EMA Review Update

EMA Guideline Review

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- Reviewed by steering committee members
  - Special thanks to Sue Currie, Marc Ghany, Anna Lok, Veronica Miller, Wendy Spearman, Terry Wright, MF Yuen and Ekene Osakwe for finalizing the output

- Approximately 40 comments submitted across 4 main categories
  - Terminology and Definitions
  - Clinical Trial Population and Endpoints
  - Treatment Discontinuation
  - Special Populations

Key Comment Areas

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- Terminology and Definitions
  - Clarify inconsistencies in definitions particularly clinical trial endpoints
    - Functional cure and partial cure to prevent ambiguity
    - Primary virologic failure vs virologic breakthrough vs post-treatment replapse
    - Clear, consistent definition of pediatric age range
- Clinical Trial Population and Endpoints
  - HBsAg quantification is not standard of care globally; Should be applied consistently into protocols beyond standard-of-care practices
  - Trials should include as broad a population as possible
    - Limitation of populations in clinical trials would limit the label

Key Comment Areas

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- Clinical Trial Population and Endpoints (cont)
  - Definition of sustained suppression of HBV DNA and HBsAg
    - Blips should be taken into account in efficacy endpoints, especially with immunomodulatory agents
  - Trial results should be reported using ITT analysis as well as subgroups
  - Genotypic and phenotypic resistance should be conducted in all participants with virologic failure, breakthrough or late post-treatment relapse
  - Finite treatment should explicitly state that 24 weeks off treatment constitutes the primary endpoint time point for initial submission with extended follow-up clearly framed as a post-marketing obligation

Key Comment Areas

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- Treatment Discontinuation
  - Clarify that treatment regimen is required to be discontinued after pre-defined treatment duration
  - "Mandatory" stopping of NUC therapy in all participants regardless of clinical readiness poses unacceptable safety risks
    - Include explicit criteria for urgent NUC initiation in participants with clinically significant hepatitis flare or decompensation
- Special Populations
  - For children <12, guideline should state that safety and PK characterization should be the primary objective of pediatric studies
  - Guideline should acknowledge that large pediatric efficacy trials are challenging to conduct