Target Product Profile and Regulatory Science Roadmap

From Targets to Clinical Candidates: Overview and Examples

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What is in an IND?

- FDA forms 1571, 1572, 3674
  - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4435682/
  - https://cersi.umd.edu/sites/cersi.umd.edu/files/S07%20-%2001%20CDER%20Milstein%20Lwin.pdf
- Mfgr. Letter of Authorization: CMC, pharmacology and toxicology
- Clinical protocol (usually Phase 1 safety, dose finding)
- Prior human experience (if available)
- Informed Consent
- Investigator Brochure

What are the strategy considerations?

(think through phase 2 and align preclinical development strategies with those goals)

- Preclinical strategy
  - Drug-like properties
  - Bioavailability, formulation and excipients
  - Reliable vs. misleading animal models
  - Scalable manufacturing
  - Reverse translational meta-analysis (retrospective – omics in the target patient populations)

What are the strategy considerations?

(think through phase 2 and align preclinical development strategies with those goals)

Pharmacology	Toxicity		Chemistry	Commercial
target(s) selectivity (RoT >10X)	acute toxicity		hydrophobicity	process scalability
target validity	chronic toxicity		hydrophilicity	quality systems
mechanism of action	on target toxicity		electrophilicity	cold chain requirements
mode of action	off target toxicity		lipophilicity	process optimization
off target therapeutic effects	metabolite on target toxicity		hydrolytic stability	steps in synthesis
therapeutic range	metabolite off target toxicity		polarity/dipolarity	catalytics/catalysts
prodrug activation	bioactivation/covalent modification		pKa	raw materials/precursor avail.
bioavailability	mitochondrial toxicity		redox stability	toxic byproduct
metabolic stability	cytotoxicity		counter ion for salts/acids	shelf life
BBB uptake permeability	genotoxicity	**none** @5-10 X	crystal lattice energy	purity thresholds
endocytosis permeability	mutagenicity	max. of	planar geometry	cost of goods- API
active uptake transporter permeability	teratogenicity	therapeutic	polar surface area	cost of goods- additives and delivery
paracellular permeability	carcinogenicity	window	conjugation optionality	trade dress
efflux permeability	nucleic acid alkylation		steric hindrance	side effects
passive diffusion permeability	gene induction		polymorphs	market channel
half life	respiratory toxicity		chiral purity	
liberation	reproductive toxicity		**Rules of thumb (RoT; heuristics)**	**Intellectual property-regulatory**
dissolution rate	hepatic toxicity		Lipinki's rules of 5	molecular novelty/chemical whitespace
formulation	glutathione depletion		Veber Rules	patent- composition of matter
route of administration	renal toxicity		Pardridge rules	patent- polymorphs
solubility	neurotoxicity		Rule of 3	patent- ionic/salt variants
absorption	cardiotoxicity		molar refractivity	patent- prodrugs, metabolites, precursors
transport pathways	hERG toxicity		number of atoms <70	patent- freedom to operate
food effect	arrythmogenic		chiral diversity/#stereoecenters	patent- label expansion optionality
intestinal permeability	GI toxicity		≤5(to 7) hydrogen bond donors	scope of patentability, patent enablement
distribution	myelotoxicity/immunotoxicity		≤9 (to 12) hydrogen bond acceptors	proprietary runway length
plasma protein binding	off target tissue uptake		MW <~500 Da	regulatory- data exclusivity optionality
V_d	LD50		LogP/LogD <5 @ pH 7.4	regulatory- orphan drug optionality
erythrocyte binding	genotype		≤4 rings	regulatory- biologic drug optionality
AUC	**Biologics**		≤10 rotatable bonds	regulatory- Hatch-Waxman optionality
target tissue uptake	immunogenicity		%F ≥ 30%	ethical sourcing of predicate materials
metabolism	proteolytic stability		Cl ≤ 30mL/min/kg in rats	off-label natural product optionality
first pass metabolism	thermodynamic stability		plasma protein binding ≤ 99 5%	pathway optionality
CYP pathways/occupancy	affinity/maturation		EC50/ED50/IC50≤1 μM to 100 nM	proprietary formulation
xenobiotic metabolism	target tissue uptake			proprietary glycoengineering
detoxification pathways	aggregates			proprietary precursors
hepatic uptake	specificity			proprietary production
hepatic efflux	heterotypic binding			
excretion	infusion requirements			
conjugation mechanism	half life/Cl			
biliary excretion	target localization			
tubular excretion	asparagine and aspartate stability			
reabsorption	pH dependent behaviors			
	source organism			

