

Conducting PK studies in Pregnant Individuals Regulatory Experience

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Disclaimer

- The reviews expressed are those of the speaker and do not necessarily reflect official policy of the FDA.

PK Studies in Pregnant Individuals

Need for PK Studies in Pregnancy

- Common use of meds during pregnancy
- Anticipated/observed PK changes during pregnancy
- PK data are critical to derive dosing in pregnant individuals

Barriers/Challenges to Conduct PK Studies in Pregnancy

- Liability, ethics, funding, lack of incentive/legislation, low interest, hesitancy
- Additional unique considerations pertaining to study design and interpretation

Current Status

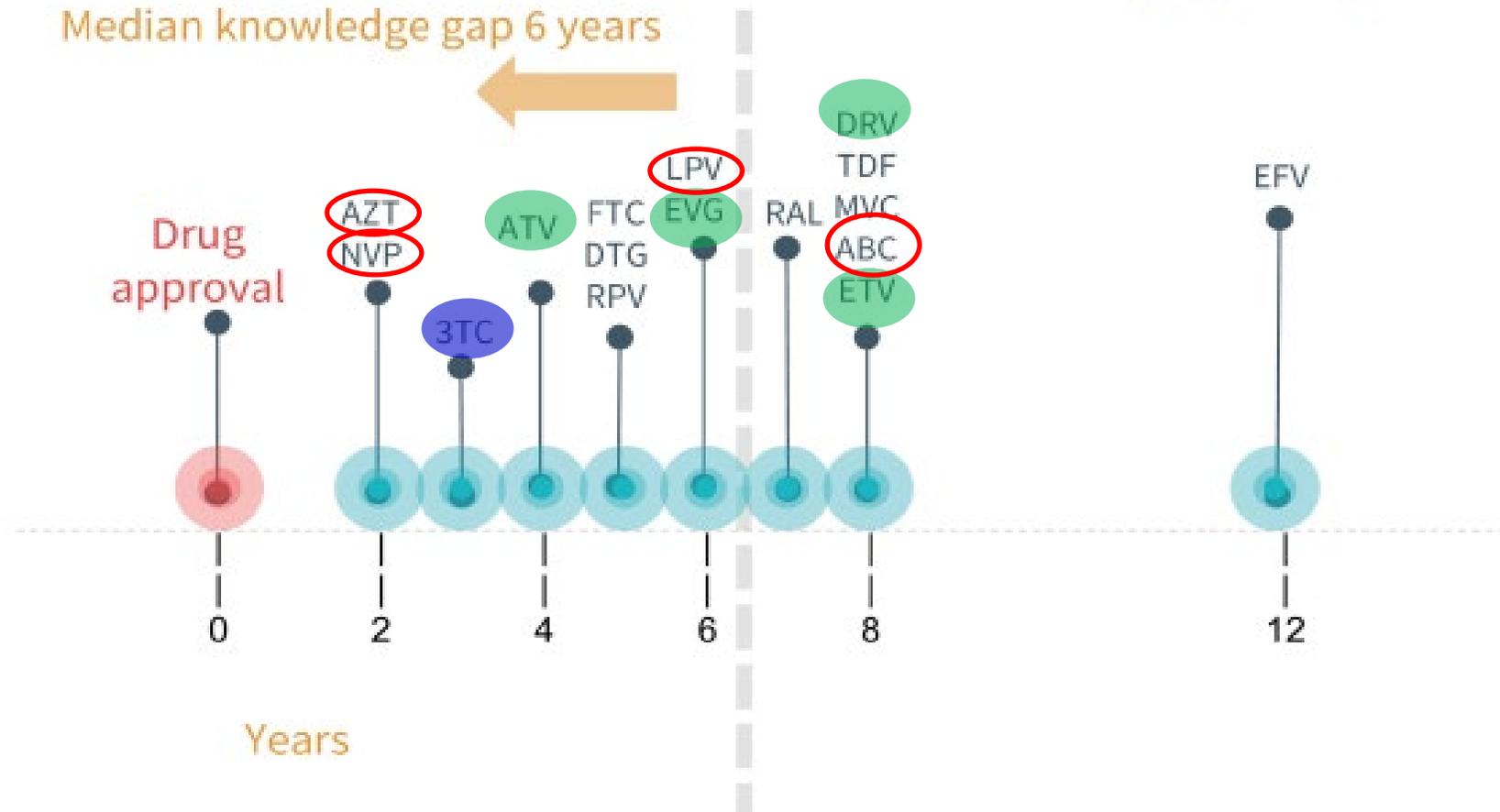
- ✓ Significant delay in initiation of a PK study in pregnant individuals
- ✓ No or limited data for most medications → No clear guidance/clinical dosing recommendations for healthcare providers and patients

