Role of RWE in Korea's Policy Making and Drug Approval Process

Ju-Young Shin, PhD, Professor

Sungkyunkwan University School of Pharmacy,

Department of Biohealth Regulatory Science

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1. Evolving Post-Marketing Safety Management in Korea

Regulatory Harmonization with RMP

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

PHARMACOVIGILANCE PLANNING

E2E

Current *Step 4* version
dated 18 November 2004

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

	Risk Management Plan
Objectives	To ensure drug safety and minimize potential risks throughout the product's entire lifecycle
Key contents	• Specific safety concerns to be addressed - Important Identified Risks - Important Potential Risks - Missing Information • Pharmacovigilance plan • **Risk minimization plan**
Scope of products	• New drug, • Orphan drug, • New prescription combination drugs, • Drugs with new routes of administration • Drugs with new indications, • Drugs with significant safety issues (Required by Regulatory Authority)
Implemented from	2012 in Japan, and 2015 in Korea

RMP in Korea

Re-examination System

Post Marketing Survey

- **Use Result Survey**
- **Special Survey**
  (epidemiologic studies, database studies, etc.)
- **Post-marketing Clinical Study**

Risk Management Plan

Important Identified Risks,
Important Potential Risks,
Missing Information

Routine PV Activities
Spontaneous reporting, signal detect, PBRER, etc.

Additional PV Activities
Active Surveillance,
Comparative Observational Studies,
Targeted Clinical Investigation,
Descriptive Studies

Routine RMMs

Additional RMMs

RMM: Risk Minimization Measures

Reflections on Evolving PMS Practice

The Re-examination system has significantly evolved, allowing more flexible and risk-adapted approaches.

Opportunities

- Traditional Use-Result Surveys are no longer mandatory.
- MAHs can select the most appropriate study design including database studies - based on the product-specific risks.
- Risk-based research enables more meaningful, patient-centered outcomes.

Challenges

- Limited internal expertise in RWD/RWE
- Need to develop PMS guideline before product launch

→ These challenges can be overcome with more experience and better infrastructure.

MFDS Guideline Tasks

Step-by-Step Plan for Development of MFDS Guideline Tasks

1yr Analysis of Latest RWD/RWE Regulatory Trends and Preparation of Draft Guideline

2yr Validation of the Appropriateness of the Guideline (Draft)

3yr Proposal of Guidelines for Utilizing RWD/RWE

2025

- Establish and operate a consultative body consisting of experts from academia, industry, research institutes, and government.
- Prepare a draft guideline identifying the required improvements or items for domestic introduction

2026

- Select case studies using global and domestic RWE examples.
- Verify appropriateness of the guideline and review through case studies on the use of RWD/RWE for drug safety and efficacy evaluations.

2027

- Review the guideline in consideration of domestic and international regulatory decision and case study results.
- Collect opinions through expert council networks.
- Propose a guideline for using RWD/RWE suitable for domestic circumstances.

✓ It is possible to ensure policy consistency through the guideline tasks for domestic RWD/RWE utilization and evaluation related to clinical trials and RWD/RWE utilization.

✓ Continuity of research can be maintained by collaborating with Professor Young Gun Yeom of Kyunghee Medical Center, who is currently carrying out the relevant tasks.

Overview of Pharmaceutical Guideline Development Tasks

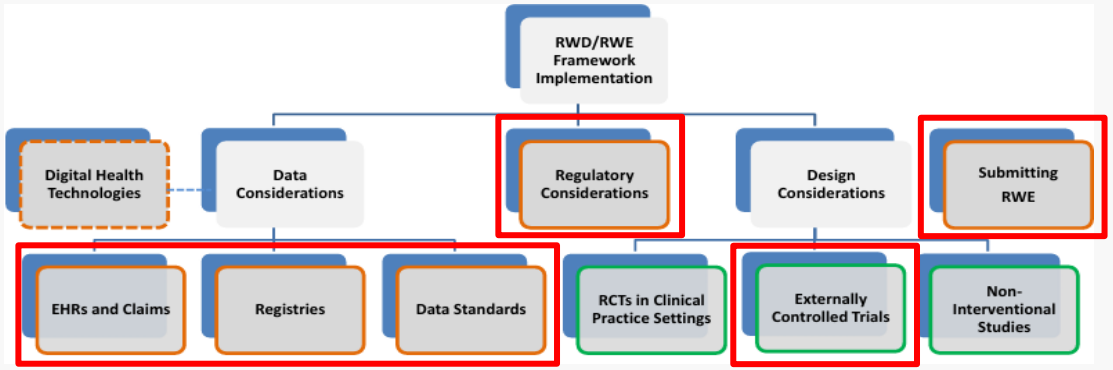
Guideline Development for RWD/RWE Utilization

- In advanced countries such as the US (FDA) and Europe (EMA), guidelines for using Real World Data (RWD) and Real World Evidence (RWE) are already being utilized in clinical trials and regulatory decision-making.
- To keep pace, Korea plans to develop seven guidelines suited to domestic circumstances (to be completed by 2027).

