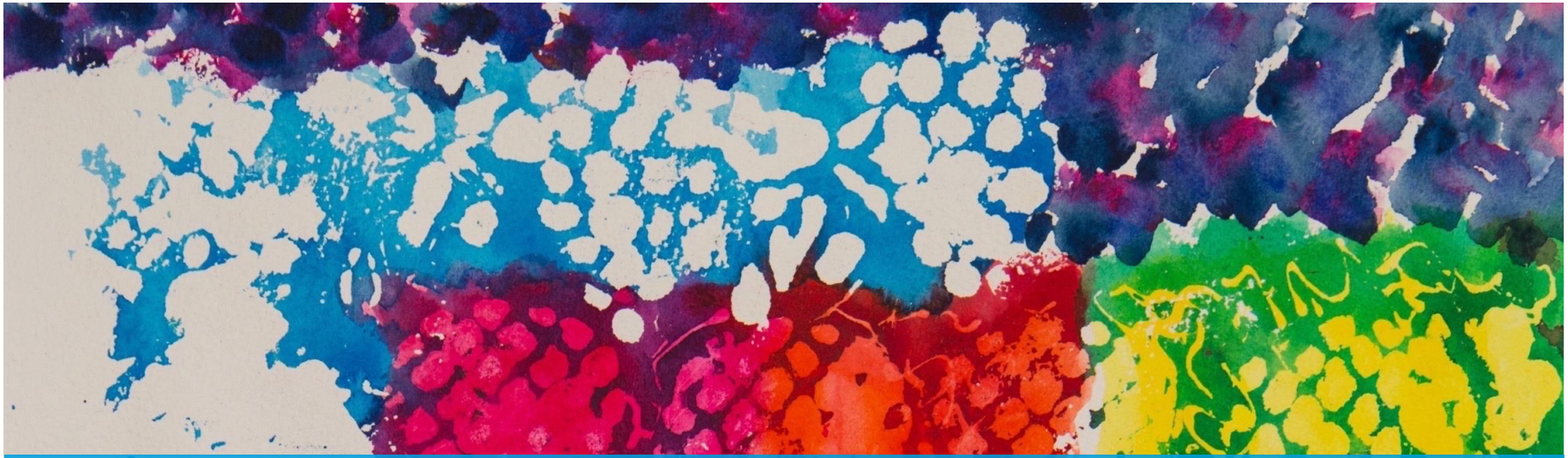

Companion Diagnostic Regulatory Requirements in China

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Cliff Enright, *Star Cradle*
Artwork from The Creative Center at University Settlement.

Disclaimer

The views and opinions expressed in this presentation are those of the individual presenter and should not be attributed to Association of Medical Diagnostics Manufacturers (AMDM), or any organization with which the presenter is employed or affiliated, or any health authority.

