工業技術研究院
Industrial Technology
Research Institute

Information Sharing on In Vitro Companion Diagnostic Devices

Albert T.W. Li
Industrial Technology Research Institute
Center for Measurement Standards

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Outline

1. What Is IVD CoDx
2. Regulatory Approved IVD CoDx
3. Challenges

Disclaimer: this presentation is prepared by ITRI for the purpose of 4th Joint Conference of Taiwan and Japan on Medical Products Regulation . For official translation and interpretation of act and regulation, please refer to Taiwan FDA.

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1. What Is IVD CoDx

- Japan: コンパニオン診断薬
- US FDA : In Vitro Companion Diagnostic Devices (IVD Companion Diagnostic Device)
- European Union IVD Regulation: companion diagnostic
- Taiwan FDA: 伴同性體外診斷醫療器材

Source:

1. US FDA In Vitro Companion Diagnostic Devices, August 6, 2014
2. 厚生労働省医薬食品局，コンパニオン診断薬等及び関連する医薬品の承認申請に係る留意事項について
3. EU, Proposal for a Regulation of the European Parliament and of the Council on in vitro diagnostic medical devices

1. What Is IVD CoDx

- A companion diagnostic device is:
  - A test that is essential for safe and effective use of a therapeutic product
  - Often, an in vitro diagnostic device (IVD)

- What does that mean?
  - "Essential" means that without the test, the therapeutic product cannot be considered safe and effective
  - Defines population, dose, etc.
  - Use of drug in other ways is unsafe/ ineffective/ unknown

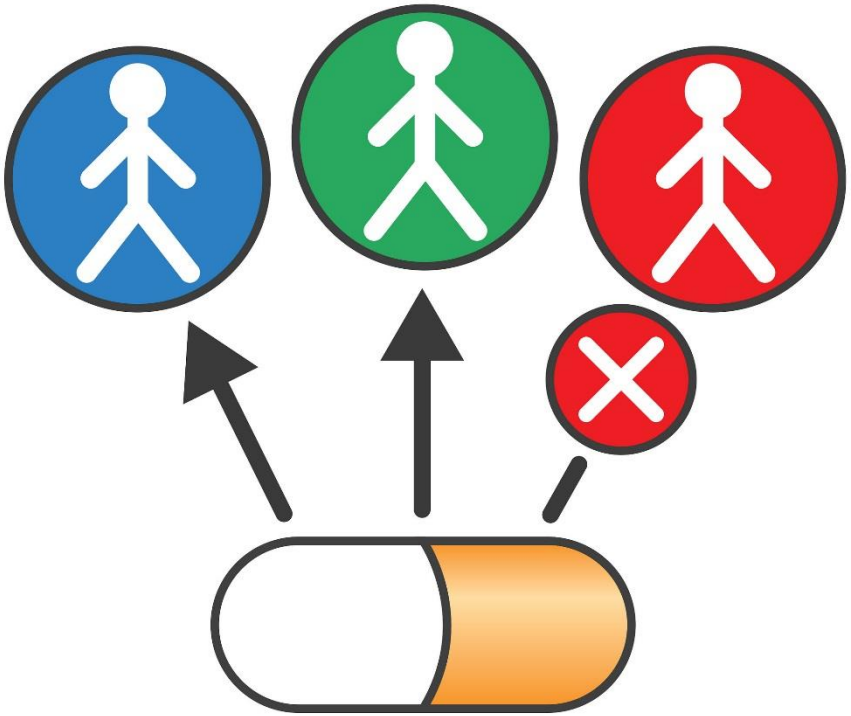
1. What Is IVD CoDx

- In Vitro Companion Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff. Aug 2014
  - An IVD companion diagnostic device is an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product.

1. What Is IVD CoDx

- An IVD companion diagnostic device could be essential for the safe and effective use of a corresponding therapeutic product to:
  - Identify patients who are most likely to benefit from a particular therapeutic product
  - Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product
  - Monitor response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness
  - Identify patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective, i.e., there is insufficient information about the safety and effectiveness of the therapeutic product in any other population

Source: US FDA In Vitro Companion Diagnostic Devices, August 6, 2014



Companion diagnostic tests show which patients could be helped by a drug and which patients would not benefit, and could even be harmed. The recent approval of a genetic test to help doctors prescribe a drug that treats colorectal cancer is just one example of the increasing importance of companion diagnostic tests in personalized medicine to ensure the safety and effectiveness of targeted therapies