① Guideline for Evaluating Claim Data
② Guideline for Evaluating Registries
③ Guideline for Setting External Control
④ Guideline for Evaluating Electronic Medical Records
⑤ Guideline for RWD/RWE Study Planning
⑥ Data Standards Guideline
⑦ Data Submission Guideline

- The new guidelines will clarify key considerations and instructions for using various RWD/RWE materials, ensuring that domestic standards align with international best practices and help advance domestic clinical research environments.
- To support RWD/RWE use, translations and adaptations of FDA guidelines will be made available, in cooperation with the Drug Safety Management Center.

【FDA's Issued RWD/RWE Utilization Guidelines】



2. From Real-World Evidence to Regulatory Decision Making: Case Examples

Post-marketing Drug Safety

Azilsartan Medoxomil

- Angiotensin II Receptor Blocker (ARB), drug for essential hypertension
- Celltrion, Inc. acquired full rights, including sales and patents, of Edarbi ® (Azilsartan Medoxomil) in nine Asia-Pacific (APAC) countries from Takeda Pharmaceutical Company in 2020.
- A fixed-dose combination of azilsartan and amlodipine is currently under development.

Safety of combination therapy of azilsartan medoxomil and amlodipine[1)]

- Showed no increased risk of adverse outcomes compared to other ARBs combined with amlodipine
- The study was submitted to the Center for Drug Evaluation (CDE) in Taiwan as supporting evidence for the long-term safety of standard dose (40mg) and high dose (80mg) azilsartan therapy.

1) Lee H, Hong B, Su CT, Bea S, Jeong HE, Jung K, et al. Safety of combination therapy of azilsartan medoxomil and amlodipine: a population-based cohort study. *Epidemiol Health*. 2025. doi: 10.4178/epih.e2025029

Post-marketing Drug Safety

Azilsartan Medoxomil

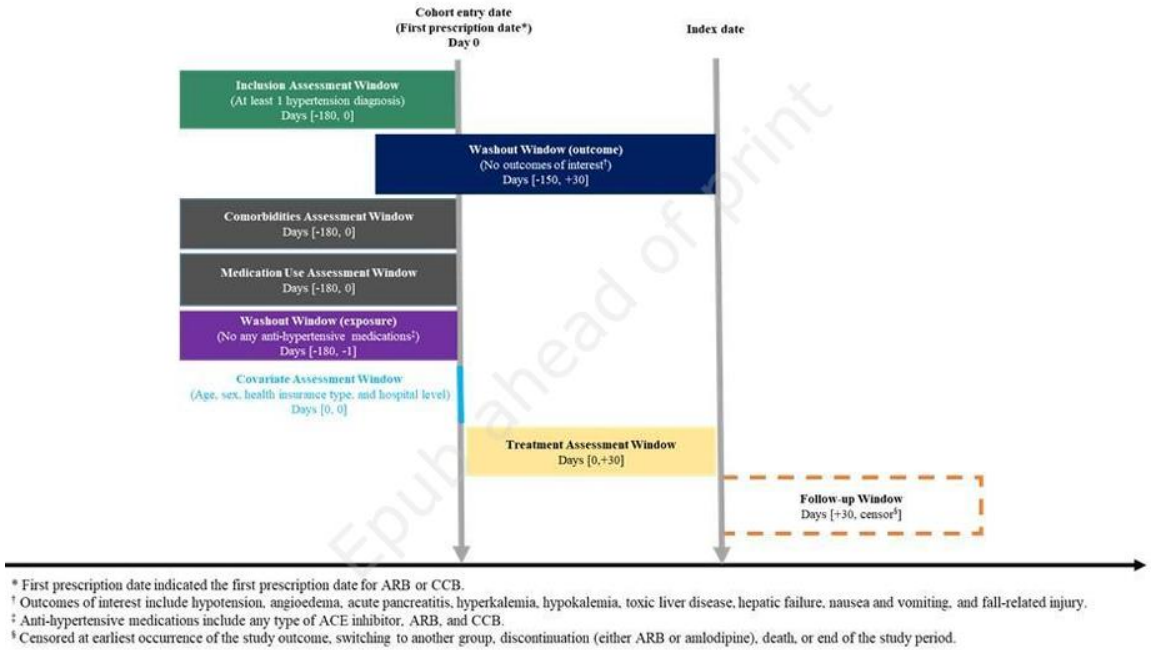
Safety of combination therapy of azilsartan medoxomil and amlodipine[1)]

- **Study objective**: to evaluate safety of combining azilsartan medoxomil with amlodipine compared to other ARBs & amlodipine in patients with hypertension
- **Study design**: Retrospective cohort study
- **Data source**:
  - South Korea: Health Insurance Review and Assessment Service (HIRA) database
  - Taiwan: National Health Insurance Research Database (NHIRD)
- **Cohort entry date**: the first prescription of ARB (azilsartan or another ARB) and/or amlodipine
- **Treatment assessment window**: a 30-day period to assess whether amlodipine was added to azilsartan (or another ARB), or vice versa
- **As-treated** follow-up approach used as the main analysis

Original article

Safety of combination therapy of azilsartan medoxomil and amlodipine: a population-based cohort study

Hyesung Lee[1], Bin Hong[2], Chris Tzu-Ting Su[3], Sungho Bea[4], Han Eol Jeong[5], Kyungyeon Jung[2], Michael Chun-Yuan Cheng[3], Zoe Chi-Jui Chang[3], Edward Chia-Cheng Lai[3], Jongyoung Lee[6]



* First prescription date indicated the first prescription date for ARB or CCB.
† Outcomes of interest include hypotension, angioedema, acute pancreatitis, hyperkalemia, hypokalemia, toxic liver disease, hepatic failure, nausea and vomiting, and fall-related injury.
‡ Anti-hypertensive medications include any type of ACE inhibitor, ARB, and CCB.
§ Censored at earliest occurrence of the study outcome, switching to another group, discontinuation (either ARB or amlodipine), death, or end of the study period.

