

**FDA Margolis Center of Excellence in
Regulatory Science and Innovation Workshop
Fetal Pharmacology and Therapeutics**

Ethical and Regulatory Considerations

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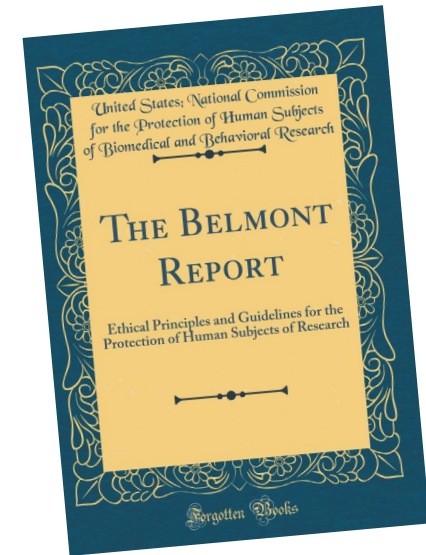
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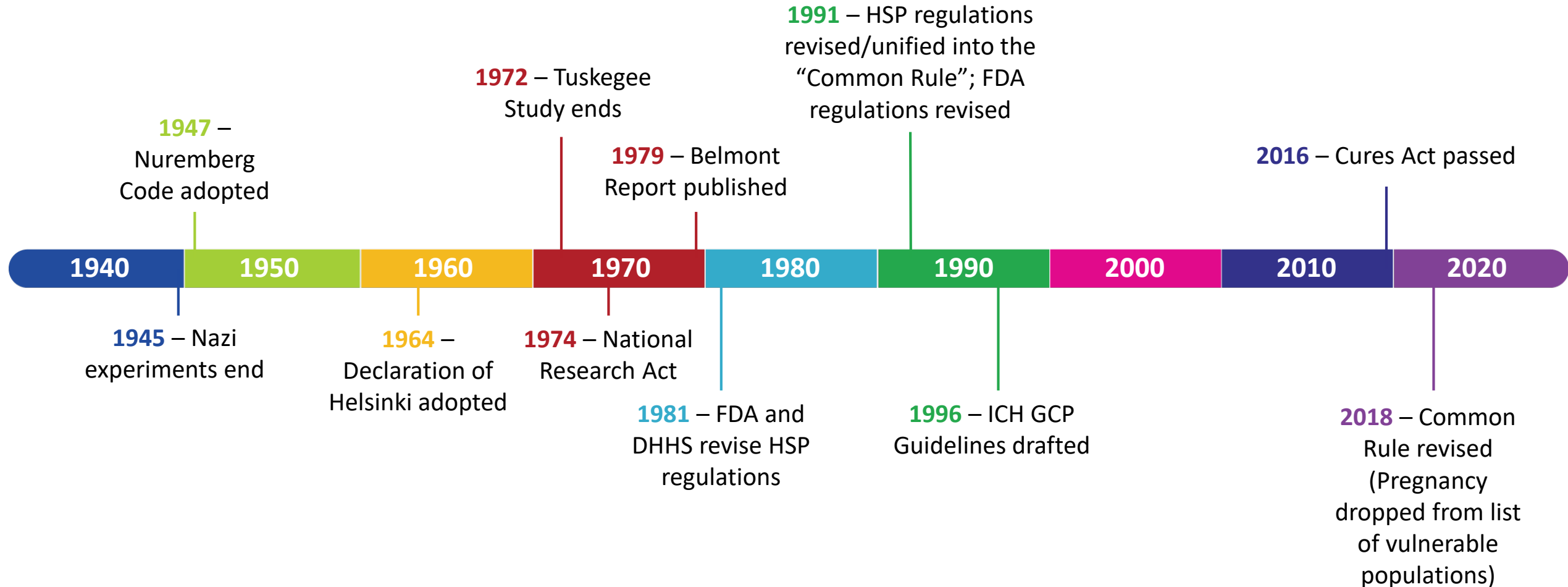
- Review the ethical considerations related to the protection of pregnant women and their fetus in clinical research
- Review the U.S. regulatory requirements related to the protection of pregnant women and their fetus in clinical research

Ethical principles to consider

- Belmont Report
 - Respect for persons
 - Beneficence
 - Justice
- Complex risk benefit analyses that take into account the pregnant woman and fetus



Timeline of contemporary research ethics



- Paternalism: Pregnant women treated as uniquely vulnerable and frequently not included in clinical research
- Brief History

HHS regulations lists pregnant women as an example of a vulnerable category of subjects (45 CFR 46.107)

HHS eliminates pregnant women as an example of a vulnerable population from the Federal Policy for the Protection of Human Subjects (Common Rule)

1977

FDA guideline excluded women of childbearing potential from participation in phase 1 and early phase 2 trials

1991

HHS regulations lists pregnant women as an example of a vulnerable category of subjects (45 CFR 46.107)

1993

FDA Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs encourages inclusion of women of childbearing potential in early trials