Source: US FDA

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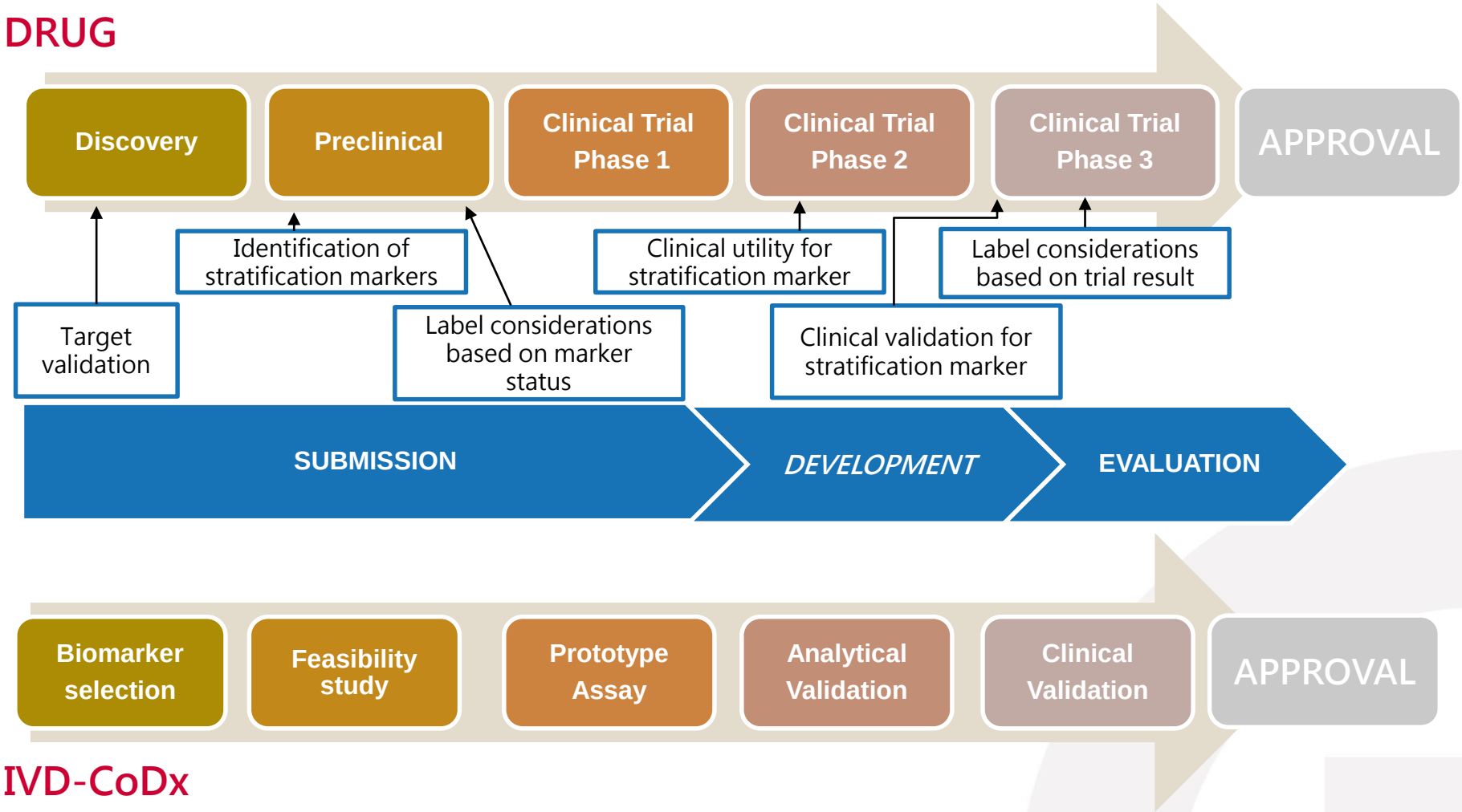
Processes for Drug and Diagnostic Development: A Concurrent Engineering Model



Examples of IVD CoDx

- **4800 BRAF V600 Mutation Test** - a companion diagnostic used with Zelboraf [a drug to treat patients with late-stage (metastatic) or unresectable melanoma] that will help determine if a patient's melanoma cells have the BRAF V600E mutation for which **Zelboraf** is specifically indicated.

- **Vysis ALK Break Apart FISH Probe Kit –** a companion diagnostic used with Xalkori [a drug to treat late-stage (locally advanced or metastatic), non-small cell lung cancers (NSCLC)] to determine if a patient has the abnormal ALK gene, for selection of patients who are for treatment with **Xalkori.**

- **HER-2 (test type)** - a companion diagnostic used with **Herceptin** [a drug to treat patients with breast cancer and over expression of HER-2] to determine if a patient has over-expression of her-2/neu in breast cancer patients for whom Herceptin(r) treatment is being considered.

