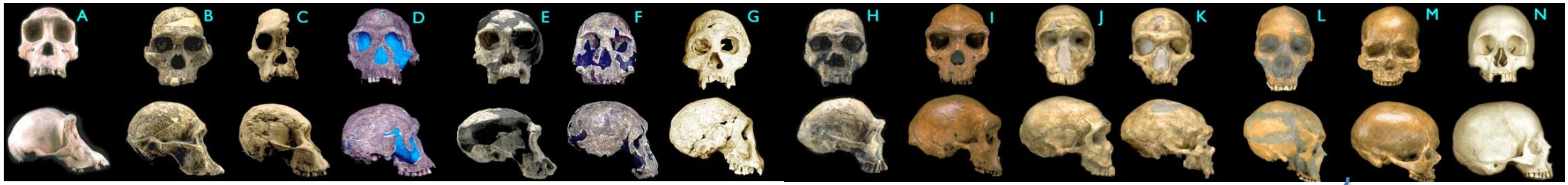
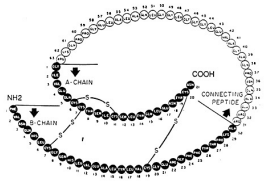
Evolution of Precision Medicines from a Regulatory Perspective

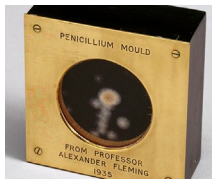
ASCPT Annual Meeting
March 15, 2019

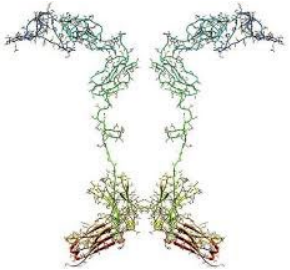
Mike Pacanowski
Office of Clinical Pharmacology
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