1) Lee H, Hong B, Su CT, Bea S, Jeong HE, Jung K, et al. Safety of combination therapy of azilsartan medoxomil and amlodipine: a population-based cohort study. *Epidemiol Health*. 2025. doi: 10.4178/epih.e2025029

Post-marketing Drug Safety

Azilsartan Medoxomil

Table 2. Propensity score-matched hazard ratios of safety outcomes comparing the azilsartan + amlodipine group versus the other ARB* + amlodipine group after applying as-treated analysis†.

Outcome	Source	No. of events/total No. (%)		Hazard Ratio (95% CI)
		Azilsartan + amlodipine	Other ARB* + amlodipine	
Hypotension	HIRA	1/1521 (0.07)	2/1521 (0.13)	1.00 (0.09-11.50)
	NHIRD	0/951 (0.00)	≤3/951 (NA)	NA
	Overall	1/2472 (0.04)	NA (NA)	NA
Angioedema	HIRA	0/1521 (0.00)	1/1521 (0.07)	NA
	NHIRD	0/951 (0.00)	0/951 (0.00)	NA
	Overall	0/2472 (0.00)	1/2472 (0.04)	NA
Acute pancreatitis	HIRA	1/1521 (0.07)	2/1521 (0.13)	0.77 (0.07-8.88)
	NHIRD	≤3/951 (NA)	≤3/951 (NA)	1.00 (0.06-15.99)
	Overall	NA (NA)	NA (NA)	0.86 (0.14–5.37)
Hyperkalemia	HIRA	0/1521 (0.00)	1/1521 (0.07)	NA
	NHIRD	≤3/951 (NA)	≤3/951 (NA)	NA
	Overall	NA (NA)	NA (NA)	NA
Hypokalemia	HIRA	0/1521 (0.00)	0/1521 (0.00)	NA
	NHIRD	4/951 (0.42)	12/951 (1.26)	1.33 (0.30-5.96)
	Overall	4/2472 (0.16)	12/2472 (0.49)	NA
Toxic liver disease	HIRA	1/1521 (0.07)	6/1521 (0.39)	0.50 (0.06-4.32)
	NHIRD	0/951 (0.00)	0/951 (0.00)	NA
	Overall	1/2472 (0.04)	6/2472 (0.24)	NA
Hepatic failure	HIRA	0/1521 (0.00)	0/1521 (0.00)	NA
	NHIRD	≤3/951 (NA)	6/951 (0.63)	NA
	Overall	NA (NA)	6/2472 (0.24)	NA
Nausea and vomiting	HIRA	6/1521 (0.39)	12/1521 (0.78)	1.01 (0.38-2.71)
	NHIRD	0/951 (0.00)	≤3/951 (NA)	NA
	Overall	6/2472 (0.24)	NA (NA)	NA
Fall-related injury	HIRA	0/1521 (0.00)	1/1521 (0.07)	NA
	NHIRD	9/951 (0.95)	19/951 (2.00)	1.50 (0.53-4.21)
	Overall	9/2472 (0.36)	20/2472 (0.81)	NA

ARB, angiotensin receptor blockers; CI, confidence interval; HIRA, Health Insurance Review and Assessment Service; NA, not applicable; NHIRD, National Health Insurance Research Database.
*Other ARBs included all types of ARBs except for azilsartan.
†Patients were followed up from index date until the occurrence of study outcome, switching to another group, discontinuation (either ARB or amlodipine), death, or 180 days following index date, whichever occurs first.
Due to privacy issues in Taiwan, the exact number cannot be retrieved if the event number is less than 4 and thus not applicable.

Original article

Safety of combination therapy of azilsartan medoxomil and amlodipine: a population-based cohort study

Hyesung Lee[1], Bin Hong[2], Chris Tzu-Ting Su[3], Sungho Bea[4], Han Eol Jeong[5], Kyungyeon Jung[2], Michael Chun-Yuan Cheng[3], Zoe Chi-Jui Chang[3], Edward Chia-Cheng Lai[3], Jongyoung Lee[6]

- Showed no increased risk of adverse outcomes compared to other ARBs combined with amlodipine
  - Hypotension
  - Angioedema
  - Acute pancreatitis
  - Hyperkalemia
  - Hypokalemia
  - Toxic liver disease
  - hepatic failure
  - Nausea and vomiting
  - Fall-related injury

1) Lee H, Hong B, Su CT, Bea S, Jeong HE, Jung K, et al. Safety of combination therapy of azilsartan medoxomil and amlodipine: a population-based cohort study. *Epidemiol Health*. 2025. doi: 10.4178/epih.e2025029

Post-marketing Drug Safety

Propacetamol

- Prodrug of paracetamol (acetaminophen), non-opioid analgesic, administered intravenously
- Due to safety concerns, propacetamol was withdrawn in Europe.
- South Korea's regulatory authority requested a post-marketing surveillance to investigate safety profile.[2)]
- Real-world evidence reassured the safety of propacetamol to support regulatory decision making in South Korea.

