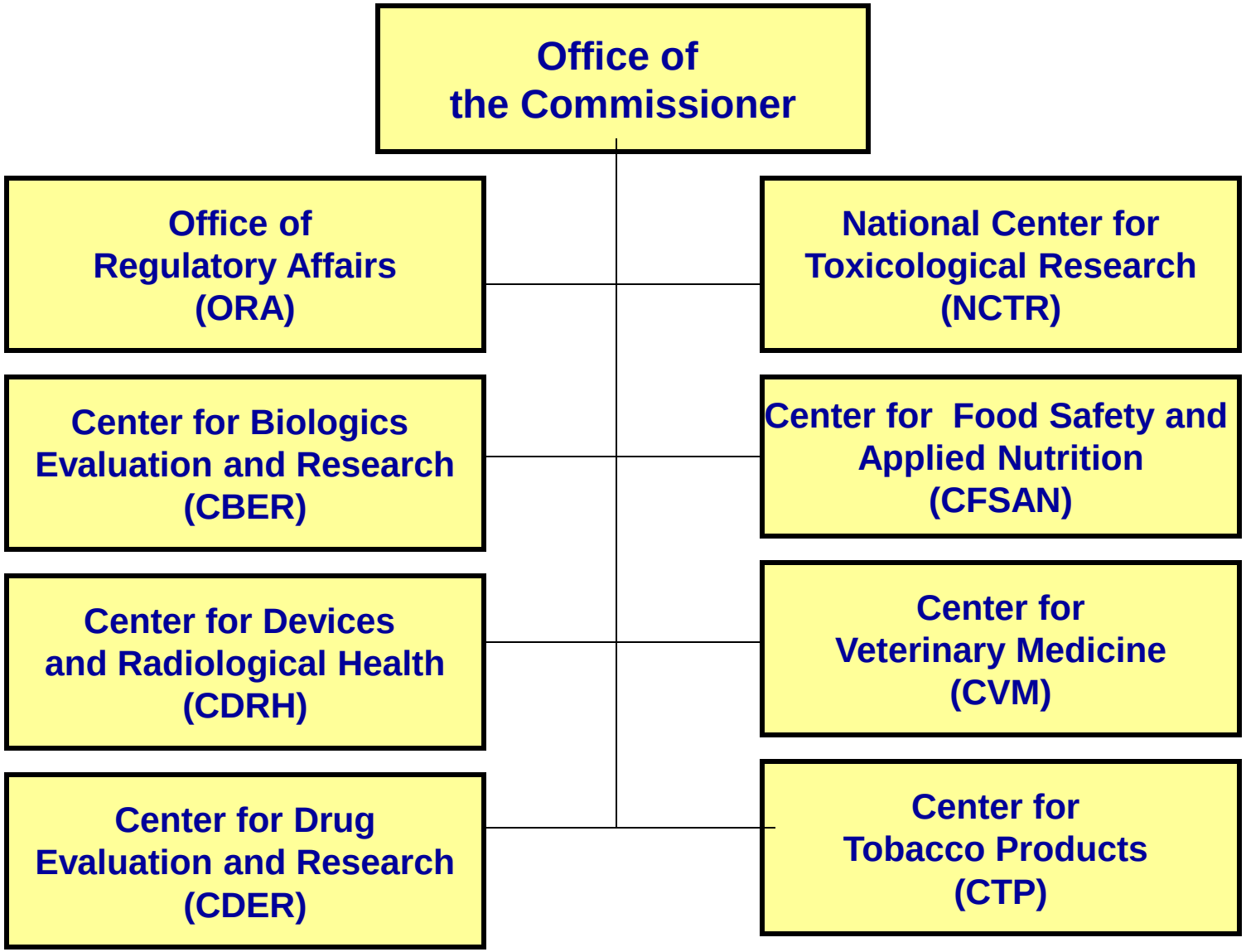
What does FDA *not* do?

- Regulate medical/veterinary practice, services, or pricing

What does FDA *not* regulate?

- Alcohol, consumer products (unless radiation emitting), illicit drugs, health insurance, meat and poultry (except drug residues), pesticides, restaurants, grocery stores, water, advertising (excluding for drugs and medical devices), reproduction/breeding

FDA administrative structure



FDA Review Centers

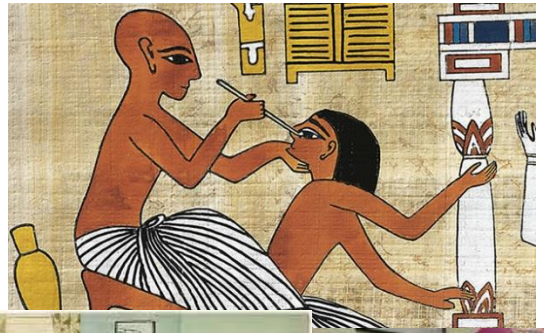
- Product review and product quality, safety and manufacturing monitoring are carried out by scientists in product Centers