US: IVD CoDx Approval

- Typically PMA pathway
- FDA prefers modular submissions
- Analytical validation critical
- Clinical validation comes from therapeutic product trial
- Manufacturing must be acceptable

Taiwan: IVD CoDx Approval

- Classification: Class III
  B.4020 Analyte specific reagents
  B.1860 Immunohistochemistry reagents and kits

- Analytical validation critical
- Clinical validation comes from therapeutic product trial
- Manufacturing must be acceptable-GMP License

What Differentiates a IVD CoDx

- IVD
  - May be used to differentiate populations
    - This information could be used, at the discretion of a clinician, to select appropriate patients for a particular therapy or to optimize dosing regimen
  - Intended use lists the property identified by the test (ex: pH, specific gravity, protein, etc.)
- CoDx
  - Required for patient selection per the labeled safety and efficacy of the therapeutic product.
  - Therapeutic product or class listed in the intended use.

Labeling Considerations

- Therapeutic product
  - Label will stipulate that the results from the IVD companion diagnostic device(s) are required for the safety and efficacy of the product.
  - Additional IVD companions or change in requirements represent a significant change and will require appropriate submission.
- CoDx
  - Indications will specify the therapeutic product(s) for which it has been cleared or approved.
  - Additional diseases, settings, or therapeutic products represent a significant change and will require appropriate submission

Summary of CoDx Safety and Effectiveness Data

I. General Information
II. Indication for Use
III. Contraindication
IV. Warnings and Precautions
V. Device description
VI. Alternative practices and Procedures
VII. Marketing History
VIII. Potential Adverse Effects of the Device on Health
IX. Summary of Preclinical Studies
X. Summary of Clinical studies
XI. Overall Conclusion drawn from all the studies

Source: US FDA In Vitro Companion Diagnostic Devices, August 6, 2014

Technical Documentation

1. Antibody Specificity Studies
   a) Analytical Specificity/ Crossreactivity study
   b) Clinical Specificity/ Crossreactivity/ Tour of normal tissue throughout the Body
2. Accelerated Stability/ Stress testing of complete Kit
3. Reproducibility studies
   a) Intra-Run Reproducibility
   b) Inter-Run Reproducibility
   c) Manual vs. Automated Methodology Reproducibility
   d) Detection System Reproducibility
   e) Lot-to-Lot reproducibility of complete Kit
   f) Inter-Laboratory Reproducibility
4. Characterization and antigen stability on control cell line

IVD-CoDx Approved by US FDA

Device Trade Name	Device Manufacturer	biomarker	Drug Trade Name	Intended Use
HercepTest	Dako	Her2/neu	Herceptin	indicated as an aid in the assessment of breast and gastric cancer patients for whom Herceptin® (trastuzumab) treatment is being considered
※ therascreen KRAS RGQ PCR Kit	Qiagen	K-RAS	Erbitux	intended to aid in the identification of CRC patients for treatment with Erbitux® (cetuximab) based on a KRAS no mutation detected test result.
DAKO C-KIT PharmDx	Dako	C-KIT	Gleevec	aid in identifying those patients eligible for treatment with GleevecTM/Glivec® (imatinib mesylate).
THxID™ BRAF Kit	bioMérieux	BRAF	Mekinist Tafinlar	intended to be used as an aid in selecting melanoma patients whose tumors carry the BRAF V600E mutation for treatment with dabrafenib [Tafinlar®] and as an aid in selecting melanoma patients whose tumors carry the BRAF V600E or V600K mutation for treatment with trametinib [Mekinist™].
※ Cobas EGFR Mutation Test	Roche	EGFR	Tarceva	intended to be used as an aid in selecting patients with NSCLC for whom Tarceva® (erlotinib), an EGFR tyrosine kinase inhibitor (TKI), is indicated.
Visis ALK Break Apart FISH Probe Kit	Abbott	ALK	Xalkori	aid in identifying those patients eligible for treatment with XALKORI®(crizotinib).