Article | Open access | Published: 13 December 2022

A study of the regional differences in propacetamol-related adverse events using VigiBase data of the World Health Organization

Han Eol Jeong, Sungho Bea, Dongwon Yoon, Juhong Jung, Seung-Mok Park, Juhee Jeon, Young-Min Ye, Jae-Hyun Lee & Ju-Young Shin

Evaluation of the Regulatory Required Post-Authorization Safety Study for Propacetamol: Nested Case-Control and Case-Time-Control Studies

Sungho Bea[1*], Dongwon Yoon[1,2*], Han Eol Jeong[1,2], Juhong Jung[2], Seung-Mok Park[3], Juhee Jeon[3], Young-Min Ye[4], Jae-Hyun Lee[5], and Ju-Young Shin[1,2,6]

- Pharmacovigilance Study. Disproportionality Analyses using VigiBase, maintained by WHO-UMC[1)]
- Nested case-control and case-time-control studies using claims database of South Korea, 2010-2019.[2)]

1) Jeong, H.E., Bea, S., Yoon, D. *et al.* A study of the regional differences in propacetamol-related adverse events using VigiBase data of the World Health Organization. *Sci Rep* **12**, 21568 (2022). https://doi.org/10.1038/s41598-022-26211-0
2) Bea S, Yoon D, Jeong HE, et al. Evaluation of the Regulatory Required Post-Authorization Safety Study for Propacetamol: Nested Case-Control and Case-Time-Control Studies. *Yonsei Med J*. 2024;65(2):120-128. doi:10.3349/ymj.2023.0207

Post-marketing Drug Safety

Propacetamol

	Cases of propacetamol (N, %)	Non-cases of propacetamol (N, %)	rOR (95% CI)	IC (IC_{025} ‡)	Signal rOR§	Signal IC¶
Anaphylactic reaction						
Asia	75 (4.1)	15,268 (25.4)	0.13 (0.10–0.16)	− 2.59 (− 2.97)		
Europe	44 (2.7)	1285 (4.1)	0.65 (0.48–0.88)	− 0.57 (− 1.07)		
Stevens–Johnson syndrome						
Asia	19 (4.8)	15,324 (24.9)	0.15 (0.10–0.24)	− 2.35 (− 3.12)		
Europe	40 (6.8)	1289 (3.9)	1.78 (1.29–2.47)	0.76 (0.23)		O
Thrombosis						
Asia	0 (0.0)	15,343 (24.8)	N/A	N/A		
Europe	39 (23.2)	1290 (3.9)	7.45 (5.19–10.71)	2.45 (1.92)	O	O
Dermatitis - Eczema						
Asia	0 (0.0)	15,343 (24.8)	N/A	N/A		
Europe	77 (39.7)	1252 (3.8)	16.73 (12.48–22.42)	3.23 (2.85)	O	O
Injection site reaction						
Asia	1157 (63.9)	14,186 (23.6)	5.72 (5.19–6.31)	1.37 (1.27)	O	O
Europe	76 (6.3)	1253 (3.9)	1.65 (1.30–2.10)	0.65 (0.27)		O

Table 3. Signal detection of propacetamol using disproportionality methods and empirical Bayesian geometric mean in WHO-UMC VigiBase from 1987 to 2020. *AE* adverse events, *rOR* reporting odds ratio, *CI* confidential interval, *WHO-UMC* World Health Organisation-Uppsala Monitoring Centre, *IC* information component. †'O' within the column 'Signal' denotes that it met the threshold for a signal. ‡IC_{025} is lowest bound of 95% CI for IC. §Safety signal detection with rOR assessed as AEs where thresholds of rOR > 2. ¶Safety signal detection with IC assessed as AEs where $IC_{025} > 0$.

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Han Eol Jeong, Sungho Bea, Dongwon Yoon, Juhong Jung, Seung-Mok Park, Juhee Jeon, Young-Min Ye, Jae-Hyun Lee & Ju-Young Shin

- Pharmacovigilance Study. Disproportionality Analyses using **VigiBase**, maintained by WHO-UMC[1)]
- **Study design**: Observational pharmacovigilance study comparing adverse events reporting patterns: **disproportionality analyses**
  - Reporting odds ratio (rOR), Information component (IC_{025})
- Propacetamol vs non-propacetamol injectable antipyretics in Asia and Europe separately.
- Reporting Ratio of propacetamol-related anaphylaxis were low for Europe and Asia.
- Signals were found for thrombosis and contact dermatitis/eczema in Europe, while these were not detected in Asia.
- In Asia, a safety signal was detected for injection site reactions.