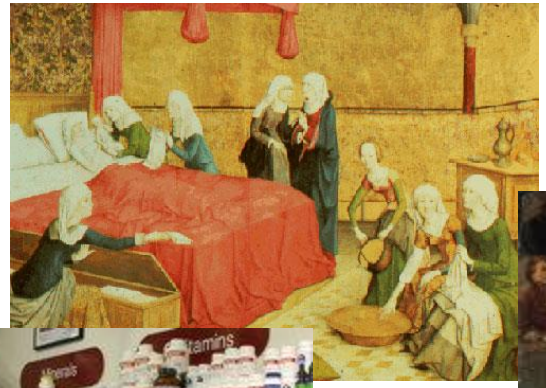
- Center for Biologics Evaluation and Research (CBER):
  - Vaccines, blood and related products, cellular, tissue and gene therapies, living organisms intended as therapeutics
- Center for Devices and Radiologic Health (CDRH)
  - Medical devices and diagnostics, and products that give off radiation, dental devices
- Center for Drug Evaluation and Research (CDER)
  - Human drugs (prescription, over-the-counter, generic, biosimilar), not dietary supplements (unless they make disease treatment claims)

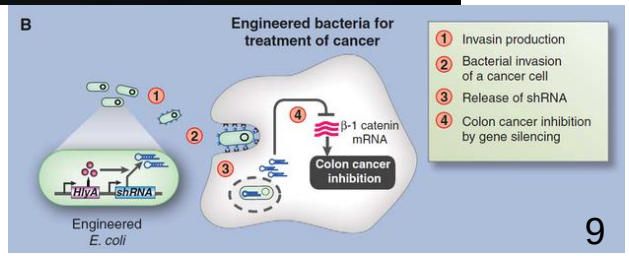
FDA Review Centers: continued

- Center for Food Safety and Applied Nutrition (CFSAN)
  - Foods, except meat and poultry products, which are regulated by USDA; food additives, labeling
  - Dietary supplements; infant formula; cosmetics
  - Regulation is primarily focused on safety
  - New laws, FSMA, provide authority for preventative and risk based controls on food production and action to limit outbreaks
- Center for Veterinary Medicine (CVM)
  - Veterinary drugs (not biologics); animal feeds, GE animals
- Center for Tobacco Products (CTP)

Human Medical Products







FDA's Legal Authorities

- Statutory Authorities (law), for example,
  - Food, Drug and Cosmetic Act
  - Public Health Service Act
  - FDAAA, FDASIA, -UFAs, etc.
  - National Environmental Policy Act
- Regulations (outline), for example, Code of Federal Regulation, Title 21
  - GMPs, section 211
  - INDs, section 312
  - Biologics, sections 600, 610, etc
- Guidance Documents (best practice, iterative)