Abbreviations

NMPA: National Medical Product Administration

CDE: Center for Drug Evaluation

CMDE: Center for Medical Device Evaluation

HGRAO: Human Genetic Resources Administration Office

IVD: In-Vitro Diagnostic

CDx: Companion diagnostic

NGS: Next Generation Sequencing

IHC: Immunohistochemistry

PCR: Polymerase chain reaction

LDT: Lab Developed Test

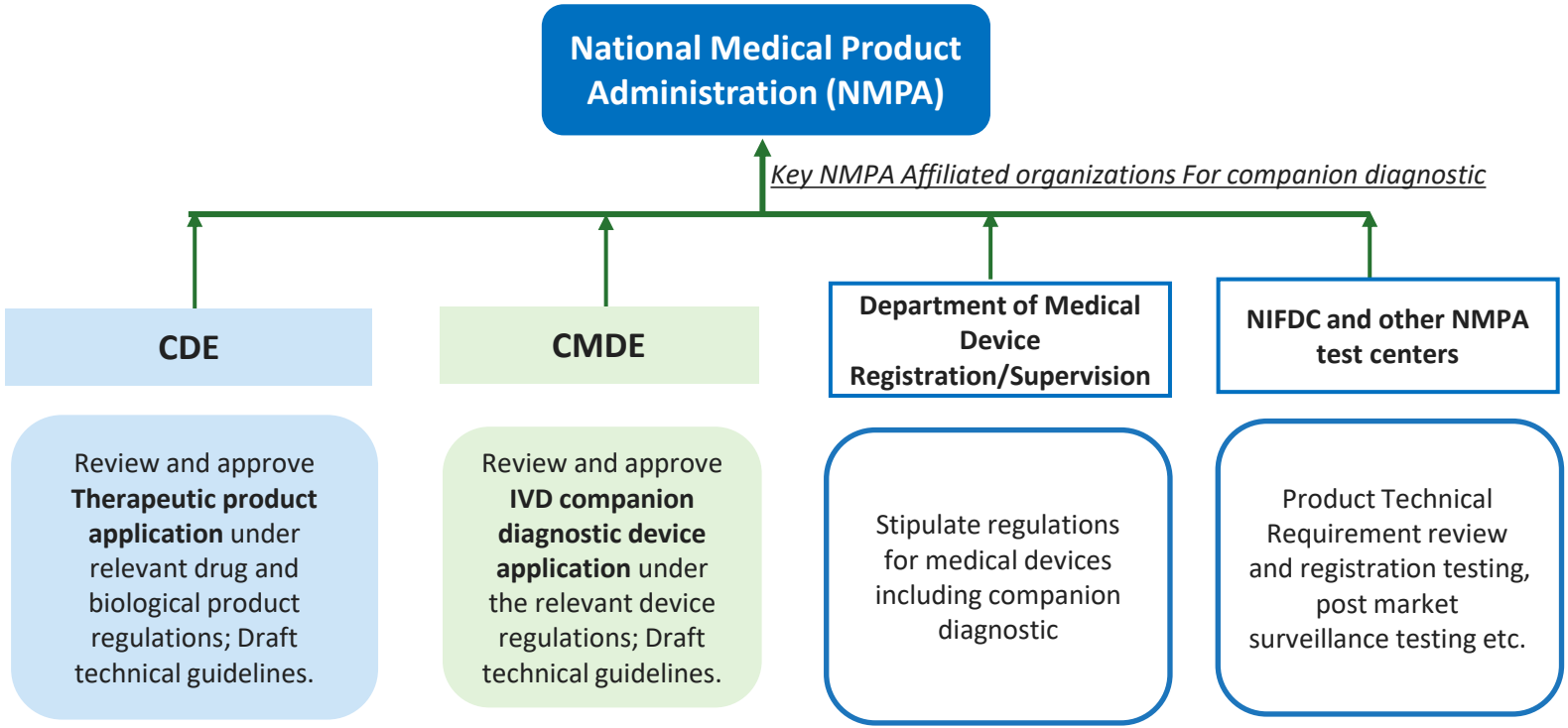
CTA: Clinical trial application

Companion Diagnostic (CDx) Definition in China

Companion diagnostic is used for the testing of specimens collected from cancer patients. The results may provide information that is essential for the safe and effective use of an oncology drug, including: identifying patients who are most likely to benefit from the drug; identifying patients likely to be at increased risk for drug related serious adverse reactions; or identifying population subgroups where the drug is safe and effective based on sufficient studies, etc.

-- Guideline on Clinical Trials of Companion Diagnostics for Marketed Oncology Drugs (Draft for Comment, Aug 2020 issued by NMPA)

China NMPA Regulatory Overview (CDx relevant)



CDE: Center for Drug Evaluation;
CMDE: Center of Medical Device Evaluation;
NIFDC: National Institutes for Food and Drug Control

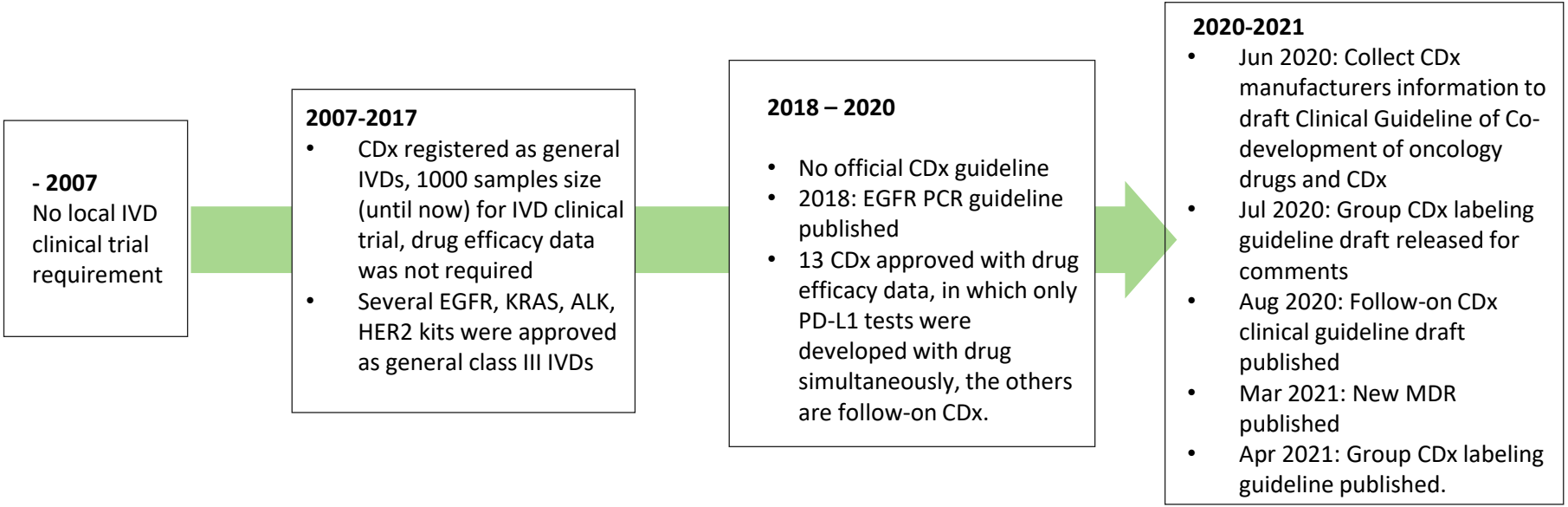
Risk-based classification and CDx relevant examples