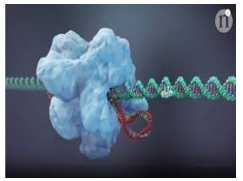
A Brief History of Medicines

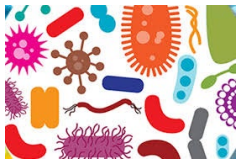


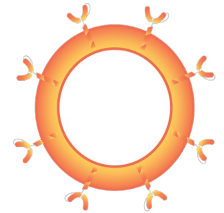




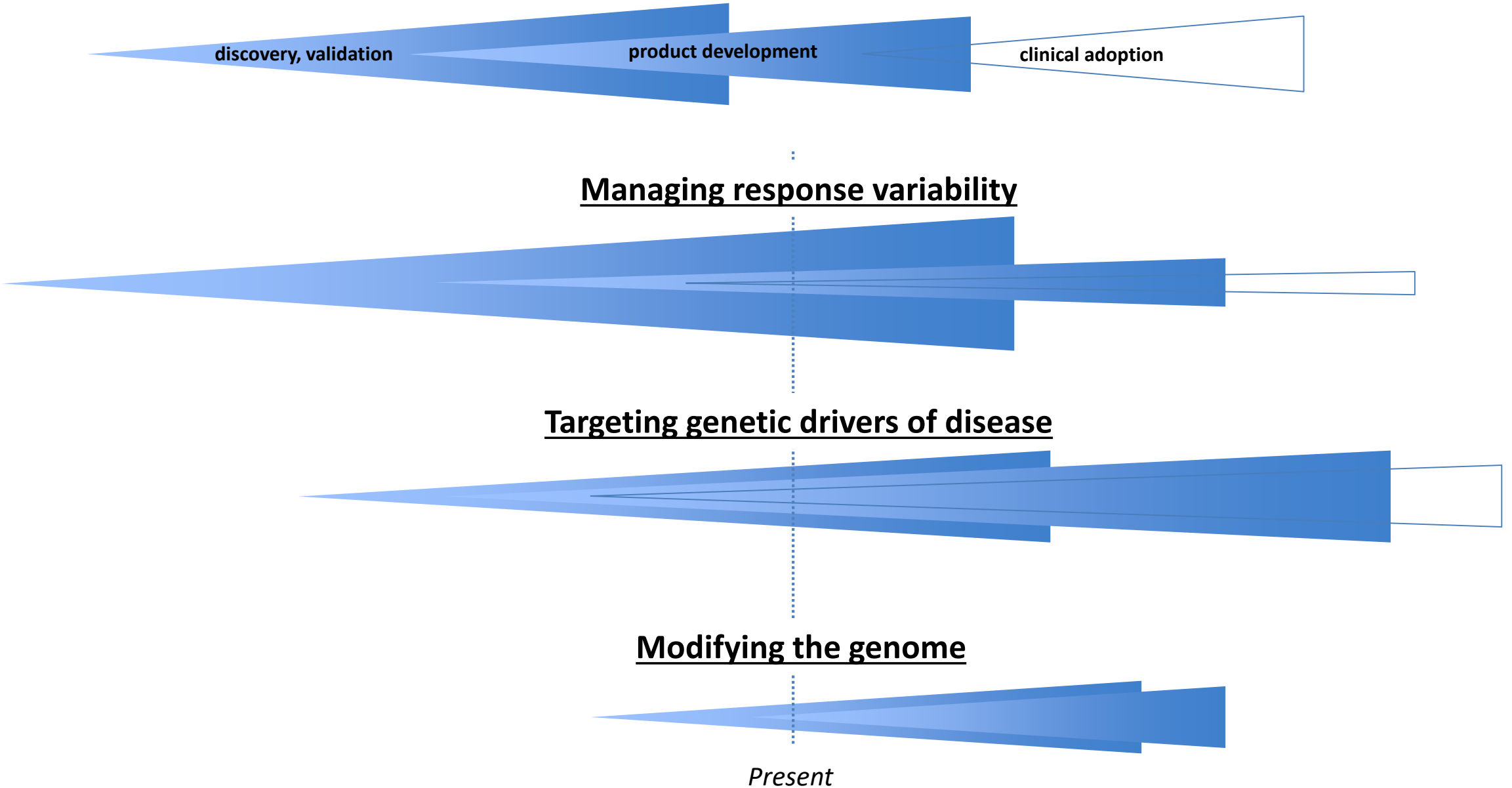




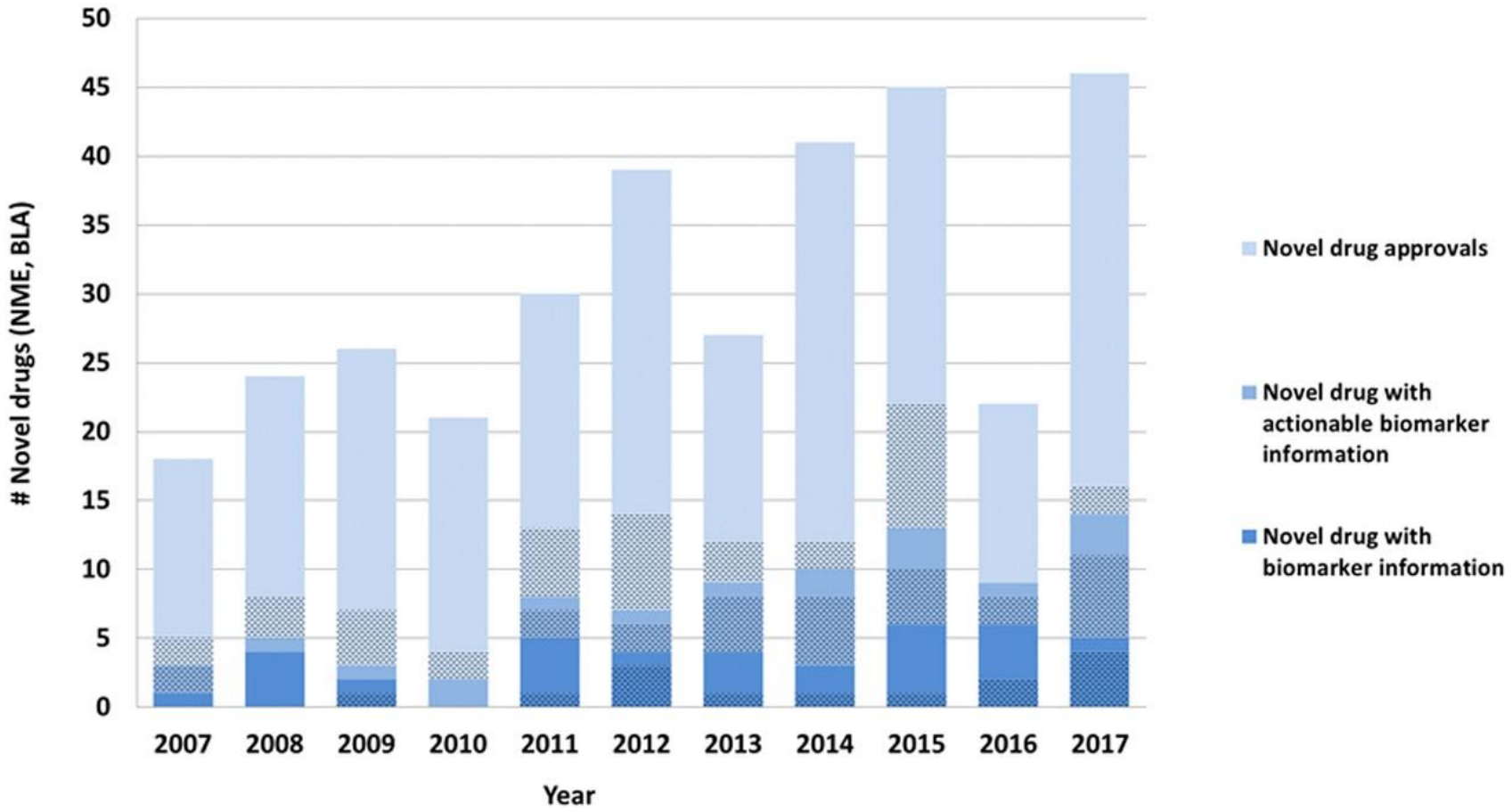




Past, Present, and Future of Precision Medicine



Labeling for New Drugs



Actionable biomarker: labeling includes a specific prescribing recommendation that is included in one of the following label sections: 1)Boxed Warning, 2) Indications and Usage, 3) Dosage and Administration, 4) Contraindications, or 4) Warnings and Precautions. Biomarkers may be any genomic biomarker or other selected protein biomarker that are used for patient selection.

PMID: 30175278

Notable CDER Approvals 2018

(Total Novel Drug N=59)

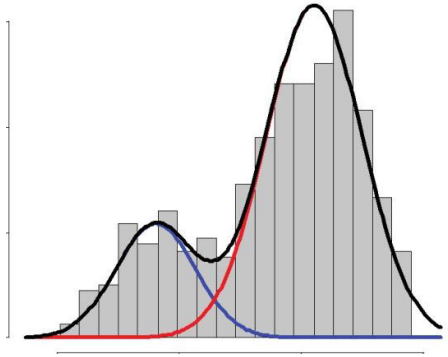
Drug	Disease or Condition	Biomarker	Use
Patisiran*, Inotersen*	Polyneuropathy of hereditary transthyretin-mediated amyloidosis	**N/A**	N/A
Tezacaftor* + ivacaftor	Cystic fibrosis	**Responsive CFTR variant**	Patient Selection
Migalastat*	Fabry disease	**Amenable GLA variant**	Patient Selection
Ivosidenib*	Relapsed or refractory AML	**Susceptible IDH1 mutation**	Patient Selection
Binimetinib*, encorafenib*	Metastatic melanoma	**BRAF V600E/K mutation**	Patient Selection
Dacomitinib*	Metastatic NSCLC	**EGFR exon 19 deletion or L858R**	Patient Selection
Larotrectinib*	Solid tumors	**NTRK gene fusion**	Patient Selection
Gileritinib*	Relapsed or refractory AML	**FLT3 mutation**	Patient Selection
Lorlatinib*	Metastatic NSCLC	**ALK gene rearrangement**	Patient Selection
Talazoparib*	Advanced or metastatic breast cancer	**Germline BRCA mutation**	Patient Selection
Afatinib	Metastatic NSCLC	**Non-resistant EGFR mutation**	Patient Selection
Amifampridine*	Lambert-Eaton myasthenic syndrome	**NAT2 genotype**	Dosing
6-MP/TG/AZA	ALL/acute nonlymphocytic leukemia	**TPMT/NUDT15 genotype**	Dosing
Avatrombopag*	Thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure	**FVL**	Warning
Lofexidene*	Opioid withdrawal symptoms	**CYP2D6 genotype**	Informational
Elagolix*	Severe pain associated with endometriosis	**SLCO1B1 genotype**	Informational

* New molecular entity

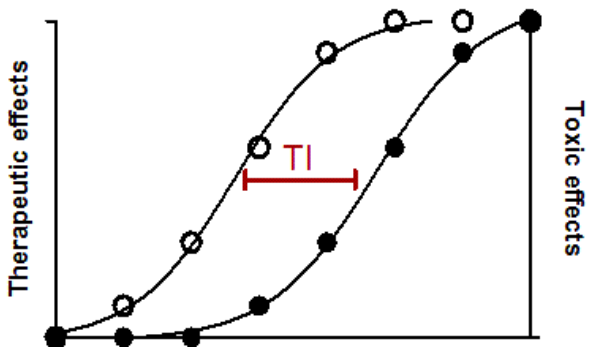
U.S. FOOD & DRUG ADMINISTRATION

Managing Response Variability

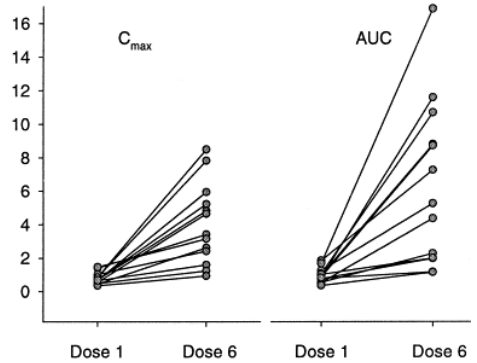
Managing Response Variability



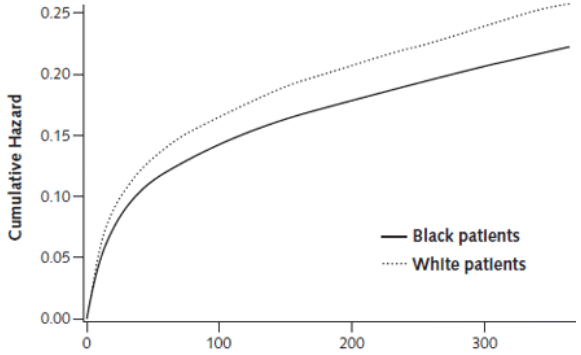
Multimodal PK



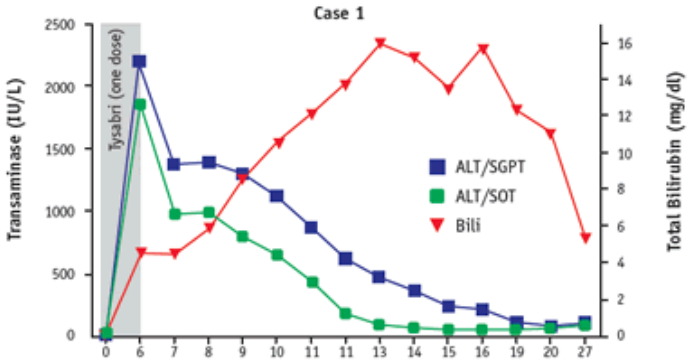
NTI



High Variability



Race Effects



Safety

For more information see: Guidance for Industry - Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM337169.pdf

Guidance for Industry

Pharmacogenomic Data Submissions

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

March 2005
Procedural

OMB Control Number 0910-0557
Expiration Date: 05/31/2014
See additional PRA statement in section VIII of this guidance
(Note: PRA information added 07/29/2011)

Guidance for Industry and FDA Staff

Pharmacogenetic Tests and Genetic Tests for Heritable Markers

Document issued on: June 19, 2007

The draft of this guidance was issued on February 9, 2006

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research

Guidance for Industry

Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

January 2013

Clinical Pharmacology
Clinical/Medical

10300fnl.doc

SMG 9120

FDA STAFF MANUAL GUIDES, VOLUME IV - AGENCY PROGRAM DIRECTIVES

BUSINESS PRACTICES AND AGREEMENTS

INTERCENTER COORDINATION OF CROSS-LABELING ACTIVITIES FOR APPROVED DRUGS/BIOLOGICS AND IN VITRO DIAGNOSTICS

Effective Date: 04/19/2013

1. PURPOSE AND SCOPE

This staff manual guide (SMG) provides procedures for FDA staff when a Center is considering or carrying out changes to an already approved drug/biologic product labeling to include an in vitro diagnostic (IVD) test recommendation or requirement, or when an IVD is submitted for clearance or approval with an intended use that could affect an approved drug/biologic product's use in practice.

