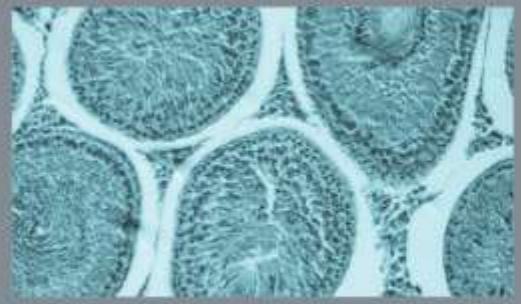
Human Gene Transfer Research Under the April 2019 Amendments to the *NIH Guidelines*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NEBSA Symposium
18 September 2019

April 2019 NIH Guidelines Amendments

Changes for HGT Research

- IBC approval is still required
- Previous "Appendix M" is deleted
  - No RAC assessment
  - Protocols no longer registered with NIH/OSP
  - Result is more responsibility for each IBC
- IBCs may reduce or cease review of consent forms and clinical trial subject safety
- IBCs continue to focus on mitigating risk to clinical and laboratory staff, general public, and environment.
- Single-subject Expanded Access INDs and Protocols are exempt.

NIH GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT OR SYNTHETIC NUCLEIC ACID MOLECULES (NIH GUIDELINES)

APRIL 2019

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

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Visit the NIH OSP Web site at:
https://osp.od.nih.gov

NIH OFFICE OF SCIENCE POLICY CONTACT INFORMATION:

Office of Science Policy, National Institutes of Health, 6705 Rockledge Drive, Suite 750, MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail), (301) 496-9838; (301) 496-9839 (fax).

For inquiries, information requests, and report submissions: NIHGuidelines@od.nih.gov

These *NIH Guidelines* shall supersede all earlier versions until further notice.

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NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)

- Research Involving Recombinant or Synthetic Nucleic Acids is Subject to the *NIH Guidelines*
  - If Institution Receives NIH Funding for Any Non-Exempt rsNA Research
  - If the HGT Clinical Trial Product was Developed with NIH Funding
  - If the Study or Sponsor are NIH-Funded
  - If site or sponsor elects "Voluntary Compliance"
  - If required by funder or local regulations
- Clinical research subject to the *NIH Guidelines* requires approval by a Institutional Biosafety Committee (IBC)

Voluntary Compliance with *NIH Guidelines*

- "Individuals, corporations, and institutions not otherwise covered by the NIH Guidelines are encouraged to follow the standards and procedures set forth in Sections I through IV."
- Special provisions are made for protection of trade secrets
- Assures adoption of best practices
- Mitigates compliance and headline risk
- Prepares sponsors for IBC approval at clinical trial sites subject to NIH Guidelines.