Classification	Class I	Class II	Class III	Remark
Risk	Low risk		High risk	
Examples (medical device)	Nucleic acid extraction system, Electrophoresis system, IHC stain instrument	Sanger sequencer, Gene amplifier, PCR amplifier, Library preparation instrument, Nucleic acid molecular hybridization instrument, Biochip scanner, Microarray chip detector, Gene hybridization signal enlarging instrument, Biochemical analyzer	Gene sequencer, Nucleic acid amplification analyzer, Real-time fluorescence quantitative PCR analyzer	**Gene sequencers are class III unless it is Sanger sequencer.**
Examples (IVD reagent)	Hemolytic agent, dilution, staining solution, individual antibody stain reagent without CDx claim	Reagents used for protein, glucose, hormone, enzyme, autoantibody testing etc. Oct 2020: some tumor markers (CEA, CA125, CA199 etc.) changed from Class III to Class II	Reagents related with pathogenic antigen, antibody, nucleic acid; Blood typing, human genes, hereditary diseases, drug target etc. Such as EGFR, ALK, MET, HIV, Syphilis…	**Companion diagnostic reagent is Class III.**
Authority for registration	Filing in Municipal NMPA	Registration **Provincial NMPA**	Registration **Central NMPA**	**All imported products filling or registration in Central NMPA**
Registration requirement	Documents filing	Registration testing Clinical evaluation NMPA submission & review	Registration testing Clinical evaluation NMPA submission & review	

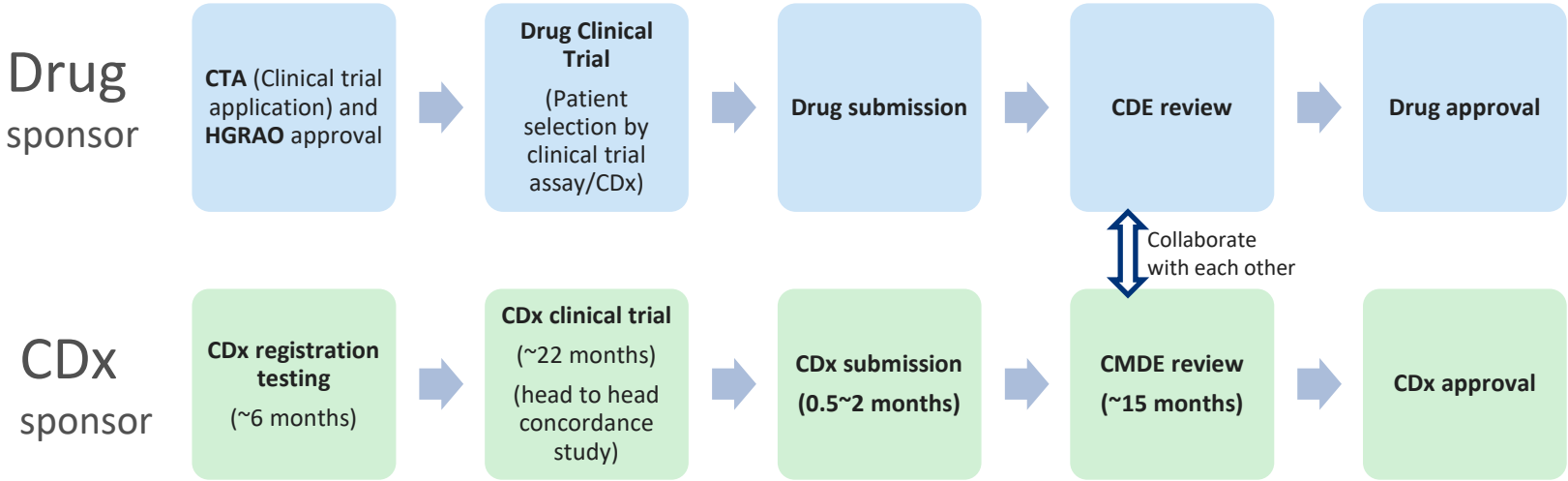
CDx Relevant Guideline from CDE and CMDE