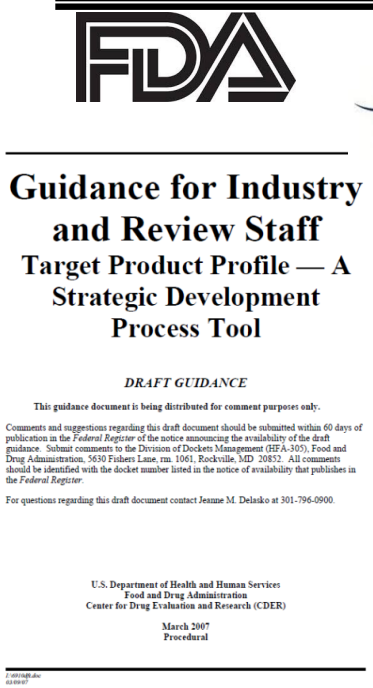
What are the strategy considerations?

(think through phase 2 and align preclinical development strategies with those goals)

- Clinical strategy
  - Right indication
    - Orphan-first strategy?
    - Label expansion strategy?
  - Right (approvable) endpoint
  - Line of sight to phase 2 efficacy
  - Right population- biomarkers and PGx
  - Competitive positioning
  - Size and duration of clinical trials

A few more examples

Failure- context of use



Guidance for Industry and Review Staff

Target Product Profile — A Strategic Development Process Tool

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Jeanne M. Delasko at 301-796-0900.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2007
Procedural

https://www.fda.gov/media/72566/download

GlobeImmune HCV vax shows promise in trial

Nov 4, 2010 7:06am

GlobeImmune's GI-5005, the company's investigational Tarmogen product, improved sustained virologic response by 12 percent in patients with genotype 1 chronic hepatitis C virus infection who had failed prior treatment with standard of care, according to data from a Phase IIb study. The data suggest GI-5005 may have the potential to be the first successful therapeutic vaccine for patients chronically infected with HCV.

"Only four to seven percent of patients with genotype 1 HCV who were null, poor or partial responders to their first course of pegylated interferon-based therapy would be expected to achieve a sustained virologic response with a second course of treatment," says Paul Pockros of the Scripps Clinic. "In this study, GI-5005 conferred a three-fold improvement in SVR, an important treatment effect in this challenging patient population."

The 2008 Fierce 15 winner received $40 million in May 2009 as part of a new partnership with Celgene, the *Boulder County Business Report* notes. The two companies said they would work jointly on multiple products to treat cancer. The company has about 40 employees. In January, GlobeImmune said it had closed on a round of financing for $18 million. However, over the summer, the company laid of 15 of its 60 employees--or 25 percent. "Basically we were adjusting the organization for what we are working on," CEO Timothy Rodell tells the *Daily Camera*. "It was a force

Indications and Usage • Dosage and Administration • Dosage Forms and Strengths • Contraindications • Warnings and Precautions • Adverse Reactions • Drug Interactions • Use in Specific Populations • Drug Abuse and Dependence • Overdosage • Description • Clinical Pharmacology • Nonclinical Toxicology • Clinical Studies • References • How Supplied/Storage and Handling • Patient Counseling Information