Human Gene Transfer Research

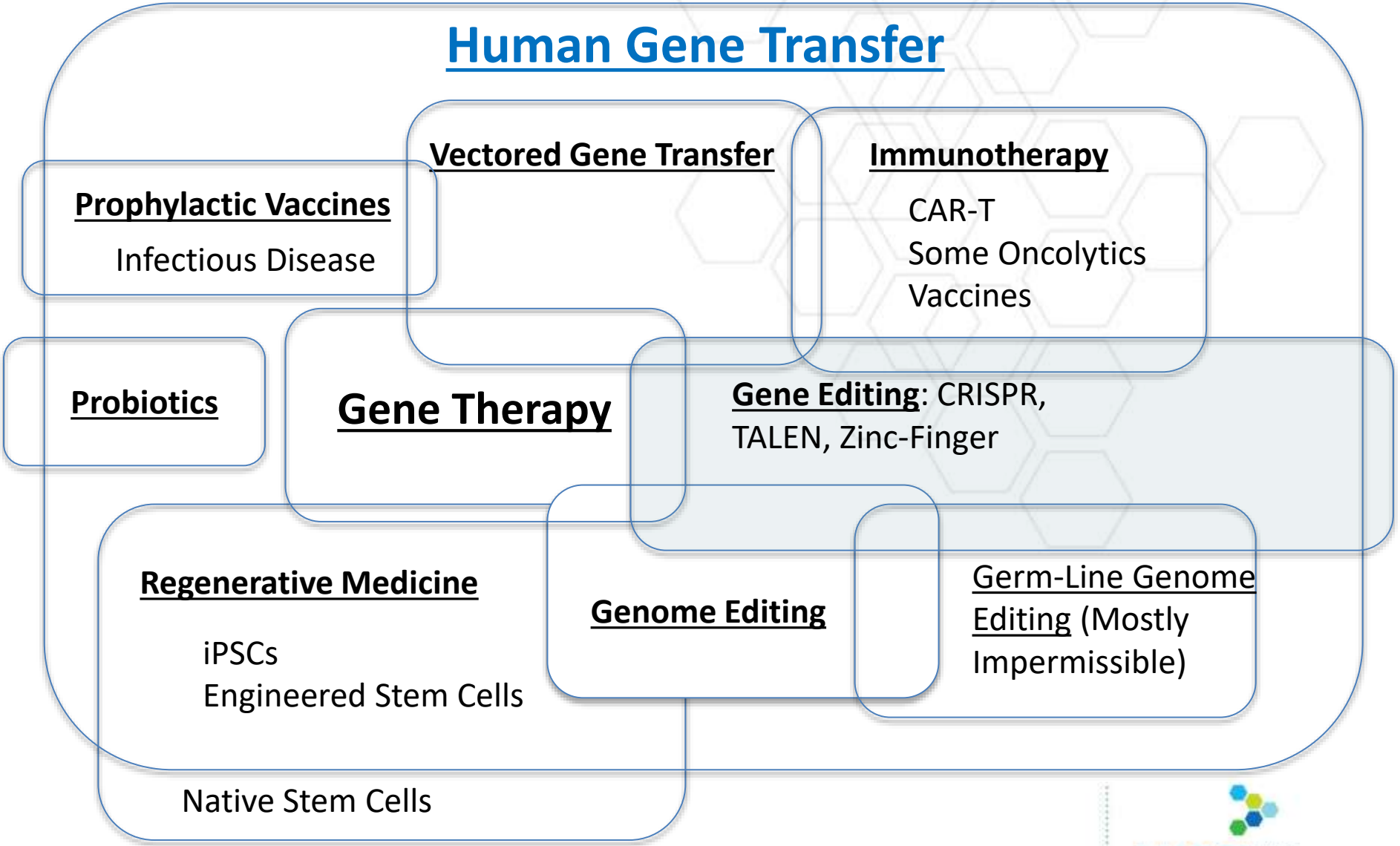
Section III-C-1. Experiments Involving the Deliberate Transfer of Recombinant or Synthetic Nucleic Acid Molecules, or DNA or RNA Derived from Recombinant or Synthetic Nucleic Acid Molecules, into One or More Human Research Participants

Human Gene Transfer is the Deliberate Transfer into Human Research Participants of Either:

1. Recombinant Nucleic Acid Molecules, or DNA or RNA Derived from Recombinant Nucleic Acid Molecules, or

2. Synthetic Nucleic Acid Molecules, or DNA or RNA Derived from Synthetic Nucleic Acid Molecules, that Meet Any One of the Following Criteria:
    a. Contain More than 100 Nucleotides; or
    b. Possess Biological Properties that Enable Integration into the Genome
    c. Have the Potential to Replicate in a Cell; or
    d. Can be Translated or Transcribed

Translational Molecular Biology



FDA-Approved HGT Products

research with these is still subject to *NIH Guidelines*

- ZOLGENSMA (onasemnogene abeparvovec-xioi) for Spinal Muscular Atrophy
  - Avexis (Novartis), approved May 2019
- DENGVAXIA (DENGUE Tetravalent Vaccine, Live)
  - Sanofi Pasteur Inc., approved May 2019
- LUXTURNA (voretigene neparvovec) for inherited retinal disease
  - Spark Therapeutics, approved Dec 2017
- YESCARTA (axicabtagene ciloleucel) for certain types of non-Hodgkin lymphoma (NHL)
  - Kite (Gilead), approved Oct 2017
- KYMRIAH (tisagenlecleucel) for certain B-cell acute lymphoblastic leukemias
  - Novartis, approved Aug 2017
- Vaxchora (cholera vaccine, live, oral)
  - PaxVax, Approved June 2016
- IMLYGIC (talimogene laherparepvec) Oncolytic Viral Therapy
  - Amgen, approved Oct 2015