1) Jeong, H.E., Bea, S., Yoon, D. *et al.* A study of the regional differences in propacetamol-related adverse events using VigiBase data of the World Health Organization. *Sci Rep* **12**, 21568 (2022). https://doi.org/10.1038/s41598-022-26211-0

Post-marketing Drug Safety

Propacetamol

Adverse events*	Patients		OR (95% CI)	
	Cases	Controls†	Crude	Adjusted‡
Anaphylaxis	61 (100)	173 (100)		
Propacetamol use	2 (3.28)	0 (0.00)	N/A	N/A
Propacetamol non-use	59 (96.72)	173 (100)	Reference (1.00)	Reference (1.00)
Thrombosis	95 (100)	268 (100)		
Propacetamol use	16 (16.84)	19 (7.09)	2.66 (1.30–5.41)	1.60 (0.71–3.62)
Propacetamol non-use	79 (83.16)	249 (92.91)	Reference (1.00)	Reference (1.00)
SJS	1 (100)	4 (100)		
Propacetamol use	0 (0.00)	0 (0.00)	N/A	N/A
Propacetamol non-use	1 (100)	4 (100)	Reference (1.00)	Reference (1.00)

	Propacetamol use		OR (95% CI)		CTC ratio (95% CI)
	Risk period	Control period	Crude OR	Adjusted OR*	
Anaphylaxis†					N/A
CCO cases	1 (1.69)	2 (1.13)	1.73 (0.10–30.76)	0.89 (0.02–32.79)	
CCO controls	0 (0.00)	5 (0.99)	N/A	N/A	
Thrombosis‡					0.56 (0.09–3.47)
CCO cases	6 (9.23)	10 (5.13)	1.86 (0.65–5.26)	0.68 (0.15–3.04)	
CCO controls	8 (5.67)	18 (4.26)	1.38 (0.57–3.36)	1.21 (0.43–3.42)	
SJS§					N/A
CCO cases	0 (0.00)	0 (0.00)	N/A	N/A	
CCO controls	0 (0.00)	0 (0.00)	N/A	N/A	

Evaluation of the Regulatory Required Post-Authorization Safety Study for Propacetamol: Nested Case-Control and Case-Time-Control Studies

Sungho Bea[1*], Dongwon Yoon[1,2*], Han Eol Jeong[1,2], Juhong Jung[2], Seung-Mok Park[3], Juhee Jeon[3], Young-Min Ye[4], Jae-Hyun Lee[5], and Ju-Young Shin[1,2,6]

- **Nested case-control** and **case-time-control studies** using claims database of South Korea, 2010-2019.[1)]
- **Data source**: Health Insurance Review and Assessment (HIRA) database
- **Nested case-control**:
  - Each case was matched to controls from the same risk set based on covariates, including calendar year at cohort entry.
- **Case-time-control**:
  - A within-person approach was used to minimize confounding by time-invariant personal characteristics.
  - External time-trend controls were included to adjust for background prescribing trends.
- In both nested case-control and case-time-control studies, propacetamol use was **not associated with an increased risk** of anaphylaxis, thrombosis, or Stevens–Johnson syndrome(SJS).

1) Bea S, Yoon D, Jeong HE, et al. Evaluation of the Regulatory Required Post-Authorization Safety Study for Propacetamol: Nested Case-Control and Case-Time-Control Studies. *Yonsei Med J*. 2024;65(2):120-128. doi:10.3349/ymj.2023.0207

Repurposing for New Indications

Losartan

- Angiotensin II Receptor Blocker (ARB), drug for essential hypertension
- In December 2023, the addition of indication "**reduction of stroke risk in patients with hypertension and left ventricular hypertrophy (LVH)**" was approved in South Korea.
- The indication expansion was based on the LIFE(Losartan Intervention For Endpoint reduction in hypertension) study[1)], published in 2022 in The Lancet. However, it included only a small number of Asian participants (n=43).
- Organon Korea LLC is currently investigating the effect of losartan (Cozaar®) use in the risk of stroke in **Korean patients** with hypertension and left ventricular hypertrophy (LVH) as a part of Korean risk management plan (RMP).

1) Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359(9311):995-1003. doi:10.1016/S0140-6736(02)08089-3

Repurposing for New Indications

Losartan

Evaluation of stroke risk associated with losartan use in Korean hypertensive patients with left ventricular hypertrophy: a population-based cohort study

- **Objective**: to evaluate the effect of losartan in Korean hypertensive patients with ventricular hypertrophy (LVH) and to compare the absolute risk of stroke between losartan and atenolol
- **Study design**: Retrospective cohort study
- **Data source**: **National health information database (NHID)** of South Korea, linked with claims data and health check-up data
- **Cohort entry date**: Date of LVH diagnosis
- Patients with a diagnosis of hypertension and a prescription for antihypertensive medication within 2 years before cohort entry
- **Primary outcome**:
  - Cumulative incidence of stroke (fatal and non-fatal) over time in the losartan group
  - Number of stroke events (fatal and non-fatal), incidence rate per 1,000 person-years, and 95% confidence interval in the losartan group
- **Intention-to-treat (ITT)** follow-up approach used as the main analysis