Failure- context of use

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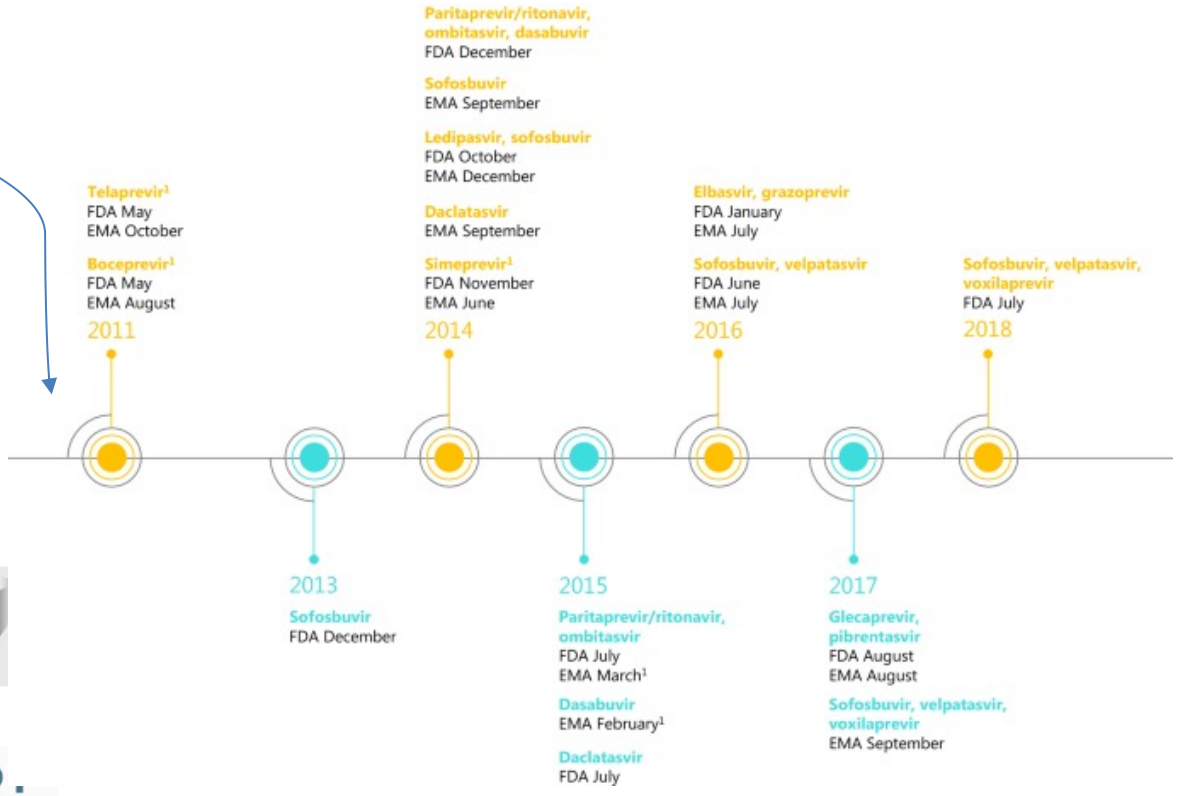
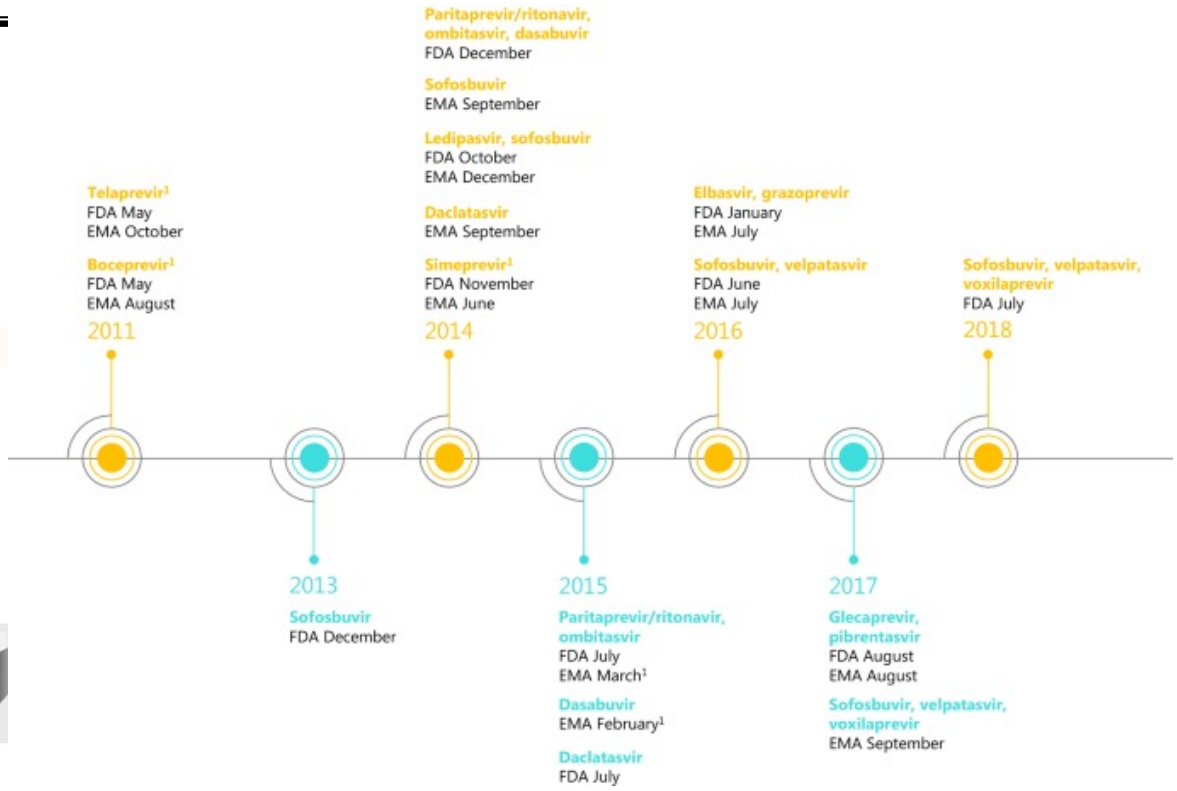
Direct Acting Antivirals