FDA-regulated Medical Products

- Pharmaceutical Drugs
  - Reviewed by CDER (Center for Drug Evaluation and Research)
  - Clinical trials conducted under an IND
  - Marketing approval via NDA
- Devices
  - Reviewed by CDRH (Center for Devices and Radiological Health)
  - Clinical trials conducted under an IDE
  - Marketing approvals via preapproval notification or PMA.
- **Biologics** (All HGT products are expected to qualify as Biologics)
  - Reviewed by CBER (Center for Biologics Evaluation and Research)
  - Clinical trials conducted under an IND
  - Marketing approval via BLA
- Combination products
  - May be reviewed as Drugs, Devices, or Biologics, depending on PMOA
  - HGT component is likely to exert PMOA

HGT Biologic-Device Combination Products

Examples

- Implantable cartridge seeded with cells transduced with therapeutic transgene.
- DNA vaccine intended for injection with specific gene gun or electroporator
- Polymer scaffold seeded with genetically modified stem cells

- In each case, the primary mechanism of action (PMOA) is probably the biologic component.

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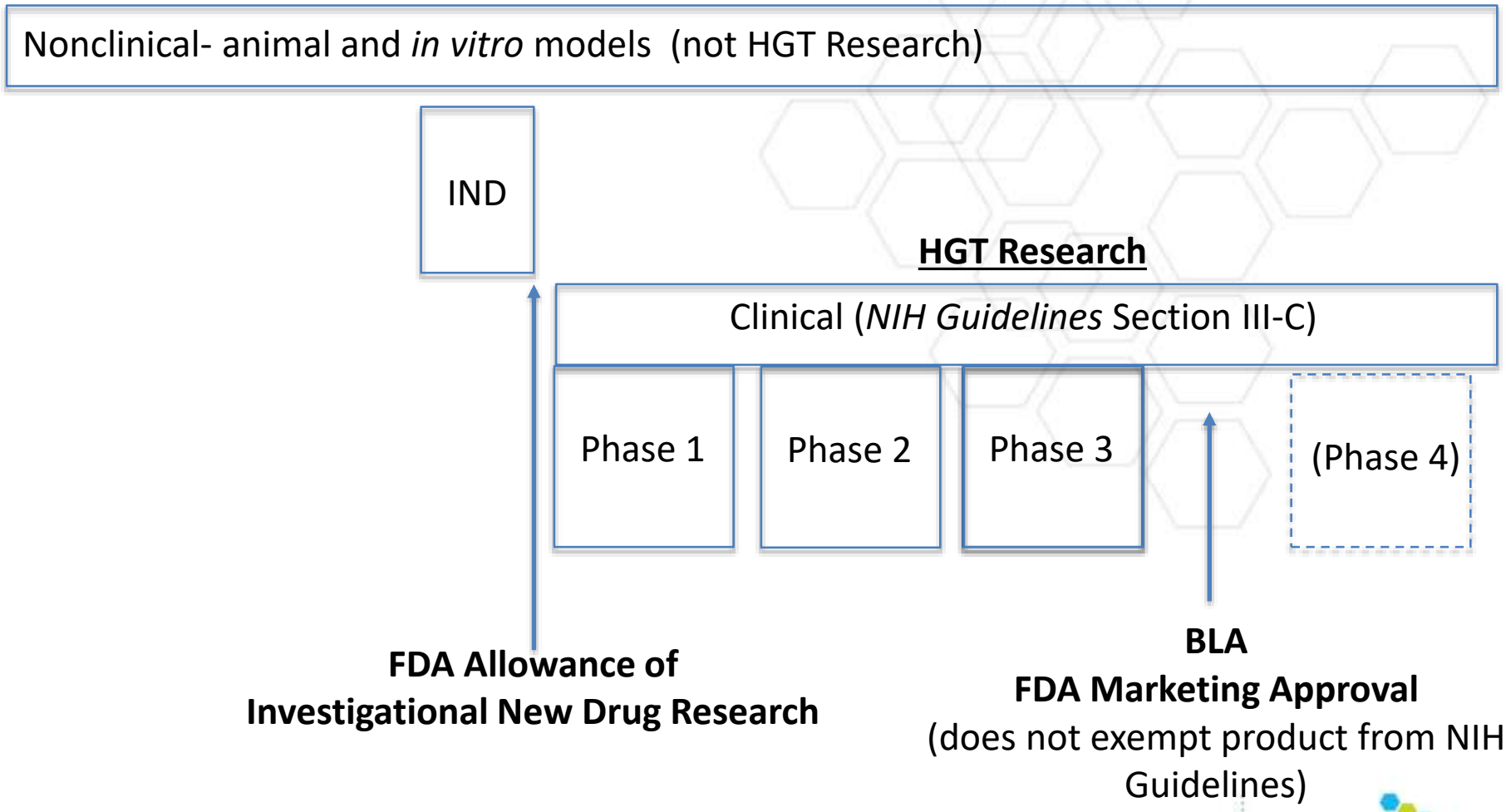
Stages of HGT Drug Development (USA)