2018

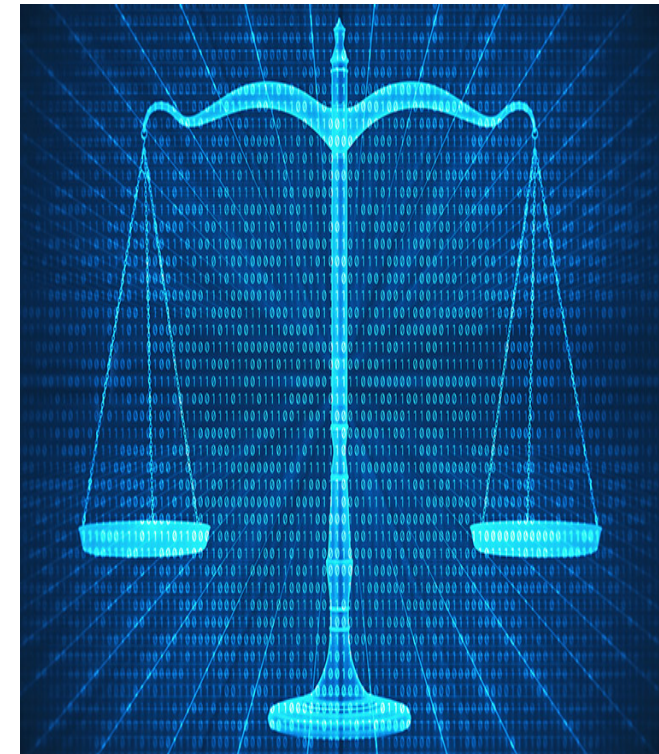
HHS eliminates pregnant women as an example of a vulnerable population from the Federal Policy for the Protection of Human Subjects (Common Rule)

2021

FDA regulations still lists pregnant women as an example of a vulnerable category of subjects (21 CFR 56.107)

- **>60 million** women in the U.S. between the **ages of 15 to 44 years** and **≈ 4 million** births in U.S./year (U.S. National Vital Statistics Report)
- Few FDA-approved products have labeling recommendations based on clinical trials
- Information about drug use during pregnancy is frequently limited to post-marketing observational studies such as pregnancy registries
- Lack of information can result in pregnant women not getting the medical care they need or using medically necessary drugs without understanding the risks and benefits.
- Physiologic changes during pregnancy may alter PK and PD which directly affects safety and efficacy
- **About 70%** of pregnant women take at least one prescription medicine during pregnancy ([U.S. Centers for Disease Control and Prevention](#))

- Safe and effective treatments
- Dose regimen may affect the health of women and fetuses
- Potential benefit to the woman or fetus that is unavailable outside the research setting



Federal Regulations for Human Subject Protections

- HHS regulations

- 45 CFR Part 46, “Protection of Human Subjects”
 - Subpart A (Common Rule) – “Basic HHS Policy for Protection of Human Research Subjects”
 - Subpart B – Pregnant Women, Human Fetuses and Neonates
 - Subpart C – Prisoners as Participants
 - Subpart D – Children as Participants

- FDA regulations

- 21 CFR part 50, “Protection of Human Subjects”
- 21 CFR part 56, “Institutional Review Board”

Federal Regulations for Human Subject Protections

21 CFR 50 and 56

- **Part 50, “Protection of Human Subjects”**

- Subpart A: General Provisions
- Subpart B: Informed Consent Requirements
- Subpart D: Additional Safeguards for Children

- **Part 56, “Institutional Review Boards”**

- Subpart A: General Provisions
- Subpart B: IRB Organization and Personnel
- Subpart C: IRB Function and Operations
- Subpart D: Records and Reports
- Subpart E: Administrative Actions for Noncompliance

- **Must also conform to all applicable regulations (e.g., 21 CFR 312 & 21 CFR 812)**

- 45 CFR 46, subpart B applies to all HHS-conducted or supported research involving pregnant women, human fetuses, neonates of uncertain viability or nonviable neonates unless exempt
- FDA recommends these requirements be satisfied for FDA-regulated research
- Pediatric regulations (subpart D) do not apply to the fetus

Research involving pregnant women or fetuses

- Appropriate nonclinical work needs to be done
- Needs to be Prospect of Direct Benefit to the women or fetus or no more than minimal risk
- Risk needs to be minimized
- Consent is required
- No inducement will be offered to terminate a pregnancy
- Individuals engaged in research will have no part in determining the viability of a neonate
- See 45 CFR 46 subpart B for more information

Ethically justifiable research involving FDA-approved marketed drugs

- Every drug development program is unique
- Adequate nonclinical studies have been completed
- Established safety database in nonpregnant women from clinical research or preliminary safety data from the medical literature are supportive
- One of the following:
 - Efficacy cannot be extrapolated
 - Safety cannot be assessed by other study methods
- Clinical trial holds prospect of direct benefit to the pregnant woman and/or fetus that is not otherwise available (e.g., pregnant women may not have responded to other approved treatments or there may not be any treatment options)

General recommendations

- Discuss in the product development plan with the FDA review division
- Consider including an ethicist knowledgeable about clinical trial design to plan these trials
- Consent document should describe relevant information from completed nonclinical reproductive toxicology studies or, if not completed, should describe the lack of full characterization of drug's effect on conception and fetal development
- Enrolled subjects should be informed of relevant new information as it is learned

- If a woman becomes pregnant while enrolled in a clinical trial, carefully consider the risks and benefits of her continuation in the trial. If potential benefits > potential risks consider:
 - Unblinding
 - Reconsenting subject if they agree to continued participation
 - Need for post-partum follow-up
 - PK sampling if appropriate
 - IRB(s) must have the professional competency necessary to review the research

- Growing consensus on the need to include pregnant and breastfeeding women in clinical research
- FDA committed to advancing research in pregnant and lactating women
 - Data needed to inform labeling and benefit-risk
 - Several recent guidances

- FDA guidance: [Enhancing the Diversity of Clinical Trial Populations – Eligibility Criteria, Enrollment Practices, and Trial Designs](#)
- FDA draft guidance: [Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials](#)
- FDA guidance: [E9 Statistical Principles for Clinical Trials](#)
- FDA guidance: [E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting](#)
- [Belmont Report](#)
- [FDA Office of Women's Health pregnancy resources](#)