#4_E16

Title	**An Introduction to ICH E16 and Biomarker Qualification** **E16 소개 및 생체지표 자격심사**
Speaker	Gideon BLUMENTHAL (Vice president, Global Regulatory Affairs, MSD)
Bio	Dr Gideon Blumenthal is a hematologist oncologist who is currently Vice President, Global Regulatory Affairs in Oncology, Merck. Prior to joining Merck, Dr Blumenthal spent over a decade at the US Food and Drug Administration Oncology office, taking on increasing leadership responsibilities during his time at the Agency. He initially served as a medical reviewer, then clinical team leader, followed by Acting Deputy Director in the Office of Hematology Oncology Products and Associate Director for Precision Oncology, and most recently served as the Deputy Center Director of the Oncology Center for Excellence. Dr Blumenthal did his internal medicine training at the University of Maryland School of Medicine, followed by a hematology oncology fellowship at the National Cancer Institute. He was an attending physician in the NCI thoracic oncology clinic. He received numerous awards, including the 2018 American Society for Clinical Oncology Public Service Award. He has co-authored over 100 articles in the Oncology and Drug Development peer reviewed literature and has authored 3 book chapters.

Topics to be covered

- **Background, content, and application of ICH E16**
- E16 implementation experience, as well as experience with various regulatory agencies (FDA, EU)

Background on ICH E16

- ICH guideline on genomic biomarkers (E15) 2007: http://www.ich.org/LOB/media/MEDIA3383.pdf
  - Definitions of genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories

- ICH E16 process
  - First meeting of E16 Working Group: 2008
  - Document for Consultation: 2009
  - Step 4: 2010

https://database.ich.org/sites/default/files/ICH%20E16%20Step%204%20presentationWebsite_Oct%202010.pdf

Definition of qualification in E16

…a conclusion that, within the stated context of use, the results of assessment with a biomarker can be relied upon to adequately reflect a biological process, response or event, and support use of the biomarker during drug or biotechnology product development, ranging from discovery through post-approval.

https://database.ich.org/sites/default/files/ICH%20E16%20Step%204%20presentationWebsite_Oct%202010.pdf

Objectives of E16

- Create a harmonized recommended structure for biomarker qualification applications that will foster consistency of applications across regions and facilitate discussions with and among regulatory authorities
- Reduce the burden on sponsors as a harmonized format will be recommended for use across all ICH regulatory regions
- Facilitate incorporation of biomarker data into specific product-related applications

https://database.ich.org/sites/default/files/ICH%20E16%20Step%204%20presentationWebsite_Oct%202010.pdf

Scope of E16

Context, structure, and format of qualification submissions

- Clinical and nonclinical genomic biomarkers
- Development of drug or biotechnology products
  - Translational medicine approaches
  - Pharmacokinetics
  - Pharmacodynamics
  - Efficacy
  - Safety

General Principles in E16

Context of use

- Corresponds to the data supporting qualification
- Clearly detailed in the submission package
- Specific use of the biomarker in product development
- Narrow or broad

Structure

- Consistent regardless of context proposed
- Flexible enough to deal with specific attributes of each submission
- Facilitate submission and review of future biomarker qualification submission expanding the use of biomarker to new contexts

Format

- Varies significantly depending on context
- Should support an evaluation of data and can include reports, tubulations, and raw data
- Should be consistent with the methodology and platform used for analyzing the biomarker in question
- Reference to standards and/or accepting methods should be described as applicable

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Qualified Biomarkers- FDA

Requester	Qualified Biomarkers	Description	COU	Decision
University of Washington	Plasmodium 18S rRNA/rDNA	Plasmodium falciparum 18S rRNA/rDNA (copies/ml) in blood by nucleic acid amplification	Monitoring biomarker informs initiation of treatment with anti-malarial following controlled human malaria infection w/ P.falciparum sporoziotes in HV for vaccine and/or drug development	2018
Critical Path Institute and FNIH	Clusterin, Cystatin-C, KIM-1, NAG, NGAL, osteopontin	Urinary nephrotoxicity bm panel by immunoassays	Safety biomarker panel to aid in detection of kidney tubular injury in phase 1 trials in healthy volunteers	2018
Polycystic Kidney Disease Consortium	Total Kidney Volume	TKV as assessed by MRI, CT, and US	Prognostic biomarker with patient age and baseline GFR for Autosomal Dominant PKD	2016
COPD consortium	Fibrinogen	Plasma biomarker by immunoassay	Prognostic biomarker used with other characteristics to enrich for COPD exacerbation	2016
Mycoses Study Group	Galactomannan	Serum/BAL fluid by immunoassay	Diagnostic biomarker used with other clinical and host factors to identify patients with invasive aspergillosis	2015
O'Brien PJ, Reagan WJ, et al.	Cardiac troponins T and I	Serum/plasma cardiotoxicity biomarkers by immunoassay	Safety biomarker to indicate cardiotoxicity in rats, dogs, or monkeys when testing known cardiotoxic drugs and may be used to help estimate non-toxic human dose	2012
International Life Sciences Institute/ HESI/ Nephrotox WG (NWG)	Clusterin, Renal Papillary Antigen	Urinary nephrotoxicity biomarkers assessed by immunoassay	Safety biomarker to be used with traditional indicators to indicate renal injury in rat	2010
Predictive Safety and Testing Consort/ NWG	Albumin, B2 Microglobulin, Clusterin, Cystatin C, KIM-1, Total Protein, Trefoil factor-3	Urinary nephrotoxicity biomarkers assessed by immunoassay	Safety biomarker to be used with traditional indicators to indicate renal injury in rat	2008

https://www.fda.gov/drugs/biomarker-qualification-program/list-qualified-biomarkers