This SMG is applicable to IVD products and drugs or biological products. Under this SMG, labeling changes of relevance are those that have the potential to impact products reviewed in more than one Center within the Agency.

This SMG does not apply to pre-market review processes for drug/biologic products co-developed with a companion diagnostic.

2. BACKGROUND

IVD tests can provide useful information to guide the selection, dosing, therapeutic monitoring, and/or toxicity management of a drug/biologic. As new

Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

Guidance for Industry

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

December 2016
Labeling

E18 Genomic Sampling and Management of Genomic Data

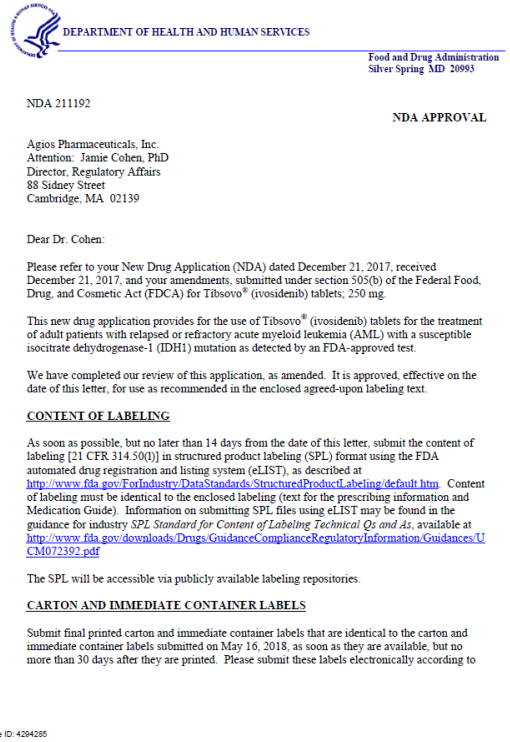
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiological Health (CDRH)
Center for Biologics Evaluation and Research (CBER)

March 2018
ICH

Characterizing Genetic Effects on Response Post-Approval

- Ivosidenib was approved for the treatment of relapsed or refractory AML with a susceptible IDH1 mutation
- Patients with more co-occurring mutations tended to have lower response rates



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 211192

NDA APPROVAL

Agios Pharmaceuticals, Inc.
Attention: Jamie Cohen, PhD
Director, Regulatory Affairs
88 Sidney Street
Cambridge, MA 02139

Dear Dr. Cohen:

Please refer to your New Drug Application (NDA) dated December 21, 2017, received December 21, 2017, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tibsovo® (ivosidenib) tablets; 250 mg.

This new drug application provides for the use of Tibsovo® (ivosidenib) tablets for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the prescribing information and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

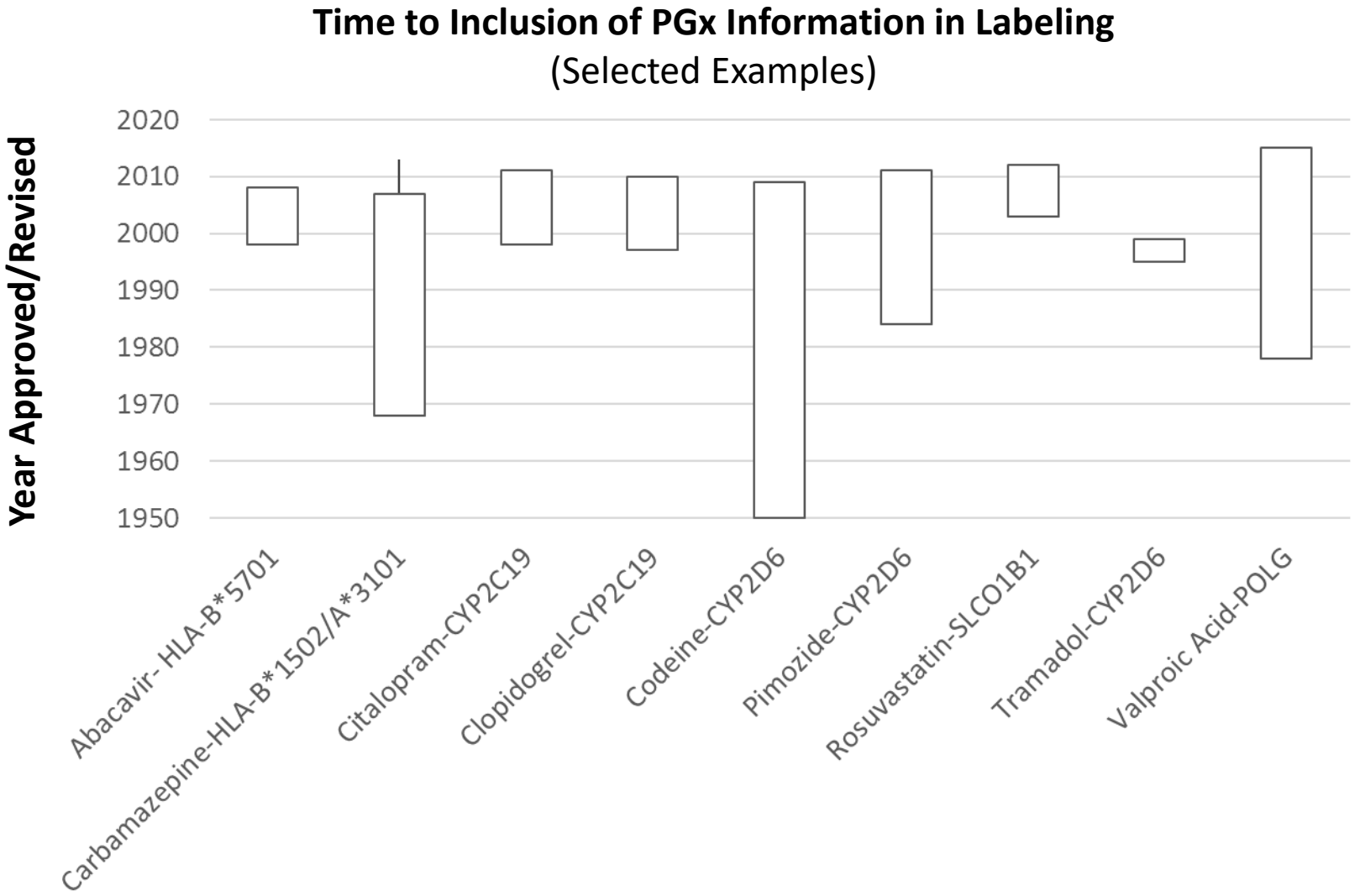
Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on May 16, 2018, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to

Reference ID: 4294285

PMR 3444-1 Characterize the long-term safety of ivosidenib in patients with relapsed or refractory acute myeloid leukemia (AML). Submit the final study report and data set with 3 years of follow-up from ongoing Study AG120-C-001, *A Phase 1, Multicenter, Open-Label, Dose-Escalation and Expansion, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-120 in Subjects with Advanced Hematologic Malignancies with an IDH1 Mutation*. Include data from approximately 205 patients with relapsed or refractory AML.

Include in the final study report the exploratory subgroup analyses and corresponding subject level data related to pre- and post-treatment cytogenetics, specific IDH1 mutations, and mutation analyses for other genes as obtained under the trial protocol.