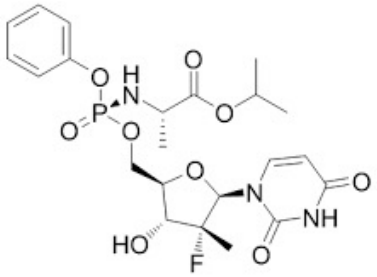
Failure- context of use

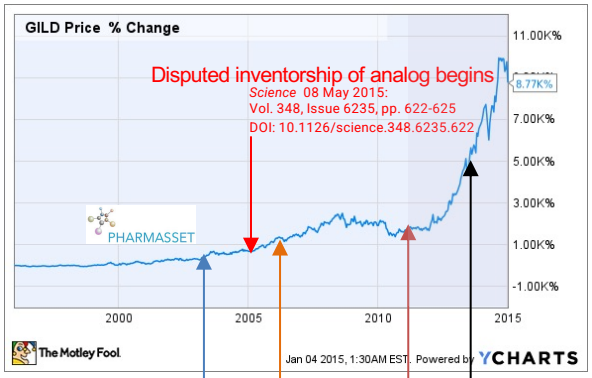
Direct Acting Antivirals



A Unicorn's story…

Sofosbuvir





Idenix PHARMACEUTICALS

Triangle Pharmaceuticals

Raymond F. Schinazi co-founds Pharmasset

Gilead buys Pharmasset for $137/share ($11.5B)