Repurposing for New Indications

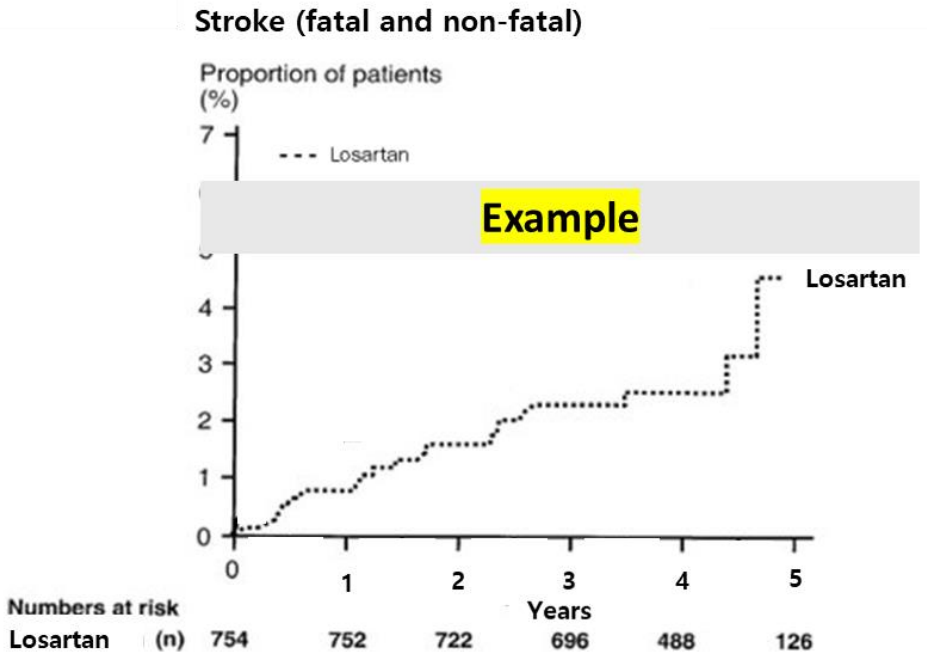
Losartan

Patient Characteristics	Diagnosis	Procedure†
De-identified patient code, age, sex, region of residence, income level, health insurance type (eg, medical aid), date of death*	ICD-10 diagnosis code, specialty, date of diagnosis, diagnosis setting (eg, inpatient)	Screening test, surgery, non-pharmacological interventions, date of procedure, procedure setting (eg, inpatient)

Prescription	Service Utilization	Health Examination Records¶
Drug chemical code†, date of prescription, days supply, dosage, route of administration, prescription setting (eg, inpatient)	Length of hospital admission, ambulatory care, medical cost, others	Height‡, weight‡, BMI‡, smoking status‡, frequency of exercise‡ lab test results (eg, blood pressure)

†coded by a domestic code system, corresponding to ATC classification
*cause of death is available upon request
‡based on self-reported questionnaire
¶Conducted biennially (non-mandatory)

Variables available through the NHIS-NHID database



Conditional Approval to Full Approval

Lazertinib

- Third-generation tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR-TKI), drug for non-small cell lung cancer (NSCLC) patients with common EGFR mutation and T790M mutation
- Lazertinib (Leclaza®) first received **conditional approval** for the second-line treatment of EGFR mutation-positive NSCLC in South Korea.
- By utilizing real-world data, Yuhan Corp. was able to fulfil the conditions for approval of Leclaza as a second-line treatment, receiving **full approval**.

Conditional Approval to Full Approval

Lazertinib

Article

Lazertinib versus Platinum-Based Chemotherapy with Epidermal Growth Factor Receptor (EGFR)-Positive Non-Small-Cell Lung Cancer after Failing EGFR-Tyrosine Kinase Inhibitor: A Real-World External Comparator Study

Junho Lee [1,†], Hyesung Lee [2,3,†], Dongwon Yoon [2,3], Eun-Young Choi [2], Jieun Woo [3], Bobae Jo [4], Sohee Kim [4], Ju-Young Shin [2,3,5,*] and Hyun Ae Jung [1,*]

Efficacy of Lazertinib in patients with EGFR-positive NSCLC following EGFR-TKI failure[1)]

- **Objective**: to compare the efficacy of lazertinib and platinum-based chemotherapy in patients who had previously received EGFR-TKI treatment
- No prior direct comparison existed between Lazertinib and platinum-based chemotherapy, and randomized controlled trial (RCT) is difficult due to ethical and economic challenges; Osimertinib is the standard for T790M-positive patients
- **Study design**: External control retrospective study (external comparator study)
- **Data source**:
  - The Lazertinib group: individual-patient-level data from LASER 201, LASER 301, LASER PMS clinical studies
  - The external comparator (Pt-based chemotherapy group): real-world individual-patient-level data from the Samsung Medical Center Clinical Data Warehouse (SMC-CDW), named ROOT-HEALTH
- 1:1 propensity score (PS) matching, Kaplan-Meier method & log-rank test, Cox proportional hazard model
- Key outcomes:
  - Primary: Progression-Free Survival (PFS)
  - Secondary: Overall Survival (OS), Objective Response Rate (ORR), Time to Treatment Discontinuation (TTD), and Disease Control Rate (DCR)

1) Lee J, Lee H, Yoon D, et al. Lazertinib versus Platinum-Based Chemotherapy with Epidermal Growth Factor Receptor (EGFR)-Positive Non-Small-Cell Lung Cancer after Failing EGFR-Tyrosine Kinase Inhibitor: A Real-World External Comparator Study. *Cancers (Basel)*. 2024;16(12):2169. Published 2024 Jun 7. doi:10.3390/cancers16122169