Incorporating Pharmacogenomic Markers into Prescribing Recommendations in the Post-Marketing Setting



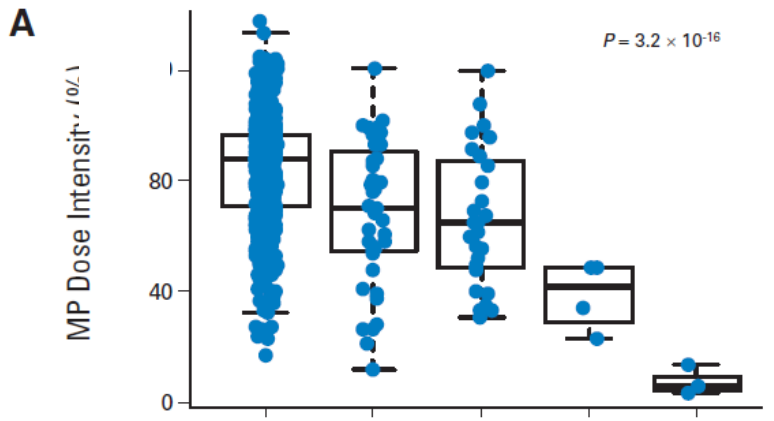
Incremental Enhancements to Improve Benefit-Risk

VOLUME 33 · NUMBER 11 · APRIL 10 2015

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Inherited *NUDT15* Variant Is a Genetic Determinant of Mercaptopurine Intolerance in Children With Acute Lymphoblastic Leukemia

Jun J. Yang, Wendy Landier, Wenjian Yang, Chengcheng Liu, Lindsey Hageman, Cheng Cheng, Deqing Pei, Yanjun Chen, Kristine R. Crews, Nancy Kornegay, F. Lennie Wong, William E. Evans, Ching-Hon Pui, Smita Bhatia, and Mary V. Relling



TPMT / *NUDT15*	WT / WT	HET / WT	WT / HET	HET / HET	HOM for either
Genetic Risk Score	0	1	1	2	2
n =	589	40	27	4	3
Median (%)	87.7	70.0	65.1	41.5	6.0
25th percentile (%)	70.8	54.4	48.9	31.6	4.5
75th percentile (%)	96.7	90.7	87.1	48.6	9.7

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205919/S-003

SUPPLEMENT APPROVAL

Nova Laboratories Limited
c/o Rare Disease Therapeutics, Inc.
Attention: Michelle Taylor
Vice President, Regulatory Affairs and Quality Assurance
12975 Brookprinter Place, Suite 170
Poway, CA 92064

Dear Ms. Taylor:

Incremental Enhancements to Improve Benefit-Risk

2.2 Dosage in Patients with TPMT and/or NUDT15 Deficiency

Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities or repeated episodes of myelosuppression *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.5)]*.

Homozygous deficiency in either TPMT or NUDT15

Patients with homozygous deficiency of either enzyme typically require 10% or less of the standard PURIXAN dosage. Reduce initial dosage in patients who are known to have homozygous TPMT or NUDT15 deficiency.

Heterozygous deficiency in TPMT and/or NUDT15

Reduce the PURIXAN dosage based on tolerability. Most patients with heterozygous TPMT or NUDT15 deficiency tolerate recommended mercaptopurine doses, but some require dose reduction based on toxicities. Patients who are heterozygous for both TPMT and NUDT15 may require more substantial dosage reductions.

5 WARNINGS AND PRECAUTIONS

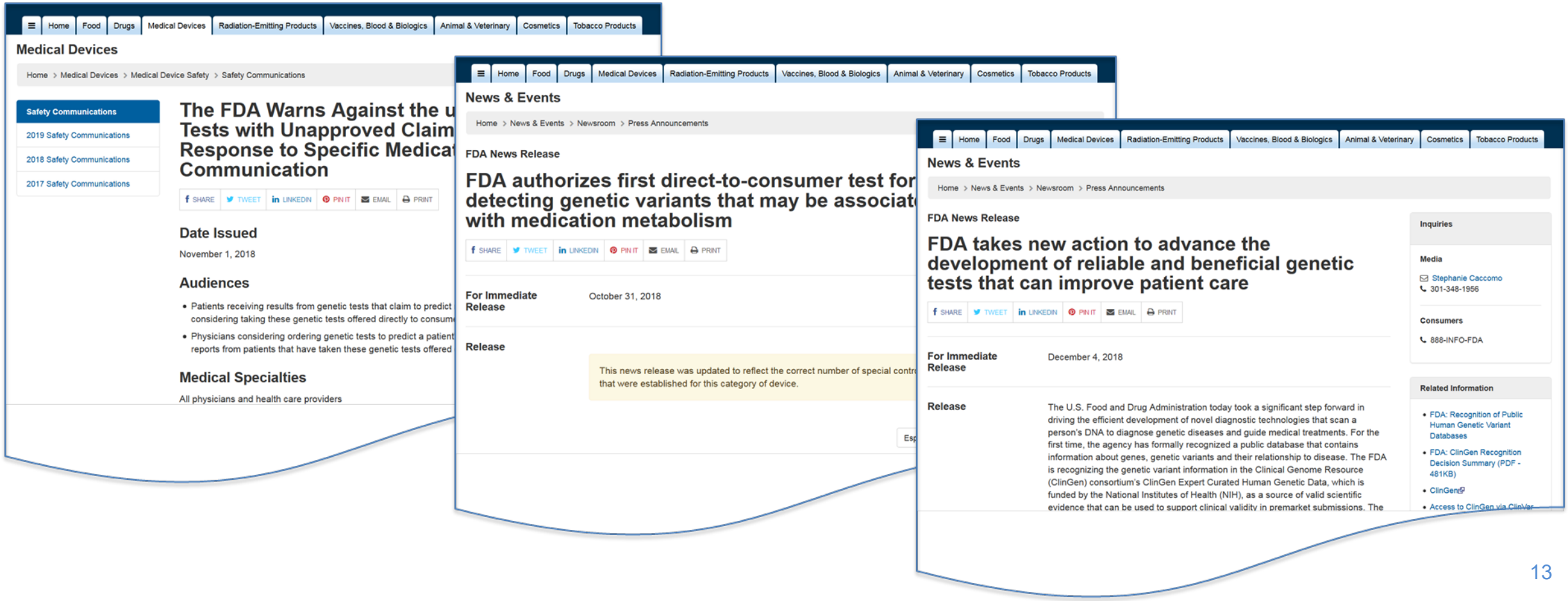
5.1 Myelosuppression

The most consistent, dose-related toxicity of PURIXAN is bone marrow suppression, manifested by anemia, leukopenia, thrombocytopenia, or any combination of these. Monitor CBC and adjust the dose of PURIXAN for severe neutropenia and thrombocytopenia.

Evaluate patients with repeated severe myelosuppression for thiopurine S-methyltransferase (TPMT) or nucleotide diphosphatase (NUDT15) deficiency. TPMT genotyping or phenotyping (red blood cell TPMT activity) and NUDT15 genotyping can identify patients who have reduced activity of these enzymes. Patients with homozygous TPMT or NUDT15 deficiency require substantial dosage reductions of PURIXAN *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.5)]*.