CDE (Center for Drug Evaluation)	CMDE (Center for Medical Device Evaluation)
Technical Guideline for Clinical Trial of Oncology Drug	Guideline on Clinical Trials of Companion Diagnostics for Marketed Oncology Drugs (Draft, 2020) (Follow-on CDx Clinical Guideline)
Technical Guideline for Endpoint of Clinical Trial of Oncology Drug	Guideline for Update of Instructions for Use and Technical Review of Oncology Companion Diagnostic Reagents Based on the Same Class of Therapeutic Products (Draft 2020; Official Apr 16, 2021) (Group CDx Labeling Guideline)
Technical Guidelines for Clinical Data Collection for Registration of Oncology Drug	Guidelines for Technical Review on Registration of Epidermal Growth Factor Receptor (EGFR) Mutation Detection Reagents (PCR method) (2018)
Technical Guidelines for the Addition of New Indications of Marketed Oncology Drugs	Guideline for Technical Review of Gene Mutation Detection Reagents Related to Tumor Personalized Therapy (2014)
Technical Guidelines for Endpoints of Clinical Trials in Advanced Non-Small Cell Lung Cancer	Guideline for Technical Review on Registration of HER2 Gene Amplification Testing (FISH method)

Evolving CDx Regulatory Requirement in China



China Drug and CDx registration process



HGRAO: Human Genetic Resources Administration Office

Clinical Data of CDx

Clinical Efficacy/Utility

Validated by:

- CDx is used in drug clinical trial or
- Bridging between CDx and clinical trial assay or
- Observational study as CMDE requirement or
- External concordance between approved CDx and investigational CDx (limit to mature and well-recognized biomarkers)

Clinical Accuracy

- Concordance with an approved assay or established assay
- 1000 sample size is required under current MDR
- New MDR and regulation allows for sample size with statistical significance
- At least 3 clinical sites in China
- Clinical sites limit to hospitals for CDx currently

Two Tiers Intended Use in NGS labeling

Intended use example of an approved NGS kit in China:

Intended use: This test kit is used for qualitative detection of EGFR/ALK/BRAF/KRAS gene mutations in FFPE tissue specimen of patients with NSCLC. In which, EGFR: 19 deletions and L858R are used as companion diagnostic for Gefitinib and Icotinib, T790M is used as companion diagnostic for Osimertinib; ALK: ALK rearrangements (fusion) is used as companion diagnostic for Crizotinib.

The mutation types and corresponding target drugs are listed as following:

Drug name	Biomarker
Gefitinib, Icotinib	EGFR: 19del, L858R
Osimertinib	EGFR: T790M
Crizotinib	ALK rearrangements (fusion)

Mutations which are not validated as companion diagnostic:

Gene	Variants
EGFR	S768I
BRAF	V600E
KRAS	G12V, G12S, G12C, G12R, G12D, G12A, G13D

In-hospital Lab Developed Test (LDT) in new MDR

Article 53: For in vitro diagnostic reagents of the same category that have not been approved in China, qualified medical institutions may, according to the clinical needs of their own institution, develop the reagents by themselves and use them under the guidance of licensed physicians in the institutions according to clinical needs. **Specific management measures shall be formulated** by the medical supervision and administrative department under the State Council jointly with the department in charge of health under the State Council.

-- Medical Device Regulation, State Council Order No. 739 (Mar 2021)

- How to define “same category”?
- What’s “qualified medical institutions”?
- How to qualify “licensed physicians”

Management measures regulation for in-hospital LDT to be published

NMPA Approved CDx

Since Jan 2018, NMPA approved 13 companion diagnostic products

- 11 Domestic manufacturers, 2 overseas manufacturers
- Technologies: 1 PCR, 10 NGS, 2 IHC
- Drug indication: NSCLC, CRC, mUC, Ovarian cancer
- Covered biomarker: EGFR, ALK, ROS1, KRAS, BRCA1/2, PD-L1

- ➢ 2 PD-L1 were co-developed with drug, the others were follow-on CDx.
- ➢ NGS panel were relatively small (#genes)

Takeaways

- NMPA regulatory requirements on companion diagnostics are evolving quickly.
- NMPA require country of origin approval for overseas medical device (including IVD) registration submission unless it is an “innovative” medical device.
- Consider not only IVD assay regulatory strategy but also instrument and accessories.
- Drug clinical trial and IVD clinical trial (Concordance study) require HGRAO approval.
- LDT regulation is in development.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