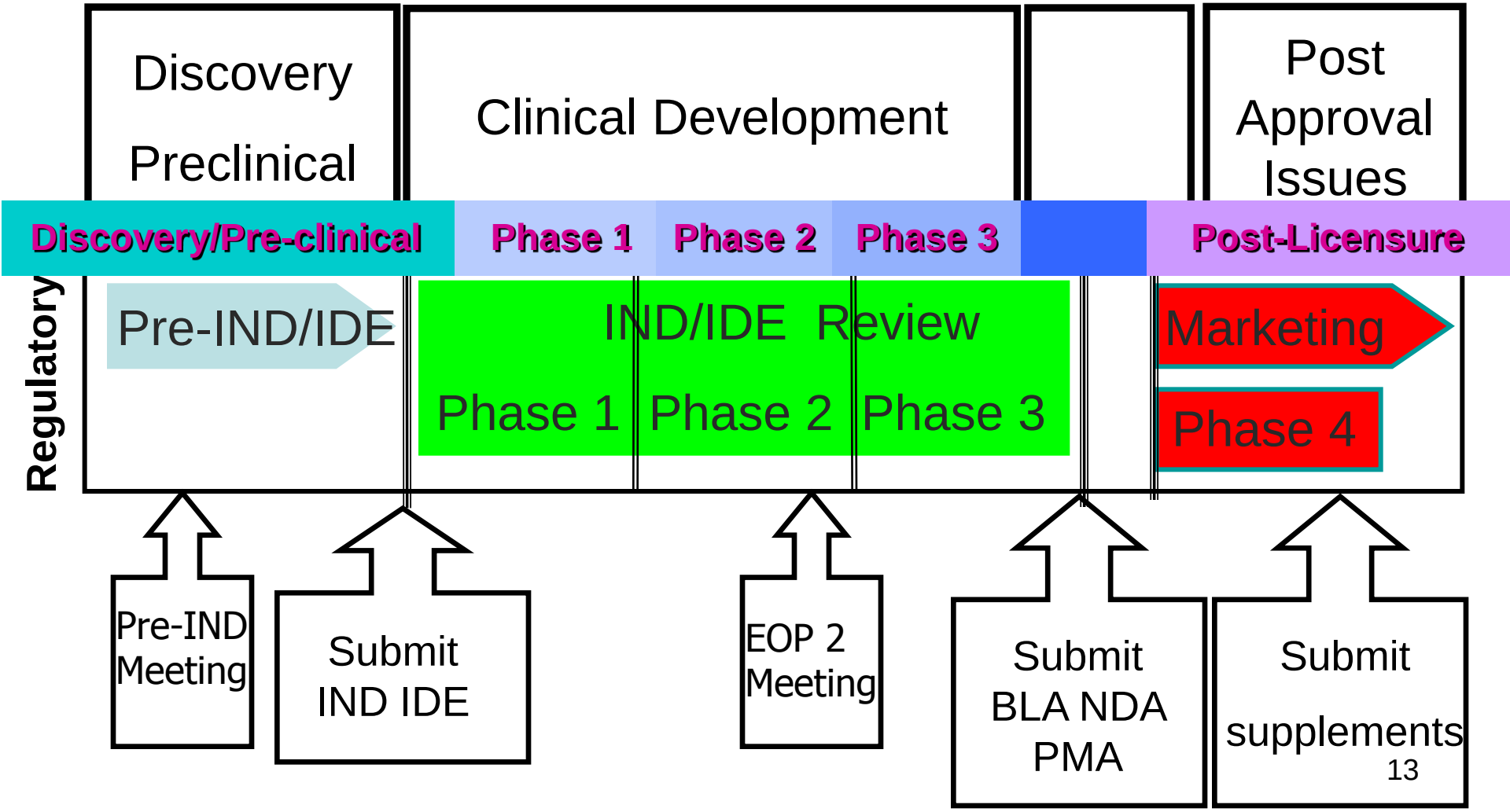
Statutory and Regulatory Authorities

* Prescription Drug User Fee Act

Medical Product Related Activities

- New product review and pre-market approval
  - Proactive interactions during review process
  - Written reviews (pre-clinical, clinical, manufacturing data, facilities) and decisions
- Monitoring
  - Manufacturing quality and safety
  - Safe handling
  - Adverse events/new risks/populations
- Communication to patients and providers
- Enforcement/Compliance
- Research targeted to safety, efficacy, quality

Medical Product Lifecycle Overview



What occurs Pre-approval?

- FDA reviews application and data to determine if product benefits outweigh risks
  - Evaluates whether studies (and data) submitted are adequate and well controlled and show that the product is safe and effective for proposed use (indication) and populations
  - Determines whether FDA agrees with sponsor's conclusions and/or whether additional information is needed
  - For generics (ANDA) data required focused on drug quality and bioequivalence vs. clinical efficacy studies needed for NDA
  - For some devices, use of the 510k pathway may allow approval based on substantial similarity to previously cleared device, clinical data may not be required
  - For novel products, an advisory committee is typically convened to consider data, including presentations by both FDA and the sponsor, and vote on questions including efficacy and safety for intended use – FDA is not bound by AC recommendations

Approaches to Speed Product Review, Access and Approval to Meet Unmet Medical Needs for Serious Conditions

- Fast Track designation (allows rolling submissions)
- Priority Review (6 vs. 10 month cycle)
- Accelerated approval – can use likely surrogate endpoints followed by confirmatory study
- Breakthrough designation: if promising initial data
- Availability under special access programs
  - eIND, treatment IND, HDE
  - For emergency medical countermeasures during public health emergency, EUA (now pre-EUA possible)