Selected Opinions and letters of support on the qualification of novel methodologies for medicine development- EMA

- Multiple sclerosis clinical outcome assessment
- Stride velocity 95th centile as a secondary endpoint in Duchenne Muscular Dystrophy measured by a valid and suitable wearable device
- Molecular neuroimaging of the dopamine transporter as biomarker to identify patients with early manifest Parkinsonism in Parkinson's disease
- Plasma fibrinogen as a prognostic biomarker (drug development tool) for all-cause mortality and COPD exacerbations in COPD subjects
- Paediatric ulcerative colitis activity index (PUCAI)
- Ingestible sensor system for medication adherence as biomarker for measuring patient adherence to medication in clinical trials
- Total kidney volume (TKV) as a prognostic biomarker for use in clinical trials evaluation patients with autosomal dominant polycystic kidney disease (ADPKD)

https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/novel-methodologies-biomarkers/opinions-letters-support-qualification-novel-methodologies-medicine-development

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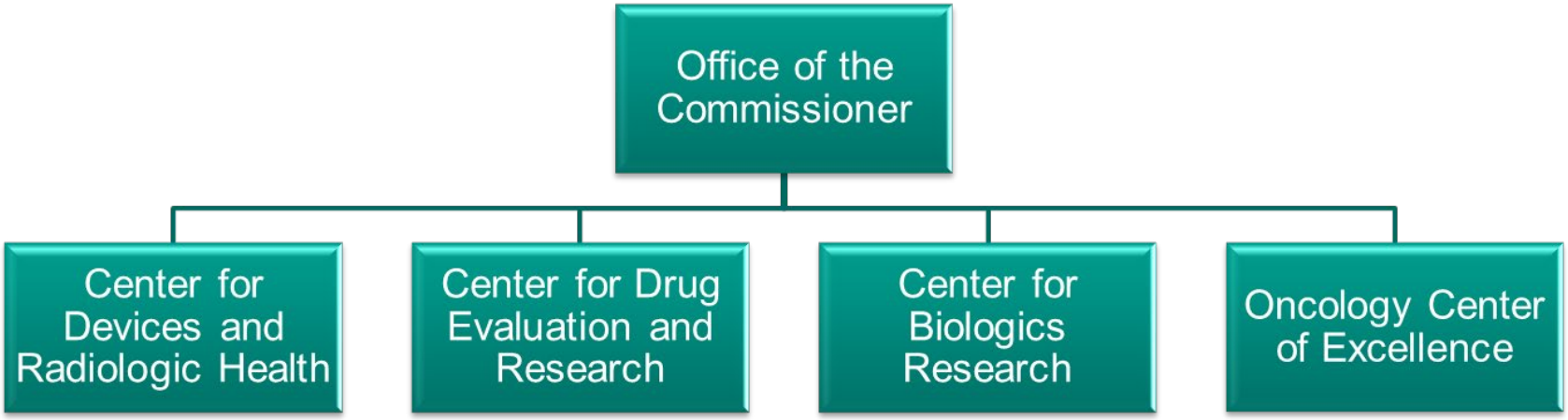
Key FDA Centers for Biomarker Development



Companion dx
Complementary dx
PMA
510(k)

CDER Biomarker Qualification Program

PMA, 510(k) related to CBER products

Precision Oncology Program

Drug development tool (DDT)* integration into drug development: Sources of information to support regulatory use

- Drug Approval Process
- Scientific Community Consensus
- DDT* Qualification Programs

* With 2016 21st Century Cures Act, the concept of drug development tool (DDT) qualification is introduced to encompass biomarkers and clinical outcome assessment (COA)

DDT/biomarker integration into drug development: three pathways

- **IND pathway**: based upon agreement with the clinical division, in the context of a specific drug development program