Pharmacogenetic Testing

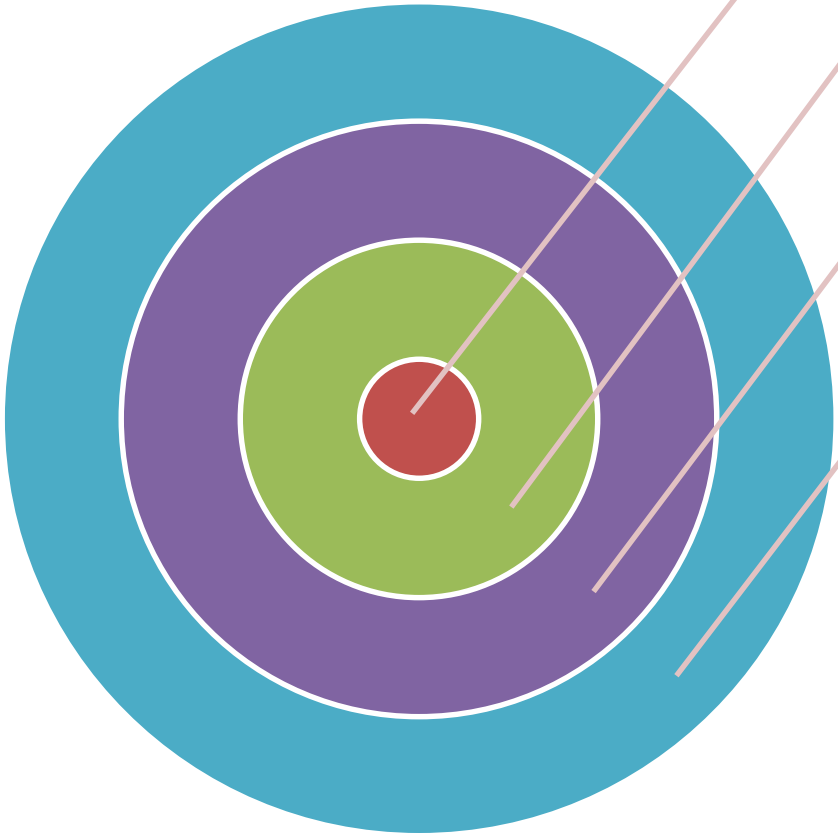
Goals: Reliable tests, resources to support clinical validation and interpretation of results



U.S. FOOD & DRUG ADMINISTRATION

Genetically Targeted Therapies

Molecular Enrichment Approaches



Evaluate a single molecular alteration

Evaluate each alteration in separate trials

Group similar alterations for single trial

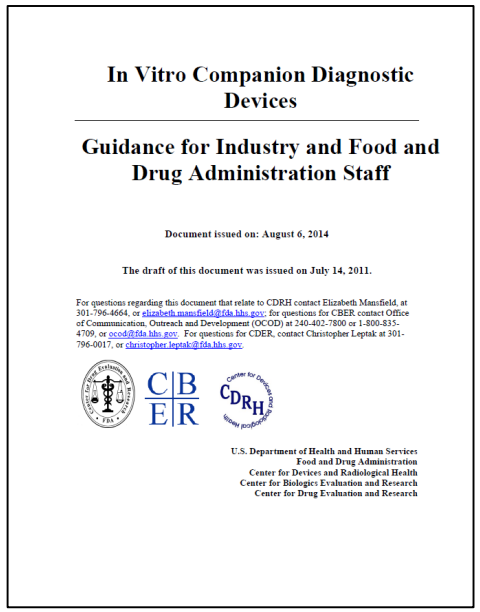
Enroll all patients with clinical disease

Highly enriched trial design

- Highly targeted drug
- Minimal molecular heterogeneity in disease

Less enriched trial design

- Less targeted drug
- All or most molecular alterations expected to respond



In Vitro Companion Diagnostic Devices

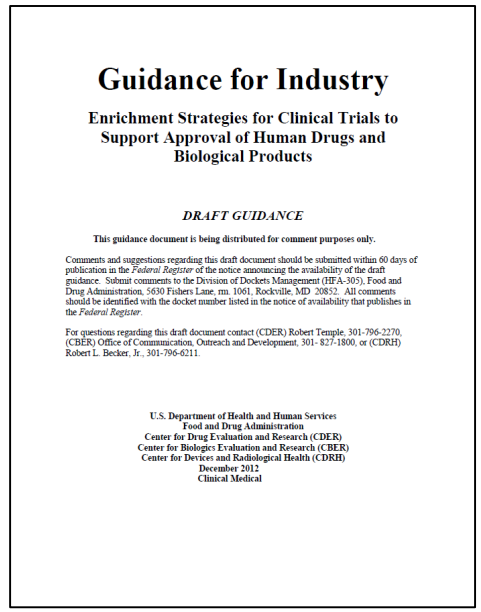
Guidance for Industry and Food and Drug Administration Staff

Document issued on: August 6, 2014

The draft of this document was issued on July 14, 2011.

For questions regarding this document that relate to CDRH contact Elizabeth Mansfield, at 301-796-4664, or elizabeth.mansfield@fda.hhs.gov; for questions for CBER contact Office of Communication, Outreach and Development (OCOD) at 240-402-7800 or 1-800-835-4709, or ocod@fda.hhs.gov. For questions for CDER, contact Christopher Leptak at 301-796-0017, or christopher.leptak@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research



Guidance for Industry

Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

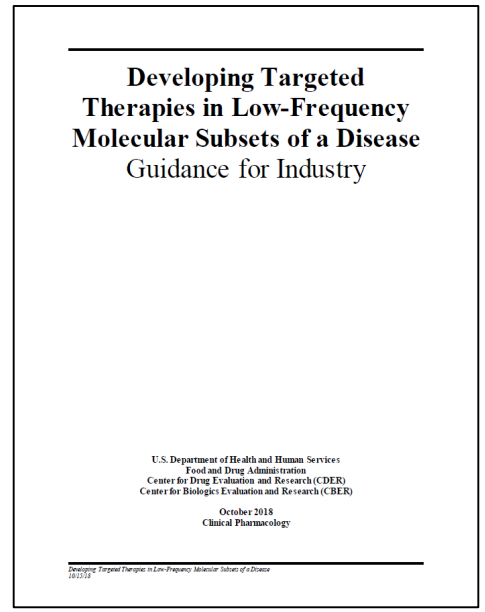
DRAFT GUIDANCE

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 (CDER) Robert Temple, 301-796-2270, (CBER) Office of Communication, Outreach and Development, 301- 827-1800, or (CDRH) Robert L. Becker, Jr., 301-796-6211.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
December 2012
Clinical Medical

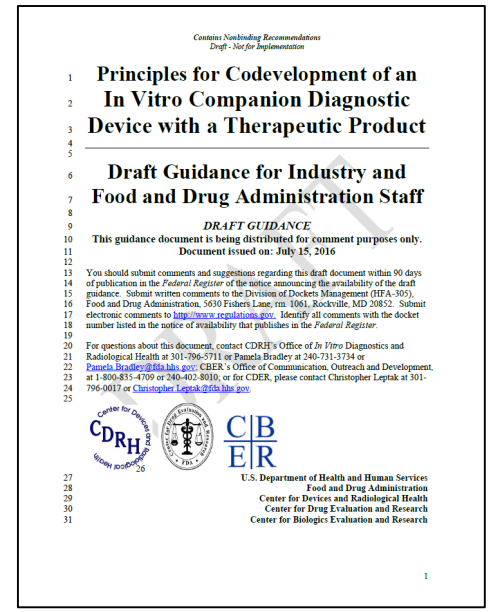


Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease

Guidance for Industry

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

October 2018
Clinical Pharmacology



Contains Nonbinding Recommendations
Draft – Not for Implementation

Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product

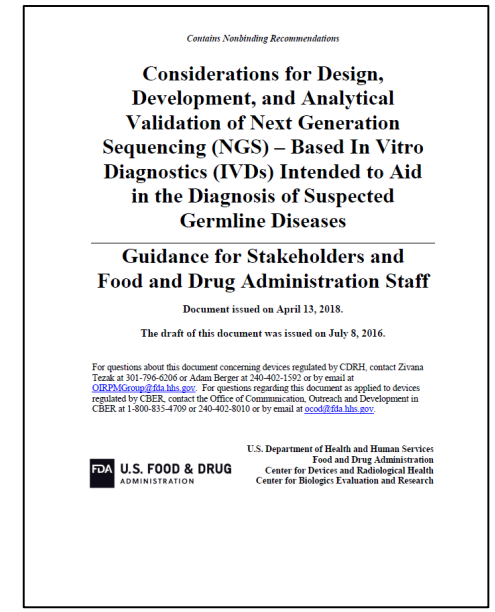
Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE
This guidance document is being distributed for comment purposes only.
Document issued on: July 15, 2016

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document, contact CDRH's Office of *In Vitro* Diagnostics and Radiological Health at 301-796-5711 or Pamela Bradley at 240-731-3734 or Pamela.Bradley@fda.hhs.gov; CBER's Office of Communication, Outreach and Development, at 1-800-835-4709 or 240-402-8010; or for CDER, please contact Christopher Leptak at 301-796-0017 or Christopher.Leptak@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research