Standards of Licensure

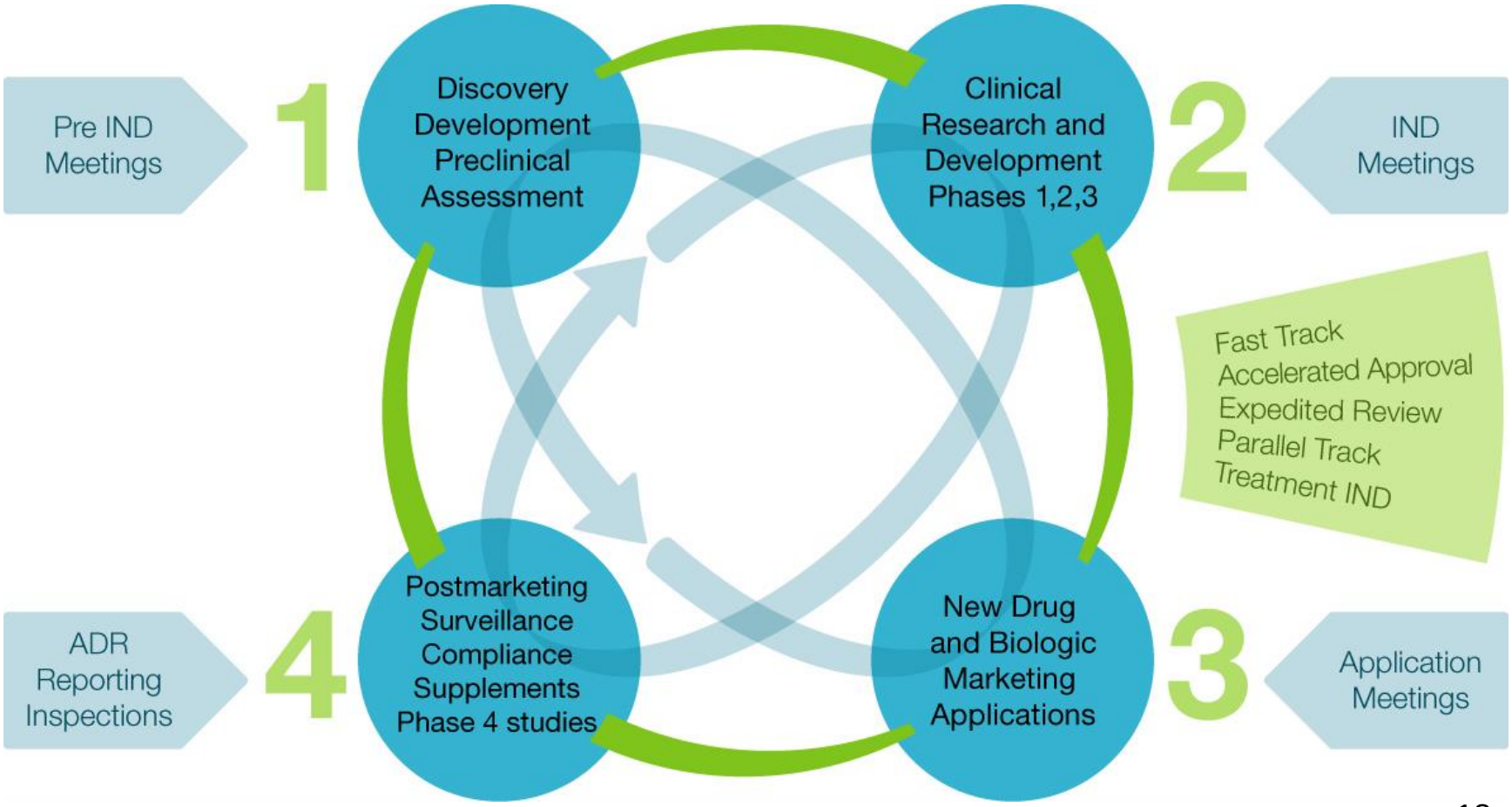
Drugs and Biologics

- Safety
- Purity
- Potency
- Stability
- cGMP Compliance

What Occurs Post Approval?

- Rare adverse events (AEs), uncommon or unpredicted drug interactions and/or efficacy issues in special populations, may not be apparent pre-approval based on 100's-1000's of RCT subjects
- Post-marketing studies (Phase IV) may be required and/or performed to address special populations, safety concerns/signals
- Review of AEs "passively" reported to FDA (e.g. through MedWatch, VAERS). Caveats: underreporting, complexity of determining etiology in clinical setting, lack of ideal control data/denominators
- Increased use of active monitoring for specific AEs (e.g. health care based or CMS based data, PRISM, Sentinel).
- Findings of concern made public and may be brought to Advisory Committees and/or result in labeling change, warning or withdrawal
- Manufacturing quality oversight and inspections also continue
- Shortage monitoring and remediation activities, counterfeit detection
- Monitoring of promotional activities

Drug and Biologic Product Life Cycle



Food

Includes

- Food for humans
- Food for animals (animal feed)
- Cosmetics

Food

"Articles used for food or drink for man or other animals, chewing gum, and articles used for components of any such article." (FD&C Act)

- Including
  - Food additives
  - GRAS substances (generally recognized as safe)
  - Color additives
  - Food contact substances (e.g., food packaging)
  - Dietary supplements

Food

The pre-market regulatory pathway for a substance added to food depends upon its intended use(s).

Food – for human consumption →**most food is excluded from pre-market review – inspection HCCP**

Pre-market regulatory pathways

- Food or color additive petition (21 CFR 171, 571; 21 CFR 71)
- Generally Recognized As Safe (GRAS) determination (21 CFR 170.30, 570.30)
- Food contact substance notification (food packaging; 21 CFR 170.100)
- Voluntary consultation for food from a new plant variety (e.g., GE plants)
- New dietary ingredient notification for dietary supplements (21 CFR 190)

Cosmetics

- FD&C Act does NOT provide for FDA pre-market approval of cosmetics, except color additives added to cosmetics.
  - Use of a color additive can be authorized through a color additive petition (21 CFR 71).
  - Firms can voluntarily file with FDA their cosmetic product ingredient composition statements (21 CFR 720).

Animal and Veterinary

CVM: New Animal Drugs

Premarket approval→ Safety and Effectiveness ←Post-approval

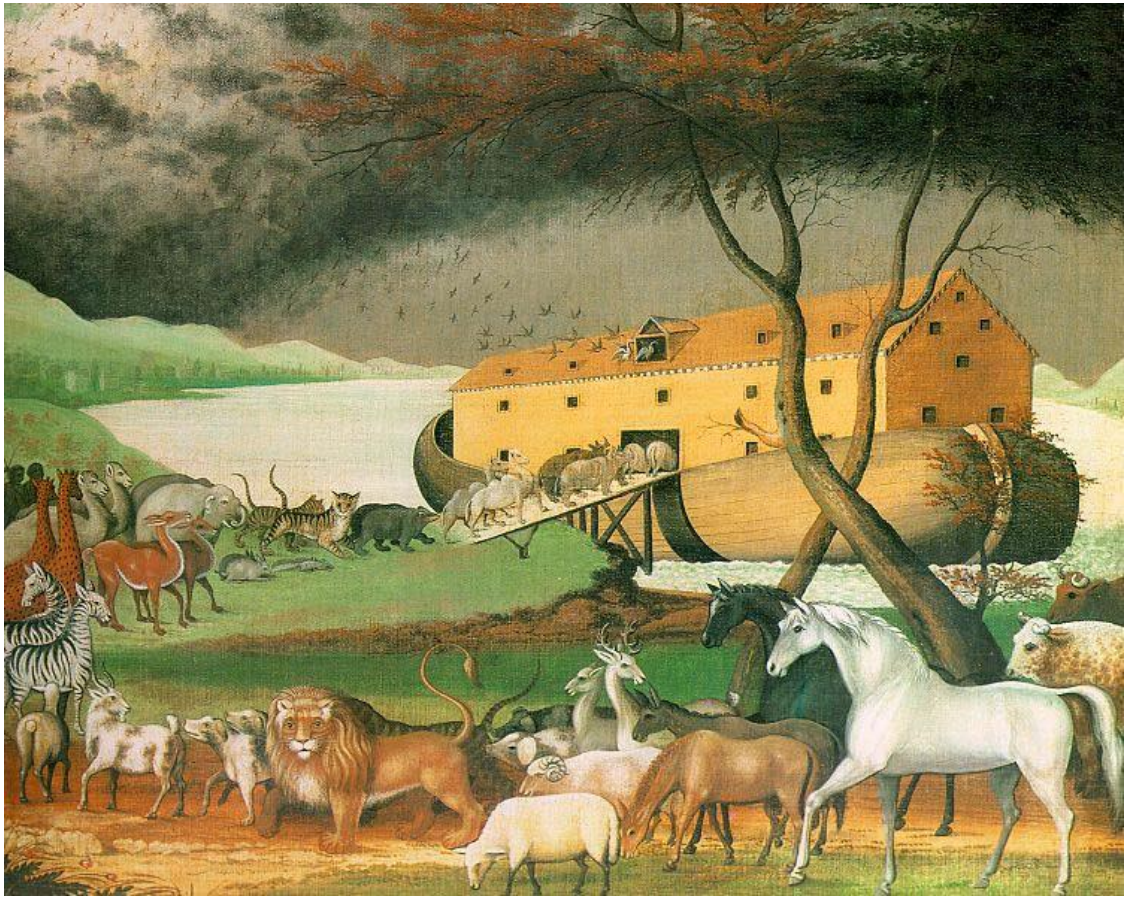
- Companion animals (e.g., dogs, cats, horses)
- Food animals (e.g., cattle, swine, poultry, fish)
  - Safety of food from treated animals (e.g., meat, milk, eggs)
  - Genetically engineered animals (more later)
  - Aquaculture
- **Minor uses, minor species approvals/oversight**
- Similar to human Orphan Drugs
  - Infrequent and limited uses in major species*
  - Use in minor species
    (e.g., fish, sheep, goats, hamsters, parrots)
- **Generic Animal Drugs**