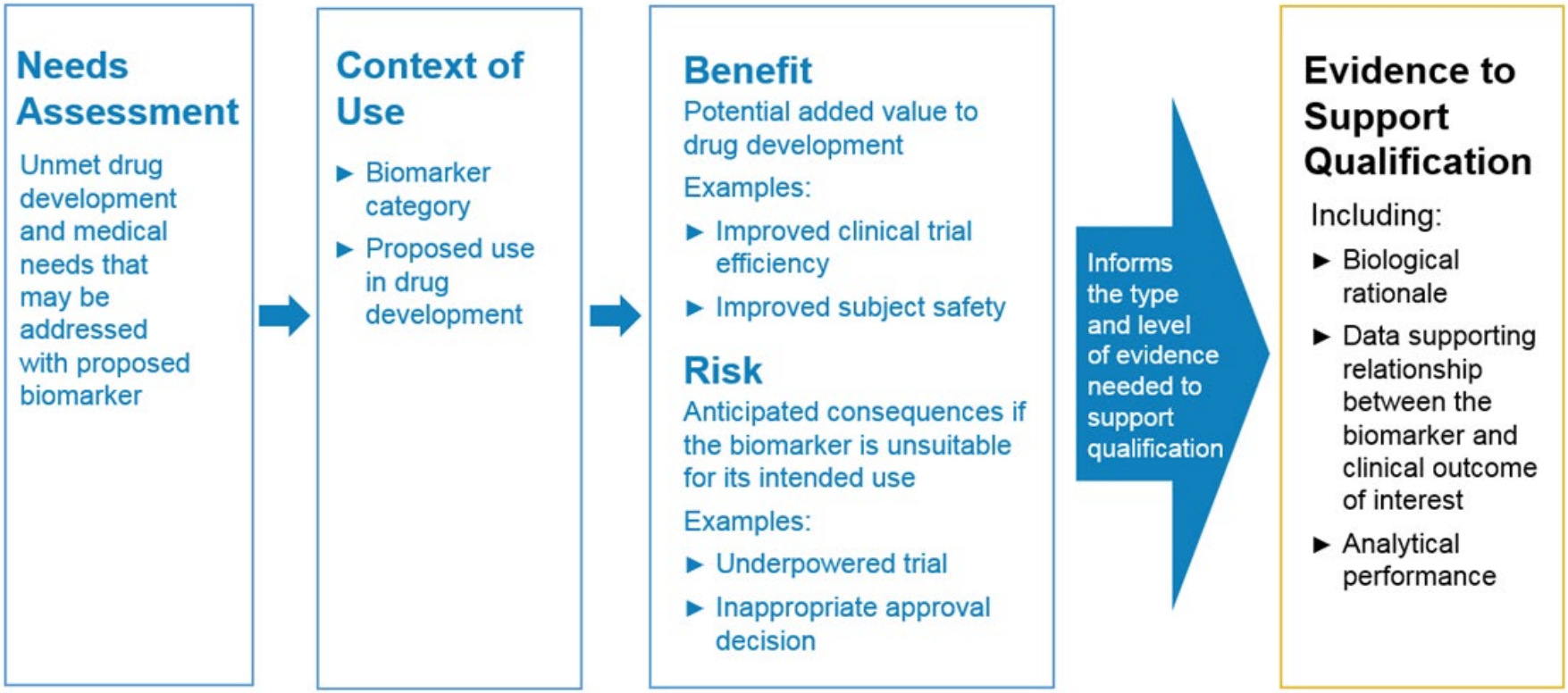
- **Scientific community consensus**: broadly/ widely used DDT, appropriate scientific support, generally accepted by experts in the field

- **DDT qualification programs:** review and acceptance based upon appropriate submission qualification package; available for use in any development program within approved context of use

Biomarker/DDT qualification process

Letter of Intent (LOI)	**Initiates the qualification process of a biomarker for a proposed context of use (COU) in drug development**
Qualification Plan (QP)	**Defines the intended development to generate the necessary supportive data to qualify the biomarker for the proposed COU**
Full Qualification Package (FQP)	**Contains all accumulated data to support the qualification of the biomarker for the proposed COU**
Qualification Recommendation	**Contains FDA's determination on whether the biomarker is qualified for the proposed COU based on a comprehensive review of the FQP**

Evidentiary Framework for Biomarker Qualification- 2018 FDA guidance



https://www.fda.gov/media/122319/download

BEST: Biomarkers, Endpoints, and other Tools Resource

- A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care
- Created by the NIH-FDA Biomarker Working group
- Publicly available at: https://www.ncbi.nlm.nih.gov/books/NBK326791/

Biomarker Classes from a Drug Perspective

Susceptibility/Risk: indicates potential for developing disease or medical condition in an individual who does not currently have clinically apparent disease or medical condition (e.g. BRCA mutations and development of breast cancer)

Diagnostic: detects or confirms the presence of disease or condition of interest or to identify individuals with a subset of the disease (e.g. HbA1c to aid in diabetes diagnoses)

Monitoring: assesses status, through serial measurement, of a disease or medical condition including degree or extent of disease (e.g. INR and anti-coagulation status)

Prognostic: identifies likelihood of a clinical event, disease recurrence or progression, in patients who have the disease or medical condition of interest in the absence of a therapeutic intervention (e.g. BRCA mutations and breast cancer recurrence)

Predictive: identifies patients who are more likely to experience a favorable or unfavorable effect from a specific treatment (e.g. EGFR mutations in lung cancer and response to erlotinib)

Pharmacodynamic/ Response: Indicates that a biologic response has occurred in a patient who has received a therapeutic intervention. May become clinical trial endpoints, and possibly surrogate endpoints (e.g. sweat chloride and response to CFTR agents)

Safety: indicates likelihood, presence, or extent of toxicity to a therapeutic intervention when measured before or after that intervention (e.g. QTc and Torsades)

THANK YOU

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