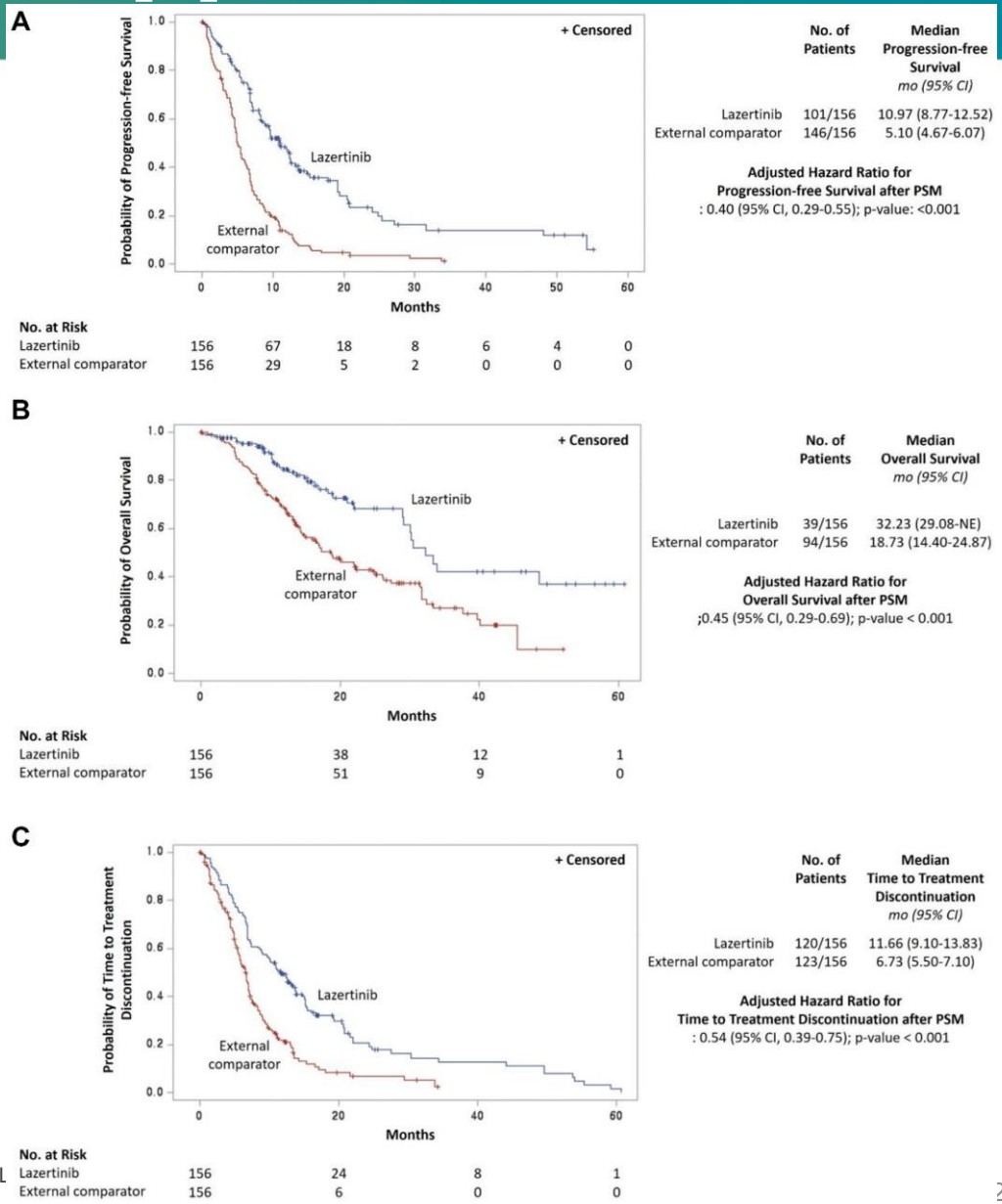
Conditional Approval to Full Approval

Lazertinib

Efficacy of Lazertinib in patients with EGFR-positive NSCLC following EGFR-TKI failure[1)]

- (A) Progression-free survival after propensity score matching.
- (B) Overall survival after propensity score matching.
- (C) Time to treatment discontinuation after propensity score matching.

- The PFS was significantly longer in those patients treated with lazertinib than in those treated with platinum-based chemotherapy after PSM.
  - Lazertinib: median PFS 10.97 months (95% CI: 8.77-12.52)
  - Pt-based chemo: median PFS 5.10 months (95% CI: 4.67-6.07)
  - Adjusted HR=0.40 (95% CI: 0.29-0.55, p<0.001)
- Lazertinib also demonstrated superior OS, ORR, and TTD compared to platinum-based chemotherapy
- <u>Lazertinib showed significantly better efficacy</u> compared with platinum-based chemotherapy.



1) Lee J, Lee H, Yoon D, et al. Lazertinib versus Platinum-Based Chemotherapy with Epidermal Growth Factor Receptor (EGFR)-Positive Non-Small-Cell L
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Conditional Approval to Full Approval

Lazertinib

- Consistent results were obtained across subgroup and sensitivity analyses
- External controls can be an acceptable alternative when it is impractical or unethical for an internal control.

Table 2. Results of subgroup and sensitivity analyses after propensity score matching.