HGT Research Protocols

- Research involving unapproved FDA-regulated drugs and biologics must be conducted under a clinical trial protocol
- Each clinical trial protocol is implemented under a specific IND
- One IND may have more than one protocol
- One investigational product may be used in more than one IND

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Expanded Access Treatments

- Also known as “compassionate use”
- Available to subjects with very serious or life-threatening conditions
- With FDA allowance, subjects not eligible to enroll in a clinical trial may qualify for Expanded Access via
  - an Expanded Access Protocol under an existing IND or
  - a separate Expanded Access IND
- **Per April 2019 amendments to NIH Guidelines, single-subject Expanded Access INDs and protocols are not subject to the Guidelines.**
- Expanded access protocols involving more than one subject are not exempt
- Expanded access ≠ “Right to Try”

FDA Regulation and *NIH Guidelines*

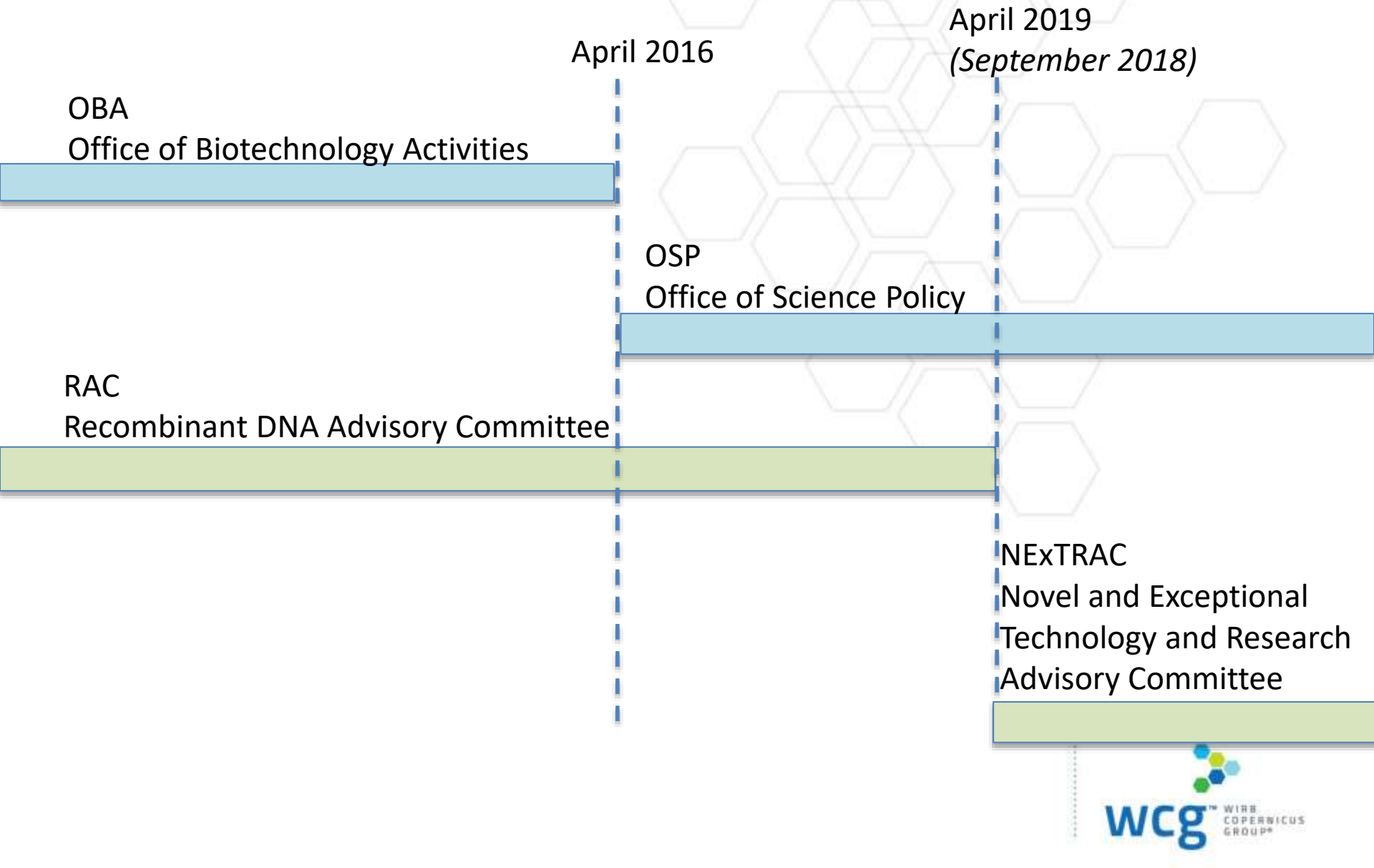
Does require IBC approval (if otherwise subject to *NIH Guidelines*):

