FDA Perspective: Development of Long-Acting Therapies for Chronic Hepatitis B

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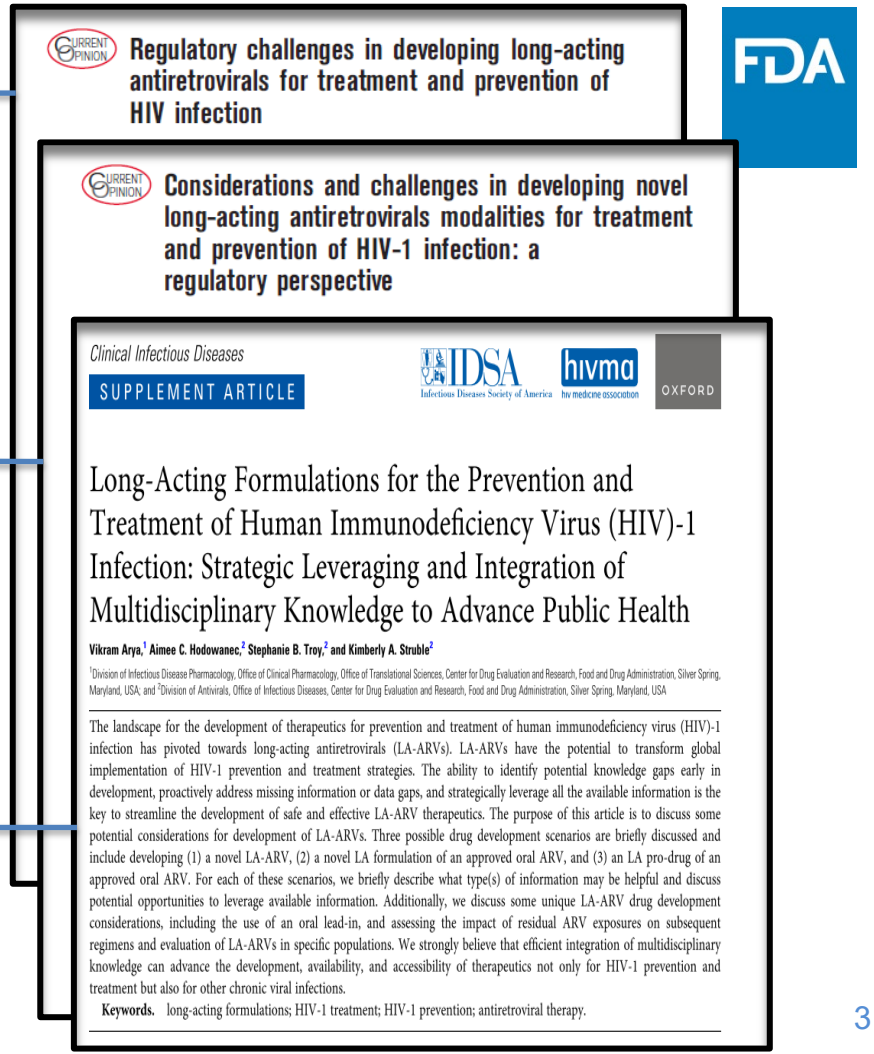
FDA Approved HBV Therapies: 2023

Brand Name	Generic Names	Year Approved
Nucleos(t)ide Analog Reverse Transcriptase Inhibitors (NrtIs)		
Vemlidy	tenofovir alafenamide	2016
Viread	tenofovir disoproxil fumarate	2008
Tyzeka	telbivudine	2006
Baraclude	entecavir	2005
Hepsera	adefovir dipivoxil	2002
Epivir-HBV	lamivudine	1998
Recombinant Human Interferon Alfa		
Pegasys	peginterferon alfa-2a	2005
Intron A	interferon alfa-2b	1992

Once weekly

FDA approved vaccines are available for the prevention of hepatitis B virus infection

Development of Long-Acting Antiretroviral Formulations



FDA-Approved Long-Acting Therapies for HIV-1 Prevention or Treatment

Drug(s)	Therapeutic Class	Indication	Oral Lead-In	Dosing	T_{max} (days)	$t_{1/2}$ (weeks)
Cabotegravir	HIV-1 INSTI	PrEP	Optional	IM Q2M	7	5.6-11.5
Cabotegravir + Rilpivirine	HIV-1 INSTI + NNRTI	Treatment of virally-suppressed adults	Optional	IM QM	CAB: 7 RPV: 3-4	CAB: 5.6-11.5 RPV: 13-28
Lenacapavir	HIV-1 capsid inhibitor	Treatment of HTE adults	Oral/Oral+SC	SC Q6M	77-84	8-12
Ibalizumab	anti-CD4 mAb	Treatment of HTE adults	No	IV Q2W	N/A	0.5

