Regulatory Requirements for Pediatric Drug Development

Linda L. Lewis, M.D.
Medical Team Leader, DAVP, FDA

HCV DrAG Meeting

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Overview

- Why study drugs in children?
- Why study HCV DAAs in children?
- Current basis for requesting pediatric studies
- Types of clinical trials required
- Examples from recent development programs
- Summary of FDA goals for pediatric DAA development

Why study drugs in children?

- Lack of pediatric use information in product labels can pose significant risk for children
- Prior to FDA pediatric initiatives: estimated 75% of drugs used in children lacked adequate labeling to ensure safe and effective use
- Lack of pediatric studies may deny access to effective drugs and expose children to off-label use or “homebrew” formulations
- Adverse reactions may result from:
  - Overdose of an effective drug
  - Incorrect use of drug/use of an ineffective drug
  - Toxic/inappropriate excipient in formulation

Why study HCV DAAs in children?

- Estimates of 23,000 to 46,000 children with chronic HCV in US
- Estimated 20-25% of those perinatally infected can have more aggressive course with development of advanced fibrosis/cirrhosis in childhood
- Approved pediatric treatment remains peg-interferon + ribavirin
  - Risks of interferon-based therapy in children include growth impairment that may not recover plus all ADRs described in adult literature
- DAAs hold promise of shorter, safer, more effective treatment

Current basis for requesting pediatric studies

- Pediatric drug development laws
  - Pediatric Research Equity Act (PREA)
    - **Requires** companies to assess safety and effectiveness of new drugs/biologics in pediatric patients
  - Best Pharmaceuticals for Children Act (BPCA)
    - **Provides a financial incentive** to companies to voluntarily conduct pediatric studies (exclusivity)
  - Title V of FDA Safety and Innovation Act (FDASIA)
    - Permanently reauthorized PREA and BPCA
    - Formalized requirement to submit a Pediatric Study Plan

More about the law

- PREA
  - Triggered by new active ingredient, indication, dosage form, dosing regimen, or route of administration
  - **Requires** studies ONLY for indication under review
- BPCA
  - Requested studies relate to chemical moiety and can include multiple indications including those not studied in adults
  - Studies are **voluntary** (but often same as those required under PREA)
- Pediatric studies required/requested under laws must be included in label even if unsuccessful

Still more about the law

- Sponsors required to submit Pediatric Study Plan
  - Intent to encourage sponsors to think about pediatric studies relatively early in product development
  - If End of Phase 2 meeting occurs: PSP must be submitted within 60 days of meeting date
  - If no EOP2 meeting: PSP should be submitted as early as possible (time agreed upon by FDA and sponsor), must be at least 210 days before NDA submission

Pediatric clinical trials for antiviral products

- All development programs start with targeting drug exposure found to be safe and effective in adult patients (modeling and simulation) to identify initial dosing proposal
- Formulation development may be most challenging aspect of pediatric program for FDCs
- Drug exposure may be confirmed in dedicated PK study or as part of efficacy/safety clinical trial, can be streamlined in adolescents receiving adult approved formulation
- Clinical trial designs
  - Randomized, controlled trials – when disease in pediatric patients significantly different from adults
  - Open-label, single arm trial – when disease similar across age groups and more confidence in extrapolating efficacy; when good PK/PD marker or endpoint (HCV RNA measurements and SVR)

Recent examples - pediatric postmarketing requirements

- Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of Drug X as a component of a combination antiviral treatment regimen in pediatric subjects 3 through 17 years of age with chronic hepatitis C.

- Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of FDC Y in pediatric subjects 3 to 17 years of age with chronic hepatitis C.

- Collect and analyze long-term safety data for subjects enrolled in the pediatric Drug Z safety, pharmacokinetic and efficacy study. Data collected should include at least 3 years of follow-up in order to characterize the long-term safety of Drug Z including growth assessment, sexual maturation and characterization of Drug Z resistance associated substitutions in viral isolates from subjects failing therapy.

FDA goals for pediatric DAA development programs

- Require sponsors of highly effective DAAs to study them in children (PK, safety, SVR) to assure appropriate use
- Allow sponsors some flexibility to study their optimal regimen
- Collect long-term data to assess growth and development and persistence of resistance in children receiving new regimens