- Introduction of HGT product into any human **research** subject
  - irrespective of FDA marketing approval
- Expanded Access/ Compassionate Use Treatment
  - except under single-patient protocols and INDs

Does not require IBC approval:

- Clinical treatment/ standard of care (non research) with an FDA-approved HGT product
- Expanded Access/ Compassionate Use Treatment under single-patient protocols and INDs

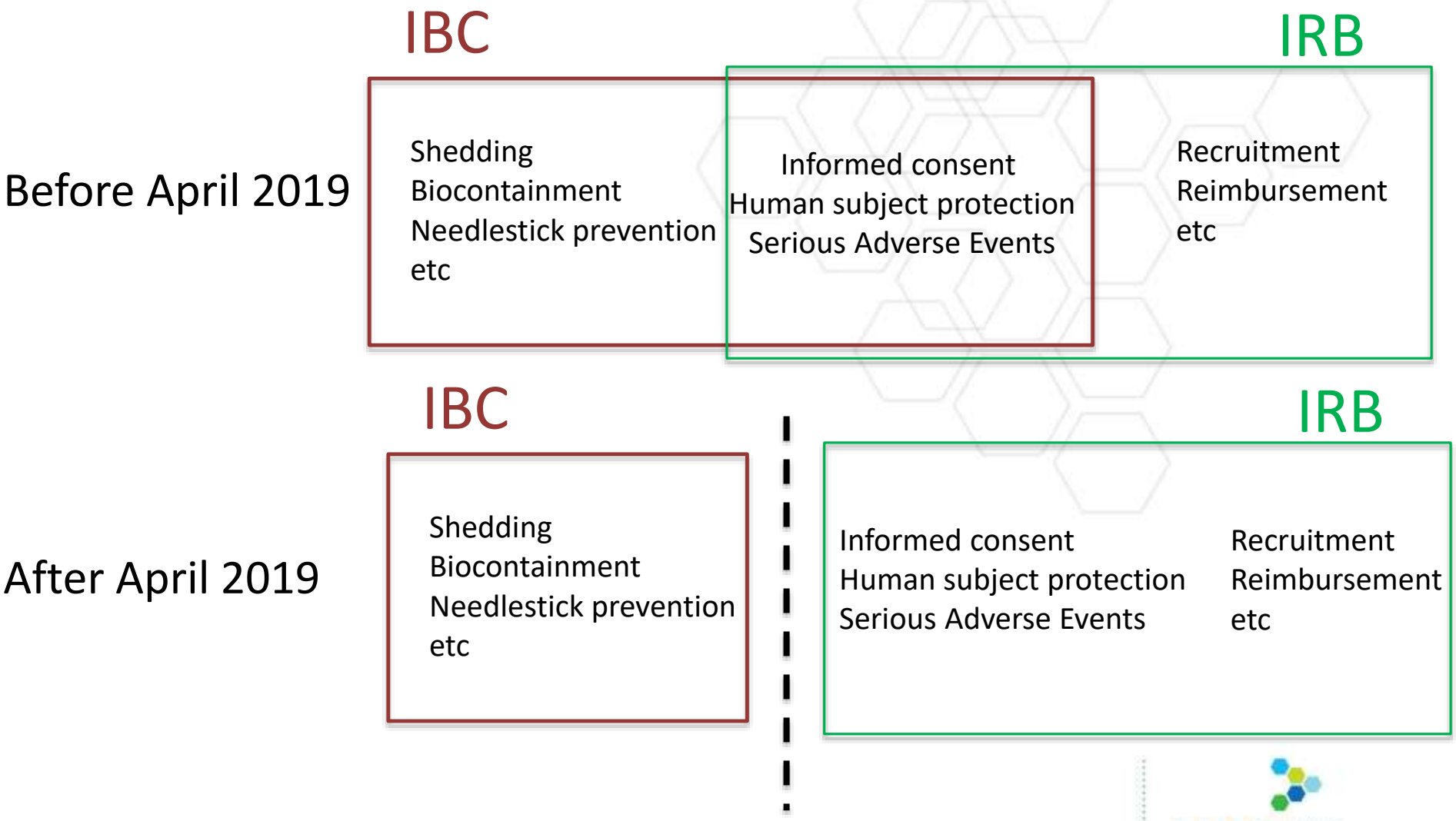
Recent Transitions in NIH Oversight



Recent Transitions in NIH Oversight

- Prior to April 2016:
  - all non-vaccine HGT protocols reviewed by RAC
  - all non-vaccine protocols entered in GeMCRIS
  - Appendix M reporting required
- From April 2016 to April 2019:
  - all non-vaccine HGT protocols assessed by NIH Director for referral to RAC
  - assessment informed by IBC and IRB letters
  - all non-vaccine protocols entered in GeMCRIS
  - Appendix M reporting required
  - very few protocols were referred to RAC
- After April 2019:
  - RAC dissolved
  - GeMCRIS discontinued
  - Appendix M deleted
  - all Appendix M reporting discontinued

IRB and IBC Oversight



IRB and IBC Oversight After April 2019 Amendment

IBC

Focus is protection of research staff, public, and the environment.

Approves Protocols, Facilities, and Biosafety Level

Monitors unexpected events involving lab-acquired illness, accidental exposures, and loss of containment.

IRB

Focus is protection of study participant.

Determines whether risk and benefit to study subjects are appropriate.

Approves Informed Consent Forms.

Monitors adverse events affecting study subjects.

IBC Review of HGT Research

Special considerations

- What risks could the product pose to staff, public health or the environment?