* Major species= horses, cattle, pigs, dogs, cats, chickens, and turkeys.

CVM

- **Animal feed** (including pet food and pet treats)
  - Safe
  - Produced under sanitary conditions
  - Properly labeled
  - Premarket approval of food additives used in food for animals
- **Veterinary devices:** post-market oversight only
- **Veterinary vaccines:** CVM does **NOT** regulate
  - USDA Animal and Plant Health Inspection Service's Center for Veterinary Biologics
- Conducts **regulatory research** relevant to animal drugs and health

Regulation of GE Animals

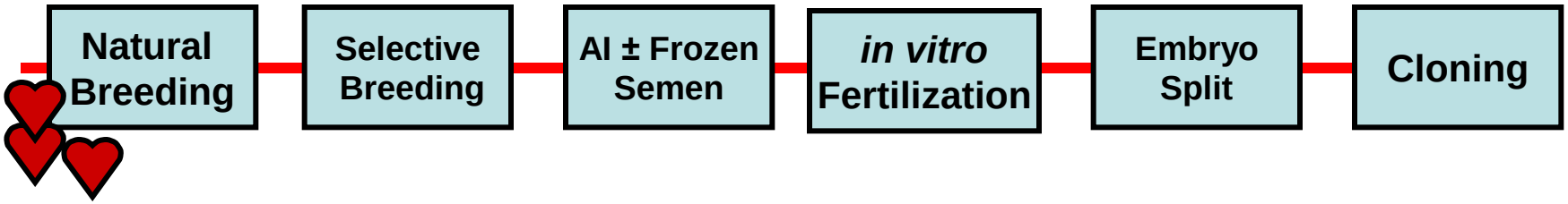


What is Animal Biotechnology?

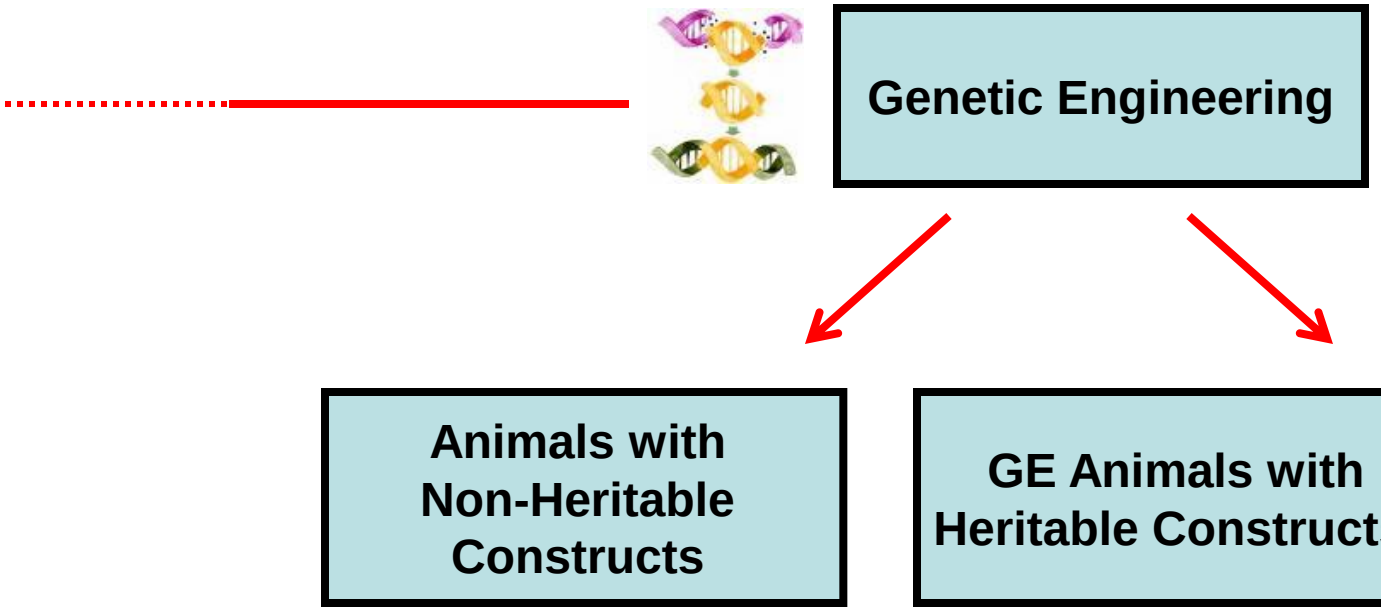
- Assisted Reproductive Technologies
  - Help distribute genetics beyond natural matings
  - AI, semen sexing, *in vitro* fertilization, embryo transfer, embryo splitting
  - 1300s-present
- Cloning
  - More rapid distribution of naturally occurring desirable traits in breeding stock
  - 1990s-present in livestock
- Genetic Engineering/Synthetic Biology
  - Introduces/modifies genes/pathways to introduce new traits
  - GE 1980s-present in livestock
  - Genome Editing (precision introduction/deletion of DNA to/from genomes)
- Next?