Contains Nonbinding Recommendations

Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS) – Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases

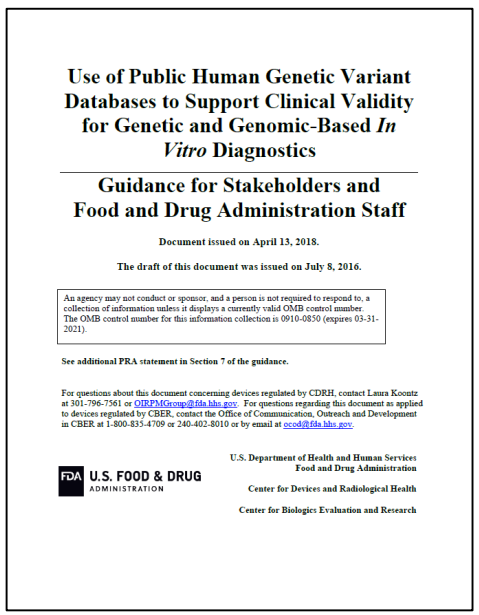
Guidance for Stakeholders and Food and Drug Administration Staff

Document issued on April 13, 2018.

The draft of this document was issued on July 8, 2016.

For questions about this document concerning devices regulated by CDRH, contact Zivana Tezak at 301-796-6206 or Adam Berger at 240-402-1592 or by email at OIRPMGroup@fda.hhs.gov. For questions regarding this document as applied to devices regulated by CBER, contact the Office of Communication, Outreach and Development in CBER at 1-800-835-4709 or 240-402-8010 or by email at ocod@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research



Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based *In Vitro* Diagnostics

Guidance for Stakeholders and Food and Drug Administration Staff

Document issued on April 13, 2018.

The draft of this document was issued on July 8, 2016.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0850 (expires 03-31-2021).

See additional PRA statement in Section 7 of the guidance.

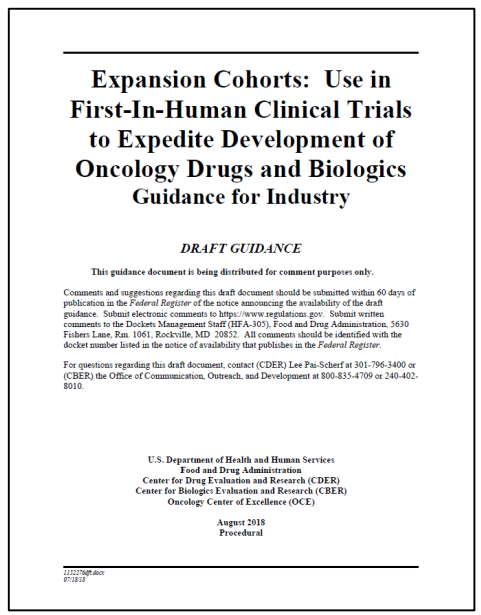
For questions about this document concerning devices regulated by CDRH, contact Laura Koontz at 301-796-7561 or OIRPMGroup@fda.hhs.gov. For questions regarding this document as applied to devices regulated by CBER, contact the Office of Communication, Outreach and Development in CBER at 1-800-835-4709 or 240-402-8010 or by email at ocod@fda.hhs.gov.

U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research



Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

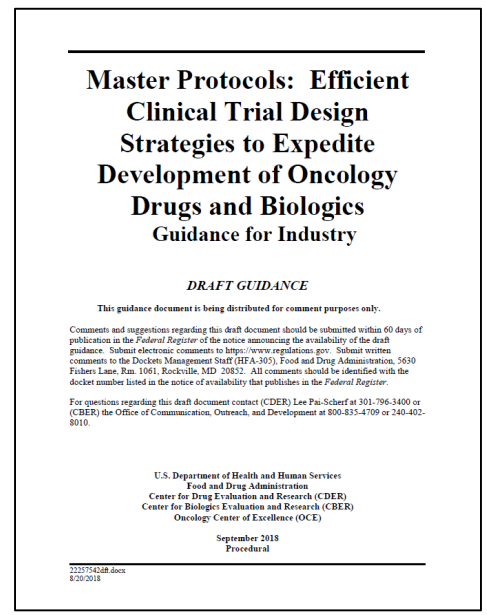
This guidance document is being distributed for comment purposes only.

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 electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (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 (CDER) Lee Pai-Scherf at 301-796-3400 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

August 2018
Procedural



Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics

Guidance for Industry

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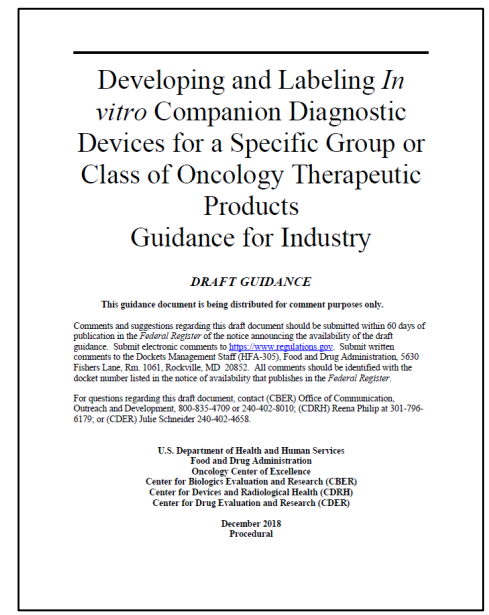
Oncology Center of Excellence (OCE)

September 2018
Procedural



Developing and Labeling *In vitro* Companion Diagnostic Devices for a Specific Group or Class of Oncology Therapeutic Products

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Center for Drug Evaluation and Research (CDER)

December 2018
Procedural

Migalastat

- Fabry disease is a rare X-linked disease caused by hundreds of different mutations in the gene encoding alpha-galactosidase A (aGalA), *GLA*
- Migalastat is a small molecule chaperone that binds aGalA, allowing it to traffic to lysosomes to break down glycosphingolipids
- Patients with "amenable" variants, based on in vitro response in a HEK-293 cell system, were enrolled in clinical trials

→ *Indicated for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene (GLA) variant based on in vitro assay data*

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

In Vitro Amenability Assay

In an in vitro assay (HEK-293 assay), Human Embryonic Kidney (HEK-293) cell lines were transfected with specific *GLA* variants (mutations) which produced mutant alpha-Gal A proteins. In the transfected cells, amenability of the *GLA* variants was assessed after a 5-day incubation with 10 micromol/L migalastat. A *GLA* variant was categorized as amenable if the resultant mutant alpha-Gal A activity (measured in the cell lysates) met two criteria: 1) it showed a relative increase of at least 20% compared to the pre-treatment alpha-Gal A activity, and 2) it showed an absolute increase of at least 3% of the wild-type (normal) alpha-Gal A activity.

The in vitro assay did not evaluate trafficking of the mutant alpha-Gal A proteins into the lysosome or the dissociation of migalastat from the mutant alpha-Gal A proteins within the lysosome. Also, the in vitro assay did not test whether a *GLA* variant causes Fabry disease or not.