- How do existing training and procedures in the clinic accommodate requirements of *NIH Guidelines*/ BMBL?
- How does will the clinic control access of general public, family members, and therapy animals to research areas?
- How does clinic implement safe injection policies?
- How do research pharmacists protect sterility of the product and also protect staff from unnecessary exposure?
- Implementation of USP 797 and USP 800 standards.

Human Gene Transfer “food” products

In 2019, a new genetically modified product was introduced for commercial sale in the USA.

It is advertised as a probiotic food product engineered to break down acetaldehyde, “a toxic byproduct of alcohol”.

As a food product it is “not intended to treat or prevent disease” and does not require FDA marketing approval.

If it were intended to treat or prevent disease, then it would require clinical trials prior to marketing as an FDA-regulated product.

Such research would require IBC approval if otherwise subject to the *NIH Guidelines*.

Very similar products, intended to treat disease, are in clinical trials under IBC oversight.

Summary and Conclusions

April 2019 amendments and HGT research

- No change in general requirement for IBC approval.
- RAC eliminated– more responsibility on IRB and IBC.
- Appendix M requirements eliminated.
- New bright line between IBC and IRB oversight.
- IBCs to focus on mitigating risk to clinical and laboratory staff, general public, and environment.
- Single-subject Expanded Access INDs and Protocols are exempt.

Thank you

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Questions?

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