※ CoDx approved in Taiwan

IVD CoDx Approved by US FDA

Device Trade Name	Device Manufacturer	biomarker	Drug Trade Name	Intended Use
※ COBAS 4800 BRAF V600 Mutation Test	Roche	BRAF	Zelboraf	intended to be used as an aid in selecting melanoma patients whose tumors carry the BRAF V600E mutation for treatment with vemurafenib.
※ INFORM HER-2/NEU	Ventana	Her2/neu	Herceptin	indicated for use as an adjunct to existing clinical and pathologic information currently used as prognostic indicators in the risk stratification of breast cancer in patients who have had a priori invasive, localized breast carcinoma and who are lymph node-negative.
※ INFORM HER2 DUAL ISH DNA Probe Cocktail	Ventana	Her2/neu	Herceptin	indicated as an aid in the assessment of patients for whom Herceptin (trastuzumab) treatment is being considered.
DAKO EGFR PharmDx Kit	Dako	EGFR	Erbitux Vectibix	identifying colorectal cancer patients eligible for treatment with Erbitux® (cetuximab) or VectibixTM (panitumumab).
Ferriscan	Resonance Health	Iron Concentration	Exjade	intended to measure liver iron concentration to aid in the identification and monitoring of non-transfusion dependent thalassemia patients receiving therapy with deferasirox.
※ therascreen EGFR RGQ PCR Kit	Qiagen	EGFR	Gilotrif	intended to be used to select patients with NSCLC for whom GILOTRIF® (afatinib) or IRESSA® (gefitinib), EGFR tyrosine kinase inhibitors (TKIs), is indicated. Safety and efficacy of GILOTRIF (afatinib) and IRESSA (gefitinib) have not been established in the patients whose tumors have L861Q, G719X, S768I , exon 20 insertions, and T790M mutations, which are also detected by the therascreen EGFR RGQ PCR Kit.

IVD CoDx Approved by US FDA

Device Trade Name	Device Manufacturer	biomarker	Drug Trade Name	Intended Use
HER2 FISH PharmDx Kit	Dako	Her2/neu	Herceptin Perjeta	indicated as an aid in the assessment of breast and gastric cancer patients for whom Herceptin (trastuzumab) treatment is being considered and for breast cancer patients for whom Perjeta (pertuzumab) or Kadcyla (ado-trastuzumab emtansine) treatment is being considered
※ PATHVYSION HER-2 DNA Probe Kit	Abbott	Her2/neu	Herceptin	indicated as an aid in the assessment of patients for whom herceptin (trastuzumab) treatment is being considered.
※ PATHWAY ANTI-HER-2/NEU (4B5) Rabbit Monoclonal Primary Antibody	Ventana	Her2/neu	Herceptin	indicated as an aid in the assessment of breast cancer patients for whom Herceptin treatment is being considered.
INSITE HER-2/NEU KIT	Biogenex Laboratories	Her2/neu	Herceptin	indicated as an aid in the assessment of breast cancer patients for whom Herceptin (Trastuzumab) therapy is being considered
SPOT-LIGHT HER2 CISH Kit	Life Technologies	Her2/neu	Herceptin	indicated as an aid in the assessment of patients for whom Herceptin (trastuzumab) treatment is being considered.
Bond Oracle Her2 IHC System	Leica Biosystems	Her2/neu	Herceptin	indicated as an aid in the assessment of patients for whom herceptin (trastuzumab) treatment is being considered
HER2 CISH PharmDx Kit	Dako	Her2/neu	Herceptin	indicated as an aid in the assessment of patients for whom Herceptin (trastuzumab) treatment is being considered.
BRACAnalysis CDx™	Myriad	BRCA1 /BRCA2	Lynparza	used as an aid in identifying ovarian cancer patients with deleterious or suspected deleterious germline BRCA variants eligible for treatment with Lynparza™ (olaparib).

Other IVD CoDx Approved by TFDA

License no.	Exp. Date	Name	Manufacturer	Country
衛部醫器製字第004963號	109/11/03	Formosa EGFR Mutation Detection Kit	Formosa Biomedical., LTD	Taiwan
衛部醫器陸輸字第000668號	110/08/03	AmoyDx EGFR 29 Mutations Detection Kit	Amoy Diagnostics Co., LTD.	China

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Technological Challenges in IVD CoDx

- Hypothesis, mechanism and study design efficacy and response rate
- Nature of test, platforms and analytical performance
- Clinical specimen, availability, representation, variation/confounding factors
- Clinical validation, power, performance, success of drug trial
- Synchronization of biomarker and drug development in timing and application
- Analytical or clinical poor performance
- Clinical utility not well demonstrated
- Limited availability of well annotated samples

Regulatory Challenges in IVD CoDx

- Current regulatory framework is being outpaced by technological advancement
- One test- one intended use structure
- Whole genome sequencing, multiplex assays present challenges
- Interpretation of complex tests and multiplatform panels
- Use of preexisting lab data for downstream diagnostic purposes
- Integrated regulatory requirements and guidelines for biomarker and drug
- Product to product and market to market differences in regulatory and reimbursement standards, US, European Union, Japan, Korea and other Asia countries

ご清聴ありがとうございました
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李子偉 alberttwli@itri.org.tw
王尹萱 yinhsuan@itri.org.tw