Animal Biotechnology

Animal cloning is on a continuum with other ARTS



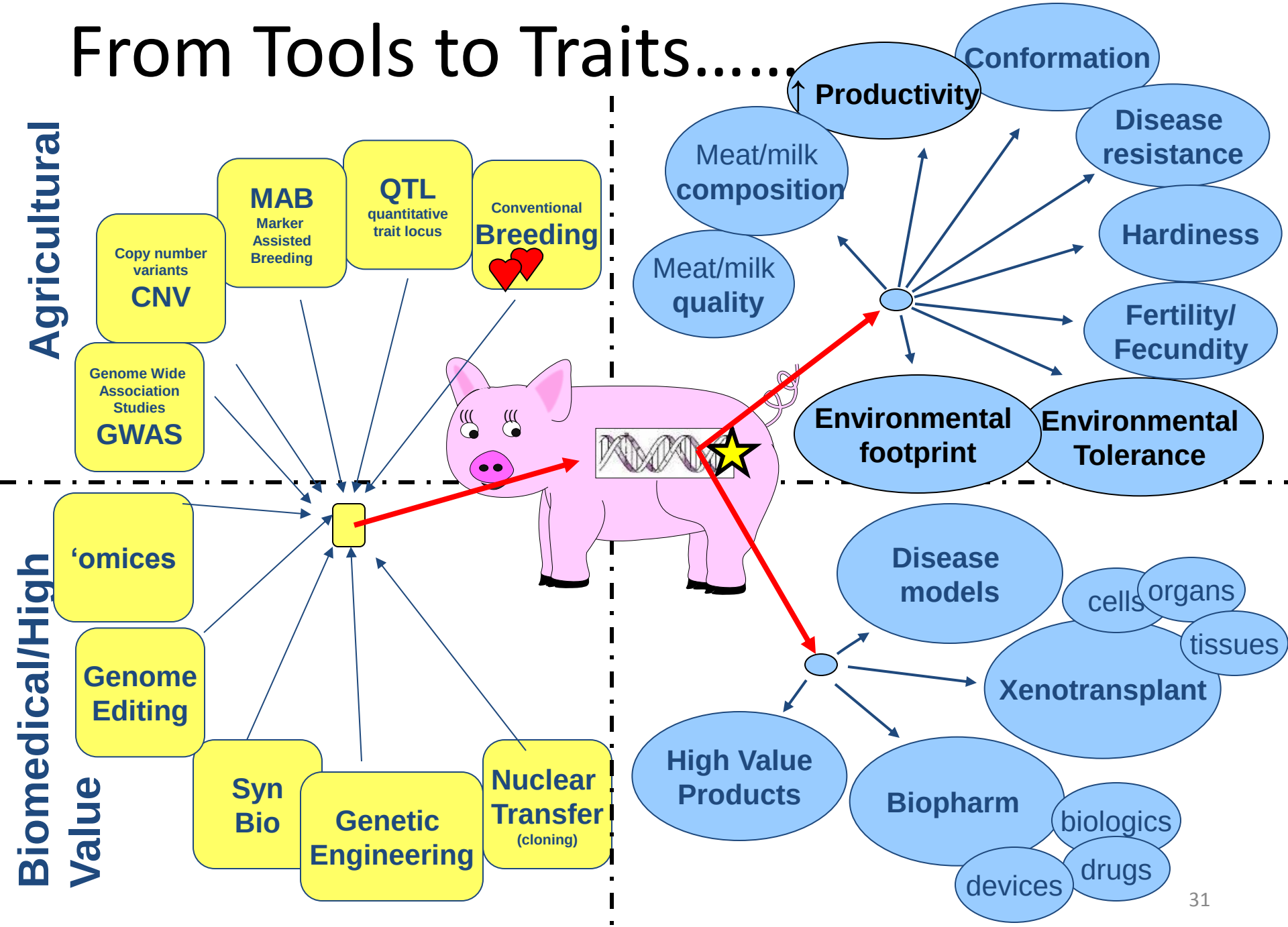
Genetic engineering is a distinctly different technology