Years between US FDA Approval and Publication of Pregnancy Data: Antiretroviral Drugs



Time-to-first published (PK) data in pregnancy

Median knowledge gap 6 years



Time-to-labeling update after the first publication

Unmarked Not available yet

- < 3 years
- 3 to < 7 years
- 7+ years

FDA Draft Guidance – Currently Under Revision



Guidance for Industry **Pharmacokinetics in Pregnancy —** **Study Design, Data Analysis,** **and Impact on Dosing and Labeling**

DRAFT GUIDANCE

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Considerations for Pregnancy PK Studies

Pre-Market vs. Post-Market

Call for pre-market (PK) studies in pregnant individuals

Inclusion of women in FDA-regulated premarket clinical trials: A call for innovative and recommended action

Mehmoosh Samaei ^a, Alyson J. McGregor ^b, Marjorie R. Jenkins ^c  

Importance of Prospective Studies in Pregnant and Breastfeeding Women Living With Human Immunodeficiency Virus

Angela Colbers, ^{1,5} Mark Mirochnick, ² Stein Schalkwijk, ^{1,3} Martina Penazzato, ⁴ Claire Townsend, ^{4,5} and David Burger ¹

Inclusion of pregnant women in COVID-19 treatment trials: a review and global call to action

Melanie M Taylor, Loulou Kobeissi, Caron Kim, Avni Amin, Anna E Thorson, Nita B Bellare, Vanessa Brizuela, Mercedes Bonet, Edna Kara, Soe Soe Thwin, Hamsadvani Kuganantham, Moazzam Ali, Olufemi T Oladapo, Nathalie Broutet



Inclusion of Pregnant Individuals in Pre-Market Clinical Trials – COVID-19

COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry

The principles outlined in this document can be used to guide drug development for children and for pregnant and lactating individuals. There is a need to generate clinical trial data to inform the use of drugs in these populations.

- Because COVID-19 during pregnancy may increase the risk of severe symptoms and preterm birth, pregnant individuals should be enrolled in the phase 3 (efficacy) clinical trials when appropriate.¹⁴

- None of the authorized or approved drug products for the treatment of COVID-19 has information on observed safety, efficacy, or PK data in pregnant individuals in factsheets (or product labeling)
 - Except for molnupiravir, the use of authorized or approved drugs are not restricted in pregnant individuals
- For many products, enrollment was not specifically excluded in later phase clinical trials. However, no or a very limited number of pregnant subjects were enrolled in clinical trials

Considerations for Pregnancy PK studies

Study Design

- Post–market PK studies in pregnant individuals
 - Most PK data in pregnant individuals are collected in post-market PK studies
 - Perceived as minimal risk for opportunistic studies
 - Data are still limited to certain therapeutic areas (e.g., drugs for infectious diseases)
 - No incentive/regulation is still the problem for post-marketing studies
 - Limited discussion on the best practice for study design, conduct, and interpretation

Considerations for Pregnancy PK Studies

Study Design

- Most studies are conducted in patients
 - Cannot control other intrinsic/extrinsic factors
- Study design is mainly driven by clinical scenarios
 - Not feasible to determine pregnancy term-dependent changes in the same subjects for drugs given as a short-term therapy (e.g., influenza)
- Discussion on the “reference” population
 - Post-partum in the same subjects vs. “matching” nonpregnant subjects (or all subjects)
 - Right timing for post-partum data collection

Considerations for Pregnancy PK Studies

Study Design

- Dose selection
 - Typical dose selection: currently approved dosing/lowest clinical dose even though exposures are expected to be lower during pregnancy
 - Multiple doses, including higher-than-approved doses, when decreased exposures are anticipated?
- Changes in protein binding
 - Significant variabilities in study conduct, assay, result interpretations
 - Often, a lack of reliable historical control data in the nonpregnant populations
- Incorporating PD or clinical outcome assessments

Considerations for Pregnancy PK Studies Interpretation and Making Recommendation

Ultimate goal: safe and effective use of medications in pregnant individuals

- What do we need?
 - Results from well designed/conducted studies
 - Leveraging innovative quantitative approaches
 - Opportunities to apply the recommendations and learn



Collaboration among stakeholders: academia, industry, healthcare providers, and regulators

Summary

- There is a growing consensus on including pregnant people in clinical research
 - Earlier than later
 - Advances are happening, but very slowly due to many challenges
 - PK studies in pregnant individuals are essential as the first and critical step to determine the right dose in pregnant individuals
- There are unique considerations for designing PK studies in pregnant individuals
- To achieve the ultimate goal, identify the right dosing regimen in pregnant individuals, stakeholder collaboration is the key