Source: USPIs. CAB, cabotegravir; HTE, heavily treatment-experienced; IM, intramuscular; INSTI, integrase strand transfer inhibitor; IV, intravenous; mAb, monoclonal antibody; N/A, not applicable; NNRTI, non-nucleoside reverse transcriptase inhibitor; PrEP, pre-exposure prophylaxis; QM, monthly; Q2M, every 2 months; Q2W, every 2 weeks; Q6M, every 6 months; RPV, rilpivirine; SC, subcutaneous

Long-acting therapies for HIV-1 prevention or treatment are heterogenous in terms of therapeutic class, indication, use of oral lead-in, dosing frequency/route, and pharmacokinetic (PK) properties

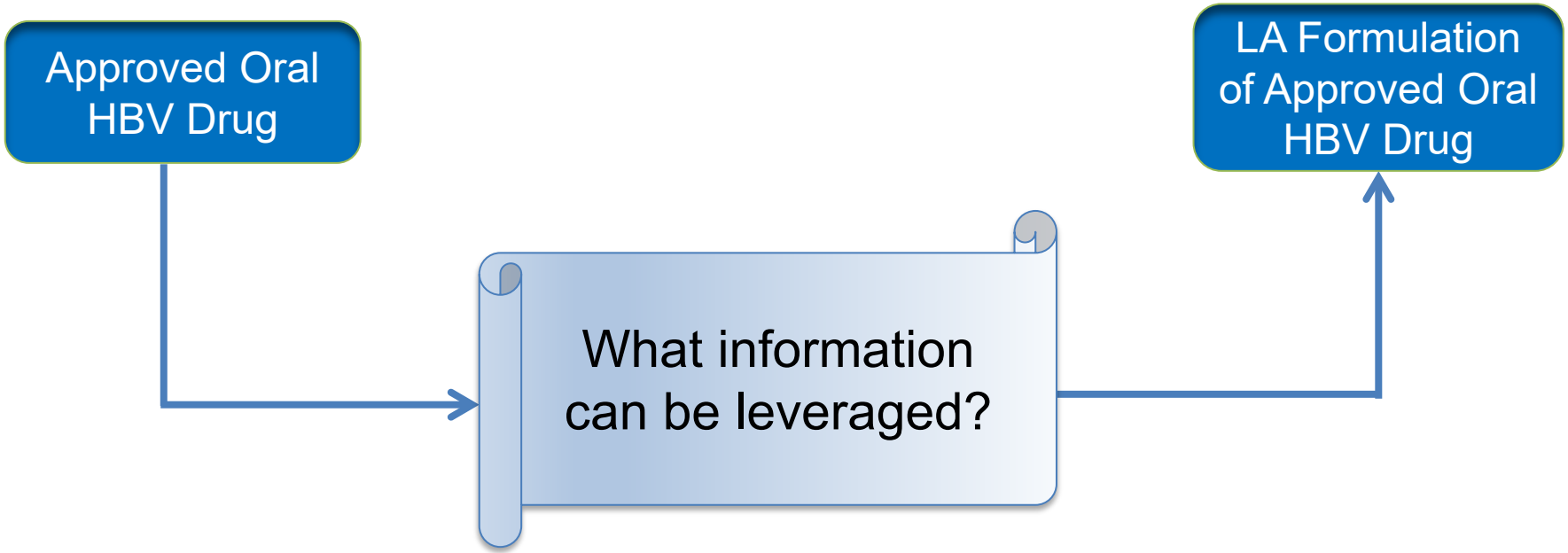
Clinical Development Scenarios

- LA Formulation of a Novel HBV Drug
- LA Formulation of an Approved Oral Drug (e.g., NrtI)
- LA Pro-Drug of an Approved Oral Drug (e.g., NrtI)

Development of Novel LA-HBV Drugs

- Generally similar drug development paradigm for LA-HBV products and immediate-release HBV drugs
  - Nonclinical virology data
  - Nonclinical pharm/tox data
  - Safety and PK data from single and multiple ascending dose trials to inform the selection of dosing regimen(s)
  - Proof-of-concept trial followed by Phase 2 and 3 trials
- Effect of intrinsic (e.g., hepatic and renal impairment) and extrinsic factors (e.g., drug-drug interactions) also assessed during development
- Application of Model-Informed Drug Development (MIDD) based quantitative tools and approaches
  - For optimization of the dosing regimen(s), and therapeutic individualization