GE Animals Being Developed

- **Agricultural Use**
  - Improved production traits
  - Disease resistance
- **Biomedical Uses**
  - Xenotransplantation
  - Production of therapeutic agents
  - Models of Human Disease
- **High Value Products**
- **Companion Animals**
- **Environmental Uses**
  - **Biocontrol of invasive species**

From Tools to Traits……



Most Relevant Drug Definitions (FD&C Act) for CVM

- **"Articles intended to use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals"**
  - Some similar to human drugs (e.g., antibiotics, chemotherapeutics, anti-inflammatories, anesthetics, anti-histamines, cardiovascular drugs)
  - Some quite different (e.g., heartworm preventatives, flea and tick preventatives)
- **"Articles (other than food) intended to affect the structure or any function of the body of man or other animals"**

  e.g., contraceptives, estrus synchronizing agents, drugs that improve efficiency of weight gain, fat/lean ratio, genetically engineered animals

Regulation of GE Animals

- DNA construct meets drug definition "*article…intended to alter the structure or function of the body of man or animal*" CVM GFI 187*
  - Includes all types of GE animals
  - All GE animals in a lineage covered
  - Case-by-case evaluation
  - Mandatory approval prior to marketing
  - Post-market surveillance

*http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/default.htm

GE Goat Producing ATryn: Biopharm Animals (approval 2009)

- Two regulated articles:
- → two approvals

- Article 1: CVM NADA approval

  rDNA construct in GE goat to produce *rh* antithrombin in milk

- Article 2: Center for Biologics Evaluation and Research Biologics License Approval for ATryn

  Anticlotting agent for individuals with hereditary clotting disorders in high risk situations

National Environmental Policy Act (NEPA)

NEPA Triggers

- Proposed “major Federal actions significantly affecting the quality of the human environment” (42 USC § 4332 (2)(C)
- Applies to any Federal action
- FDA has its own implementing regulations (21 CFR Part 25)
- For FDA, in general, “major agency actions” include
  - Approvals (new drug (human or animal), biologic, device, diagnostic, food additive)
  - NOT voluntary consultations or GRAS notifications
- Categorical Exclusions may apply
  - Often routinely at investigational phase
  - Under low risk conditions
  - IFF no “extraordinary circumstances” exist (does synbio?)

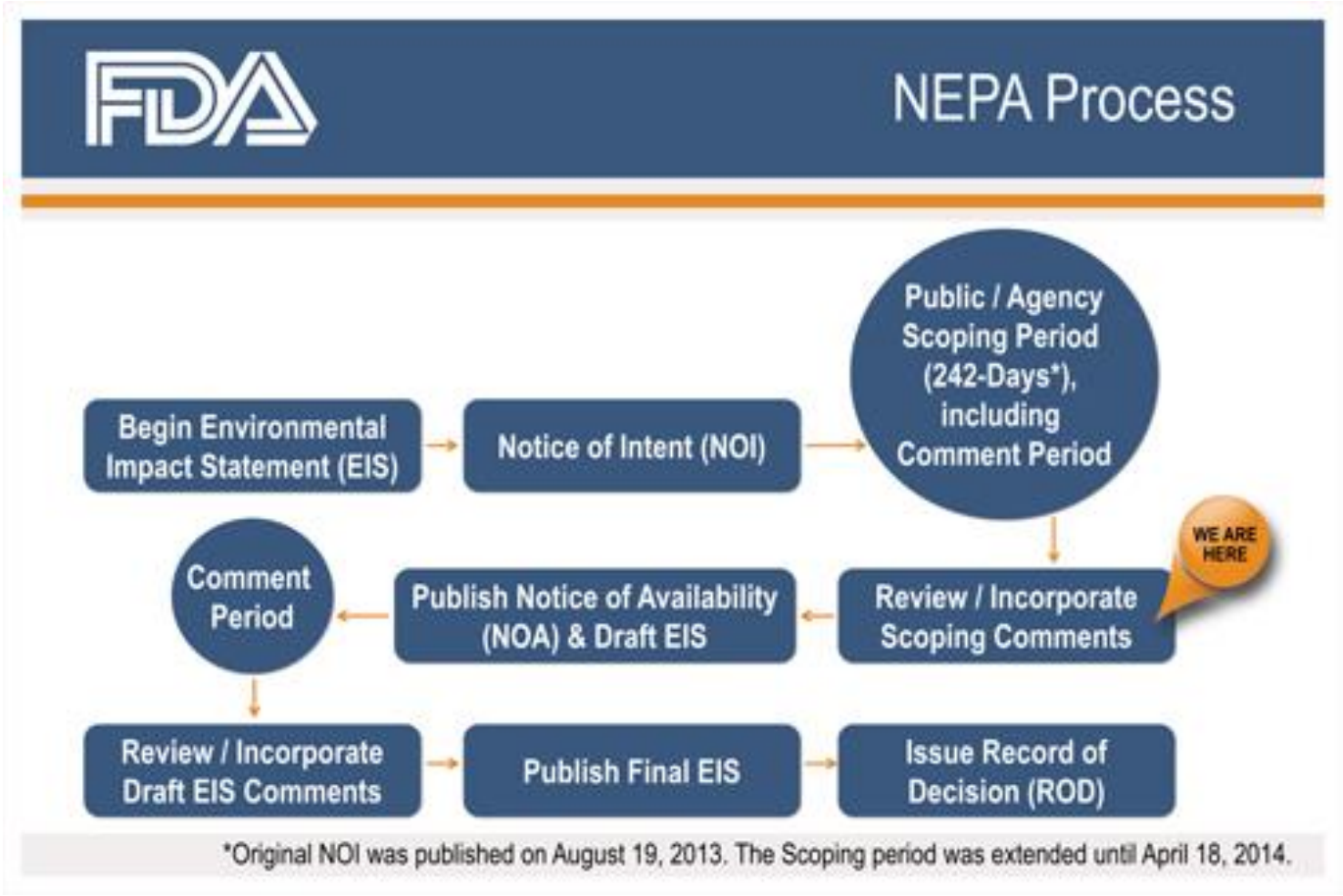
NEPA Assessments (40 CFR 1501, 1508)