Pharmasset IPO at $9/share

Sofosbuvir approved

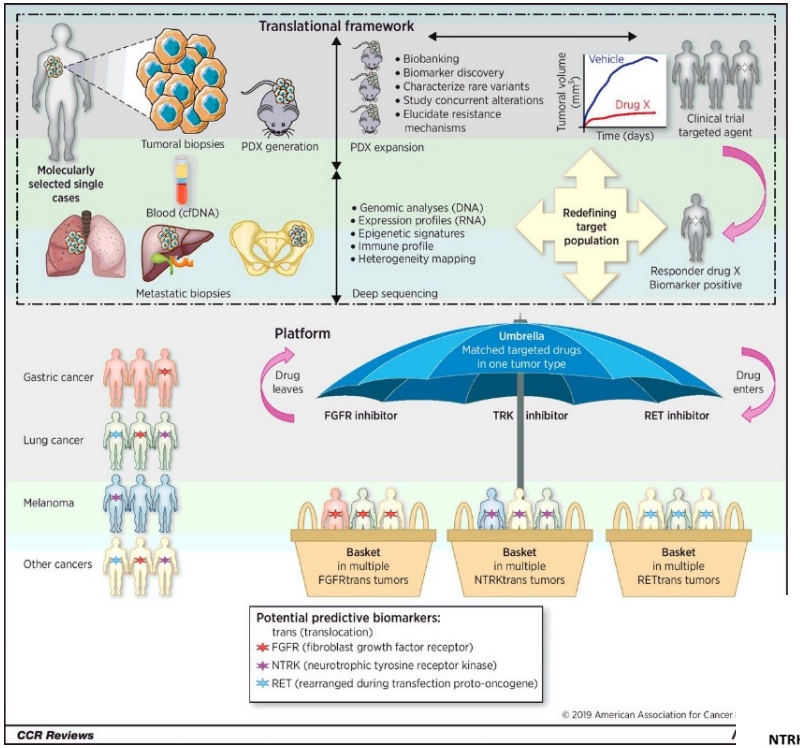
FDA

EMORY UNIVERSITY

PHARMASSET

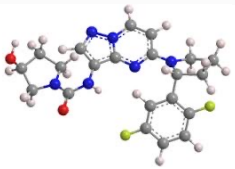
- **Raymond F. Schinazi designed the molecules that are standard of care for both HCV and HIV treatment**
- **Superfast timeline (relatively speaking)**
  - **Precursor molecule invented in 2005**
  - **sofosbuvir invented in 2007, IPO same year- raised $45 M**
  - **FDA approved in 2013**
  - **Fastest product launch in history of industry: 5% of the prevalent population treated within first year after FDA approval-**
- **60K HCV patients CURED**

Basket Trial



DOI: 10.1158/1078-0432.CCR-18-3694 Published June 2019

VITRAKVI (larotrectinib) 25-mg/100-mg CAPSULES 20-mg/mL ORAL SOLUTION



FDA approves larotrectinib for solid tumors with NTRK gene fusions

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On November 26, 2018, the Food and Drug Administration granted accelerated approval to larotrectinib (VITRAKVI, Loxo Oncology Inc. and Bayer) for adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, that are either metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment.

This is the second tissue-agnostic FDA approval for the treatment of cancer.

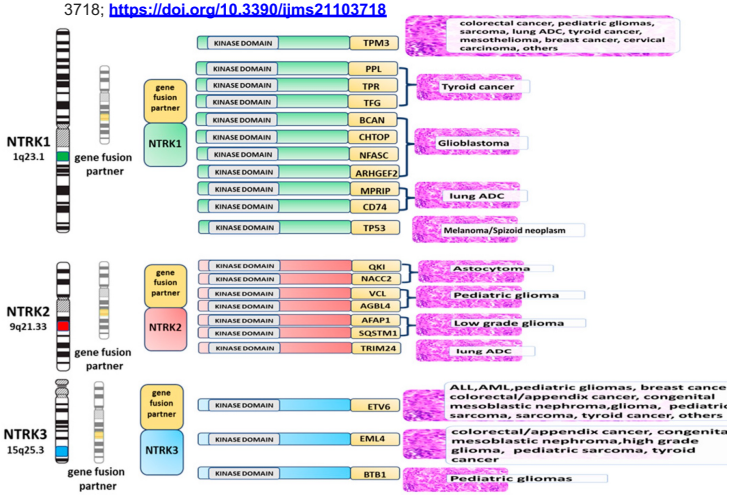
Approval was based on data from three multicenter, open-label, single-arm clinical trials: LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431). Identification of positive NTRK gene fusion status was prospectively determined in local laboratories using next generation sequencing (NGS) or fluorescence *in situ* hybridization (FISH). NTRK gene fusions were inferred in three pediatric patients with infantile fibrosarcoma who had a documented ETV6 translocation by FISH. The major efficacy outcome measures were overall response rate (ORR) and response duration, as determined by a blinded independent review committee according to RECIST 1.1.