LA Formulation of an Approved Oral HBV Drug



LA Formulation of an Approved Oral HBV Drug – Few Considerations

- Initial dosing regimen selection/dosing regimen optimization of the LA-HBV formulation
  - PK/PD/ADME data generated using the oral product can be leveraged using various quantitative methodologies
  - Available information regarding the effect of intrinsic and extrinsic factors on the PK of the drug can facilitate therapeutic individualization
- Comparison of systemic exposures of the drug after administration of LA-HBV formulation and approved oral HBV drug may support extrapolating efficacy
  - Efficacy data is needed if exposure-response information is not deemed supportive
- A full safety evaluation is likely needed unless scientific rationale to support additional safety data are not needed
  - Safety database depending on what is observed during Phase 1/2 trials and known safety profile of the oral drug

PD, Pharmacodynamic; ADME, Absorption, Distribution, Metabolism, and Excretion

LA Pro-Drug of an Approved Oral HBV Drug

- Development considerations are similar to the “novel formulation of an approved HBV drug” scenario
- Prior information regarding the effect of intrinsic and extrinsic factors on exposures can facilitate therapeutic individualization

Safety Considerations

- Safety risks inherent to LA formulations and mode of administration
  - e.g., injection site reactions for an injectable LA product
  - e.g., hypersensitivity reactions with monoclonal antibodies
  - e.g., possible extended exposure to sub-therapeutic levels
- Stringent safety measures during clinical development
  - e.g., enrollment criteria, sentinel dosing, close monitoring, stopping criteria
- Severe acute exacerbations of HBV infection may occur after discontinuation of LA therapy
  - Plans for managing participants who miss doses, discontinue treatment, or experience virologic breakthrough or relapse
- Close monitoring with both laboratory and clinical follow-up after discontinuation of anti-HBV therapy
  - Resumption of alternative anti-HBV therapy may be warranted

Potential Virology-Related Issues with LA HBV Therapies

- Suboptimal drug exposures leading to treatment-emergent resistance:
  - During treatment initiation (e.g., due to slow absorption)
  - During “PK tail” after treatment is discontinued or after missed doses
- Reduced efficacy of subsequent therapies (e.g., approved NrtIs) due to:
  - Cross-resistance
  - Antagonism of antiviral activity
  - Drug-drug interactions (DDIs)
- Baseline resistance due to virus/host polymorphisms, leading to non-response
- Mitochondrial toxicity (especially for NrtIs)

Desirable Properties of LA HBV Therapies

- Fast absorption, use of oral lead-in, or ability to initially combine with approved NrtIs
- High barrier to resistance and low likelihood of cross-resistance with approved NrtIs
- Lack of antagonism or significant DDIs with approved NrtIs, or ability to rapidly discontinue treatment
- Highly conserved target; broad activity against HBV genotypes and isolates
- Low potential for mitochondrial toxicity, or ability to rapidly discontinue treatment
- Aligned with patient preferences, high adherence

Virology Considerations for LA HBV Therapies

- Complete nonclinical virology study reports to support initial IND application
- Clinical virology analysis plan (or resistance monitoring plan) to be included with initial Phase 2 or Phase 3 protocols
- HBV genotyping (e.g., using sequencing or serology) performed at baseline and during virologic breakthrough; aim for representation of major HBV genotypes (A, C, B, D in U.S.) in pivotal trials
- For drugs that target host proteins, assess the role of factors such as sex, racial group, and target gene polymorphisms, haplotypes, or expression levels on efficacy

Summary

- LA-HBV drugs have the potential to transform global implementation of HBV treatment strategies
- Many similarities between small molecule development vs. new LA modalities
  - Typical drug development pathway similar to small molecules (Phase 1 - Phase 3)
- Development of LA-HBV products can be streamlined by strategically leveraging available data for oral HBV drugs
- New modalities may provide therapeutic options to address patient needs and preferences
- Efficient integration of multidisciplinary approaches, and collaborative engagement with all stakeholders has the potential to advance the development and availability of HBV therapeutics

Helpful Resources

For assistance with specific product development programs, sponsors are encouraged to communicate with the Division of Antivirals through the pre-IND consultation program

- See the Division of Antivirals Pre-IND Letter of Instruction webpage: https://www.fda.gov/drugs/pre-ind-consultation-program/division-anti-viral-dav-pre-ind-letter-instruction

For additional information, please refer to the FDA guidance documents:

- Chronic Hepatitis B Virus Infection: Developing Drugs for Treatment
- Antiviral Product Development-Conducting and Submitting Virology Studies to the Agency
- Submitting Next-Generation Sequencing Data to the Division of Antiviral Products

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