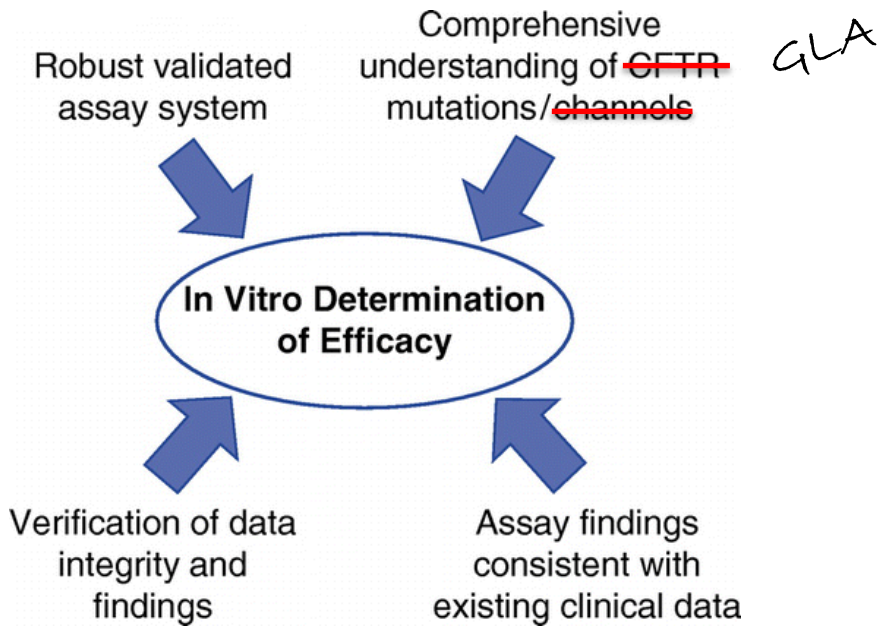
The *GLA* variants which are amenable to treatment with GALAFOLD, based on the in vitro assay data, are shown in Table 2. Inclusion of *GLA* variants in this table does not reflect interpretation of their clinical significance in Fabry disease. Whether a certain amenable *GLA* variant in a patient with Fabry disease is disease-causing or not should be determined by the prescribing physician (in consultation with a clinical genetics professional, if needed) prior to treatment initiation. Consultation with a clinical genetics professional is strongly recommended in cases where the amenable *GLA* variant is of uncertain clinical significance (VUS, variant of uncertain significance) or may be benign (not causing Fabry disease).

Table 2: Amenable *GLA* Variants Based on the In Vitro Assay

DNA Change (Long)	DNA Change (Short)	Protein Change (1-letter Code)	Protein Change (3-letter Code)
c.7C>G	c.C7G	p.(L3V)	p.(Leu3Val)
c.8T>C	c.T8C	p.(L3P)	p.(Leu3Pro)
c.[11G>T; 620A>C]	c.G11T/A620C	p.(R4M/Y207S)	p.(Arg4Met/Tyr207Ser)
c.37G>A	c.G37A	p.(A13T)	p.(Ala13Thr)
c.37G>C	c.G37C	p.(A13P)	p.(Ala13Pro)
c.43G>A	c.G43A	p.(A15T)	p.(Ala15Thr)

. . .

Migalastat



- *Are the consequences of individual mutations sufficiently well understood?*
- *Dose the in vitro assay directly measure the function of the human protein affected by the disease?*
- *Is the drug's mechanism well-understood and consistent with the mechanism of disease?*
- *Are clinical data from both drug-responsive and -nonresponsive mutations available?*
- *Has the assay been formally validated?*
- *Are raw instrument data available so that results can be recreated?*

Weaver (DARS); Durmowicz, et al. Ann Am Thorac Soc 2018.

Tissue Agnostic Drug Development

- Traditional cancer drug development paradigm
  - Based on tumor type, e.g.,
    - Previously untreated pancreatic cancer
    - HCC after previous sorafenib treatment
  - Based on a biomarker within a tumor type, e.g.,
    - HER-2 positive breast or gastric cancer
    - RAS wild-type colorectal cancer

The NEW ENGLAND JOURNAL of MEDICINE

First FDA Approval Agnostic of Cancer Site — When a Biomarker Defines the Indication

Steven Lemery, M.D., M.H.S., Patricia Keegan, M.D., and Richard Pazdur, M.D.

Lemery, et al. NEJM 2017

Larotrectinib

- Tropomysin receptor kinase inhibitor
- Antitumor activity in cells with constitutive activation of TRK proteins resulting from gene fusions
- Efficacy based on data from patients with NTRK1/2/3 gene fusions enrolled in three single-arm trials
- Indicated for adults and children with solid tumors that have NTRK gene fusion (without known acquired resistance mutation), are metastatic/nonresectable, have no alternative

Tumor Site

	N	ORR
Soft tissue sarcoma	11	91%
Salivary gland	12	83%
Infantile fibrosarcoma	7	100%
Thyroid	5	100%
Lung	4	75%
Melanoma	4	50%
Colon	4	25%
GIST	3	100%
Cholangiocarcinoma	2	SD, NE
Appendix	1	SD
Breast	1	PD
Pancreas	1	SD

Fusion Partner

	N	ORR
ETV6-NTRK3	25	84%
TPM3-NTRK1	9	56%
LMNA-NTRK1	5	40%
Inferred ETV6-NTRK3	3	100%
IRF2BP2-NTRK1	2	CR, PR
SQSTM1-NTRK1	2	PR, PR
PDE4DIP-NTRK1	1	PR
PPL-NTRK1	1	CR
STRN-NTRK2	1	PR
TPM4-NTRK3	1	CR
TPR-NTRK1	1	PR
TRIM63-NTRK1	1	PR
CTRC-NTRK1	1	SD
GON4L-NTRK1	1	NE
PLEKHA6-NTRK1	1	SD

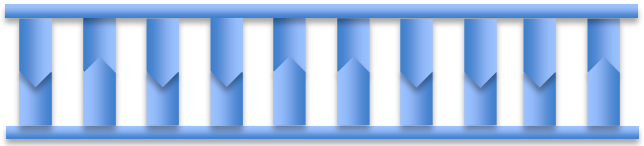
VITRAKVI 11/20/18
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210861s000lbl.pdf

Considerations for Tissue Agnostic Drug Development

- Establishment of indication-defining biomarkers
- Differences in mutations and resistance mechanisms across cancers
  - BRAF and MEK inhibitors in BRAF V600 colorectal cancer
- Design of clinical trials
  - Available therapies, unmet medical need, magnitude of benefit, size of patient population
- Companion diagnostic development

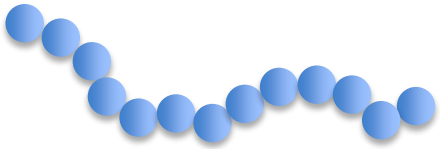
Lemery S, et. al. *N Engl J Med*. 2017;377(15):1409-1412.