Efficacy was evaluated in the first 55 patients with unresectable or metastatic solid tumors harboring an NTRK gene fusion enrolled across the three trials. All patients were required to have progressed following systemic therapy for their disease, if available, or would have

Content current as of: 12/14/2018

Regulated Product(s) Drugs

Marino et al. 2018; Int. J. Mol. Sci. **2020**, *21*(10), 3718; https://doi.org/10.3390/ijms21103718



Chapter 53

Precision medicine at the academic-industry interface

Patrick J. Silva[1,2] and Kenneth S. Ramos[1,2,3,4,5]

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Introduction

Precision medicine has emerged as a healthcare delivery platform that emphasizes the individualization of care, through the integration of novel technologies and approaches into the diagnosis, treatment, and clinical management of patients and populations. A major driver for this movement has been the sobering reality that healthcare, as we know it today, will not be sustainable long term, without approaches that help to augment diagnostic accuracy and precision, deliver targeted therapies that improve efficacy and decrease toxicity and help stratify populations into subpopulations.

The notion that precision medicine is not an inherently new approach must also be recognized, as differential diagnosis and blood typing for blood transfusions have been a cornerstone of medicine for over a century. A major facet of the current precision medicine evolution is the test-then-treat paradigm, where a biomarker (often a single molecule or a disease-related variant of a normal molecule), is measured or detected to inform decisions about the presence, absence, or scope of disease. The test-then-treat paradigm is not new, but the tools and throughput with which to test, coupled with novel therapeutics, have expanded exponentially in recent years. Higher content analytic assays and the expanding menu of drugs to target specific pathways have driven demand for clinically actionable decision rules and clinical guidelines, by which the biomedical industry makes investment and product development decisions.

The development of new decision rules largely happens at the academic-industry interface. Translational research in academic medical centers, supported by the private sector, is a cornerstone of the regulatory science, underlying the evolution of the regulatory pathways for new therapeutics, approved to objectively determine molecular defects instead of using the traditional pathological classifications of disease that have driven therapeutic marketing approvals of the FDA, EMEA, and other agencies.

Background

The completion of the Human Genome Project (HGP) in 2001 was a major milestone, which enabled precision medicine with the tools of high-throughput analytics [1]. The reference genome sequence resulting from the HGP provided insights on the *structure* of the genome but was not revealing of *function*, particularly in disease processes. The cost of the project has been estimated at $2.7 billion [2]. By the mid-2000s, it was practical to objectively measure changes in gene expression, and differences in genome sequences of diseased individuals, relative to the reference genome or healthy individuals. There were still major hurdles to leveraging genome sequences and expression profiles in clinical decision-making: (1) the cost of sequencing a genome was orders of magnitude in excess,

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b Dr. Ramos is currently Professor of Medicine, Texas A&M College of Medicine, Houston TX, Center for Genomic and Precision Medicine, Adjunct Chair of Medical Genetics Houston TX, Executive Director, Texas A&M Institute of Biosciences and Technology Houston TX, Associate Vice President for Research, Texas A&M University Health Science Center College Station, TX, Assistant Vice Chancellor for Health Services, The Texas A&M University System, College Station TX and Professor of Medicine at University of Arizona Health Sciences, Tucson AZ. He maintained an academic appointment at University of Arizona.

Resources

- FDA guidance documents, specifically Target Product Profile (TPP) https://www.nature.com/articles/nrd.2016.264 https://www.fda.gov/media/72566/download
- Advisors experienced in drug development (TMC Accelerator for Cancer Therapeutics)
- Review a clinical trial for a comparable drug and/or the indication of interest on Clinicaltrials.gov
- Review the label of a comparable drug
- …& and collaborate with the GCC Faculty!!