- Agency must prepare an Environmental Assessment to determine
  - Whether physical environmental impacts of the action on the human environment of the United States, if any, are
    - Sufficiently significant to warrant further characterization in an Environmental Impact Statement.
    - May consider mitigations (CEQ guidance 1/21/2011)
      - Mitigations may include conditions of use for any approval
- If not, agency issues a Finding of No Significant Impact (FONSI)

Environmental Impact Statement (EIS)

- EIS prepared when EA or other information indicates proposed action may significantly affect the environment
- Describes a proposed action and alternatives
  - Often has significant public notice and comment component (see FDA FSMA EIS process)
  - Allows for potential impacts to be disclosed and understood by the lead agency and public in advance of implementing of the action
  - May consider social, economic, and cultural effects

FDA's NEPA Process for FSMA EIS



Record of Decision (ROD)

- Provides decision
- Identifies alternatives considered (including the environmentally preferred alternative)
- Discusses mitigation plans (e.g., enforcement, monitoring)
- Discusses factors considered when determining whether, and how, to proceed with the proposed action
  - Including whether practical means to avoid or minimize environmental harm have been adopted, and if not, why they were not.

Challenges

and …the known unknowns…

FDA Faces Many Challenges

- Rapid scientific breakthroughs and emerging technologies resulting in novel products that may raise unique testing and safety issues
- New and evolving public health threats
- Globalization of public health, science, manufacturing and supply chains
- Providing accurate and useful consumer information in age of information overload from multiple sources

Emerging Challenges/Opportunities:

Some Examples

- Bioterrorism, pandemics, emerging infections
- New food pathogens
- Complex, global supply chains for foods, drugs, source materials and ingredients
- Antibimicrobial Resistance
- Emerging chemical concerns such as “endocrine disruptors”, trace contaminants

- Counterfeit and sub-potent drugs
- Gene and cell therapies
- Personalized medicine (and related diagnostics)
- “Big data”
- Novel materials: nanotech, tissue engineering, 3D printing etc., human-machine interfaces
- Engineered foods, from organisms or *in vitro* food
- Synthethic Biology

A name is not a regulatory trigger

GMO….genetically engineered……transgenic……gene/genome edited/ing……techniques of modern biotechnology……SynBio

…Are NOT regulatory triggers for the Federal Food, Drug and Cosmetic Act.

So What is the Regulatory Trigger?

The term “drug” (for example) means

- (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and
- (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
- (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and
- (D) articles intended for use as a component of any article specified in clause (A), (B), or (C).

Challenges: Product vs Process

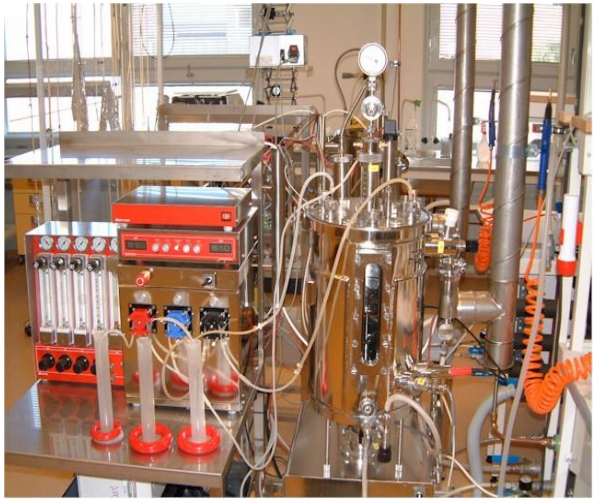
- FDA regulates “articles” or products; not the processes by which they are made.

BUT

- Manufacturing processes may affect safety, effectiveness, purity, potency, or other consideration.

Quality and Safety Issues Associated with Manufacturing Biological Products

- Raw materials and seed banks
- Production, e.g. fermentation, harvesting, purification, storage of the bulk, formulation, final fill
- Characterization
- Process validation
- Testing



Potential Challenges

- Does FDA have a definition for SynBio, and does it matter?
  - Would products from SynBio fit under our regulatory rubric, given that we regulate product and not product?
  - Are there any examples in which products of SynBio might require additional scrutiny?
  - When does SynBio stop being GE 2.0?
  - Does SynBio trigger additional concerns under NEPA?

Path Forward:
Dialogue and Preparedness with appropriate resources

- The best way to understand the likely regulatory path(s) a product may have to navigate is to talk with FDA early about the product and its intended use(s).
- Early interaction also aids in
  - identifying safety and other regulatory issues early in the development process, and
  - making the regulatory process more predictable.
- Advancing Regulatory Science and the Coordinated Framework are essential in addressing challenges from emerging science, technologies and noval products

THANK YOU