Genetically Targeted Technologies/Therapies



DNA

RNA



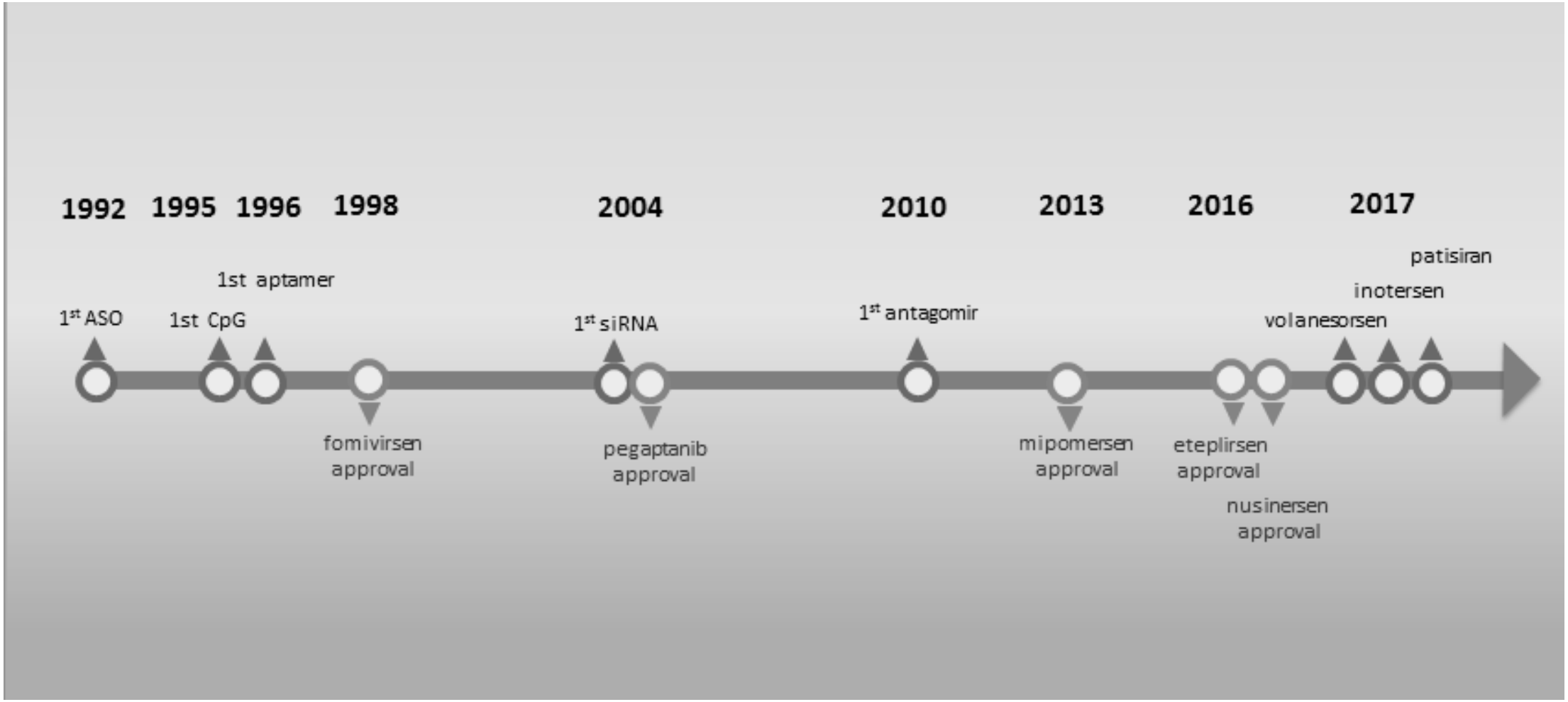
Protein

CRISPR/Cas9

Antisense (mipomersen, inotersen)
Splice-altering (eteplirsen, nusinersen)
siRNA (patisiran)
microRNA
mRNA replacement

Aptamers (pegaptinib)
CpG/TLR

History of Oligo IND/NDA Submissions and NDA Approvals



Courtesy of Xuan Chi (OND, DCRP) and PTCC Oligonucleotide Subcommittee 2018

Synthetic Oligonucleotides

Unique Challenges

- Nonclinical pharmacology
  - Animal toxicology – target may not be conserved
  - PK – primate models to estimate exposure and dosage
- Clinical pharmacology
  - Organ impairment – renally cleared, some hepatically targeted
  - Drug interactions – endo/exonuclease metabolism, limited interaction potential
  - QT – unlikely to interact with HERG
  - Immunogenicity – recognized as non-self, anti-drug antibodies can develop
- Safety
  - Thrombocytopenia (consistent, moderate vs. severe, sporadic)
  - Immune-mediated AEs

N-of-1

A tailormade drug developed in record time may save girl from fatal brain disease

By **Jocelyn Kaiser** | Oct. 19, 2018 , 9:00 PM

For years, a Colorado couple searched for an explanation for why their bright, active little girl was having increasing trouble walking, speaking, and seeing. In December 2016, Julia Vitarello and Alek Makovec learned that 6-year-old Mila Makovec almost certainly had Batten disease, an inherited and fatal neurodegenerative disorder. Now, in a stunning illustration of personalized genomic medicine, Mila is receiving a drug tailored to her particular disease-causing DNA mutation—and it appears to have halted the condition's progression.

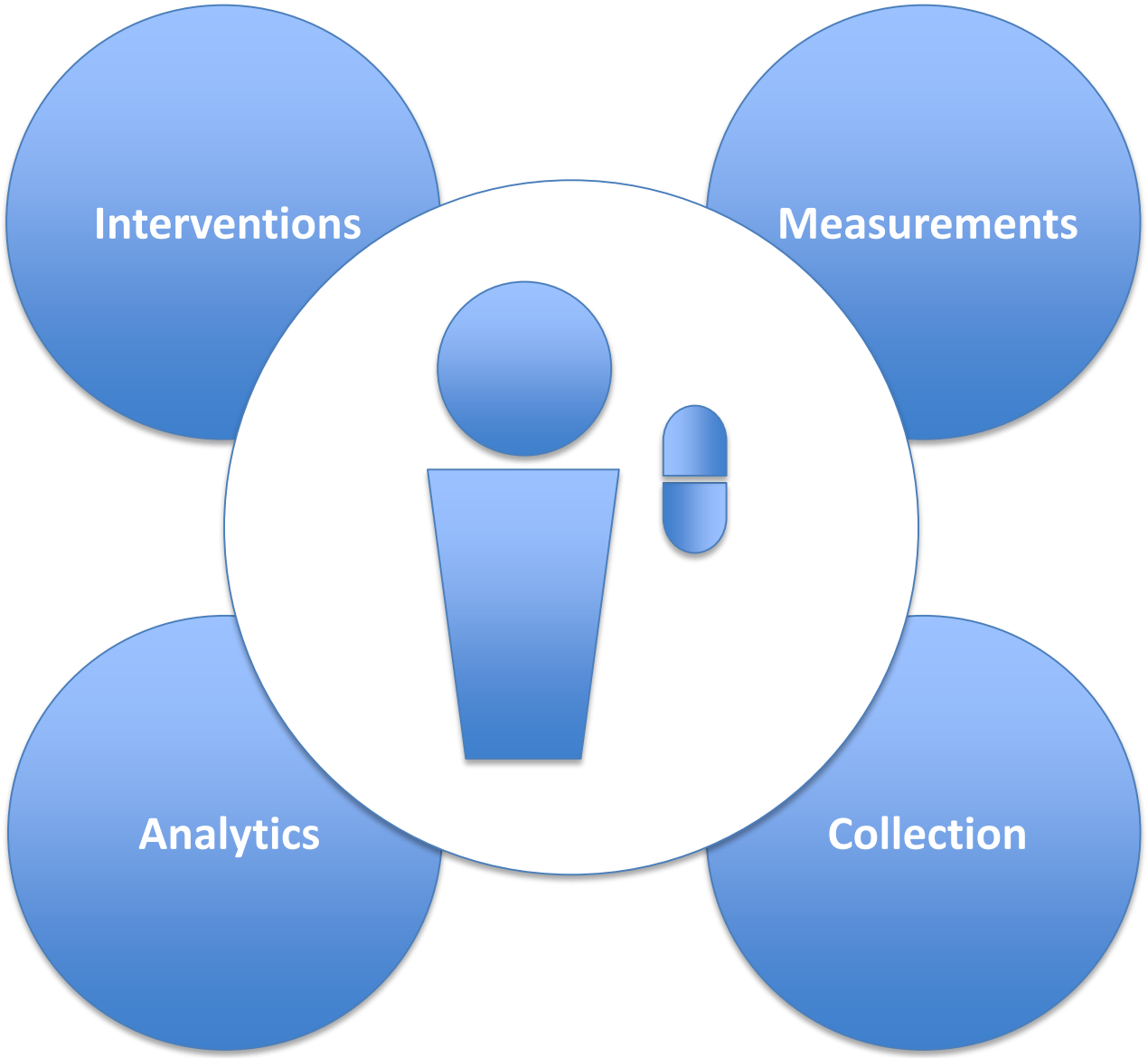
Today at the annual meeting of The American Society of Human Genetics in San Diego, California, researchers told the story of how in less than a year, they went from sequencing Mila's genome to giving her a **synthetic RNA molecule that helps her cells ignore her genetic flaw** and make a needed protein. The same steps could help some other patients with diseases caused by unique mutations in a single gene, they said.

https://www.sciencemag.org/news/2018/10/tailormade-drug-developed-record-time-may-save-girl-fatal-brain-disease

U.S. FOOD & DRUG ADMINISTRATION

The Future

Gene therapy
RNAi
Precision medicines
Regenerative medicine



Omics
Wearables
Surrogates
PROs

Artificial intelligence
Machine learning
Modeling and simulation
Systems
Data lakes

Complex, innovative trials
EHRs
Telemedicine

Summary

- Technological advancements have facilitated the translation of pharmacogenetics and paved the way for development of targeted therapies

- FDA has communicated via guidance to industry current thinking on emerging technologies and continues adapting to the changing landscape

- Further understanding genomic and other mechanisms of disease will give rise to an increasing number of complex and personalized treatment modalities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