	Adjusted HR (95% CI) [a]			Adjusted OR (95% CI) [a]	
	PFS	OS	TTD	ORR	DCR
Subgroup analyses					
Overall	0.40 (0.29–0.55)	0.45 (0.29–0.69)	0.54 (0.39–0.75)	1.92 (1.08–3.39)	1.96 (0.93–4.13)
Age group					
<65 years	0.40 (0.25–0.62)	0.50 (0.27–0.91)	0.55 (0.35–0.88)	1.45 (0.66–3.17)	0.98 (0.36–2.71)
≥65 years	0.40 (0.23–0.68)	0.68 (0.34–1.36)	0.74 (0.44–1.24)	2.00 (0.81–4.98)	2.16 (0.68–6.88)
Sex					
Male	0.32 (0.18–0.58)	0.36 (0.16–0.83)	0.52 (0.29–0.96)	3.05 (1.16–8.03)	4.04 (0.91–18.00)
Female	0.44 (0.28–0.69)	0.65 (0.36–1.17)	0.58 (0.37–0.92)	1.81 (0.80–4.08)	2.53 (0.92–6.94)
Smoking status					
Ever smoker	0.38 (0.20–0.72)	0.36 (0.15–0.84)	0.54 (0.28–1.04)	2.60 (0.87–7.75)	1.94 (0.46–8.20)
Never smoker	0.34 (0.22–0.51)	0.55 (0.32–0.93)	0.48 (0.32–0.73)	2.06 (0.99–4.29)	2.70 (1.02–7.11)
Sensitivity analyses					
Main analyses [b]	0.40 (0.29–0.55)	0.45 (0.29–0.69)	0.54 (0.39–0.75)	1.92 (1.08–3.39)	1.96 (0.93–4.13)
Applying IPTW	0.50 (0.43–0.58)	0.62 (0.50–0.76)	0.67 (0.58–0.79)	1.62 (1.20–2.19)	3.04 (2.01–4.60)
Restricted to the lazertinib group [c]	0.37 (0.25–0.55)	0.54 (0.33–0.87)	0.46 (0.31–0.69)	2.12 (1.04–4.32)	2.72 (1.13–6.52)
Alternative PS model 1 [d]	0.39 (0.27–0.55)	0.51 (0.32–0.82)	0.53 (0.38–0.75)	1.79 (0.998–3.21)	1.78 (0.84–3.76)
Alternative PS model 2 [e]	0.46 (0.32–0.65)	0.62 (0.39–0.99)	0.63 (0.44–0.89)	1.90 (1.05–3.42)	2.09 (0.99–4.43)

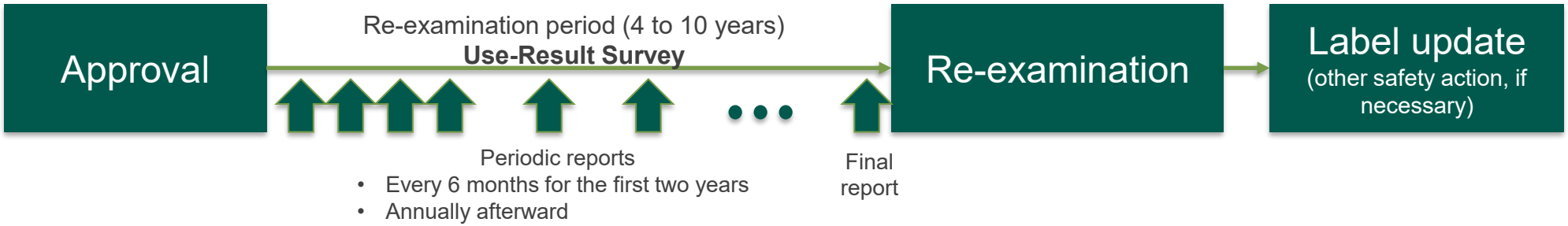
PFS: Progression-Free Survival
OS: Overall Survival
ORR: Objective Response Rate
TTD: Time to Treatment Discontinuation
DCR: Disease Control Rate

1) Lee J, Lee H, Yoon D, et al. Lazertinib versus Platinum-Based Chemotherapy with Epidermal Growth Factor Receptor (EGFR)-Positive Non-Small-Cell Lung Cancer after Failing EGFR-Tyrosine Kinase Inhibitor: A Real-World External Comparator Study. *Cancers (Basel)*. 2024;16(12):2169. Published 2024 Jun 7. doi:10.3390/cancers16122169

3. Challenges in RWD Utilization and the Way Forward

Challenges

- Industry and CROs remain **familiar with conventional pathways** (re-examination, clinical trials, etc.).
  - The pharmaceutical industry has yet to fully adapt to the use of real-world data in post-marketing safety surveillance: **Re-examination** process remains an important component.
    - ✓ Re-examination: **use-result survey**, special surveillance (epidemiologic studies, database studies, etc.), post-marketing clinical study
- **Terminology remains unsettled**: Key concepts related to RWD/RWE have yet to be clearly defined and standardized in the local regulatory and research context.



Challenges

- Structural and human resource constraints:
  - **Shortage of domestic reviewers and researchers** with deep understanding of RWE methodologies and regulatory science
  - **Lack of experience and environment** to utilize medical big data
    - ✓ Few applications of domestic drug license review data
    - ✓ Sometimes, lack of sufficient patient populations in Korea to support adequately powered studies
  - **Lack of specific guidance** on how to utilize RWD
  - **Limited access to real-world data:** High regulatory hurdles to national claims data for industry use
- Limitations of real-world data
  - Hospital EMR data could face: Follow-up loss and fragmented patient history, Data linkage and standardization issues across institutions

Database Access (DIA survey, ongoing)

Survey Structure

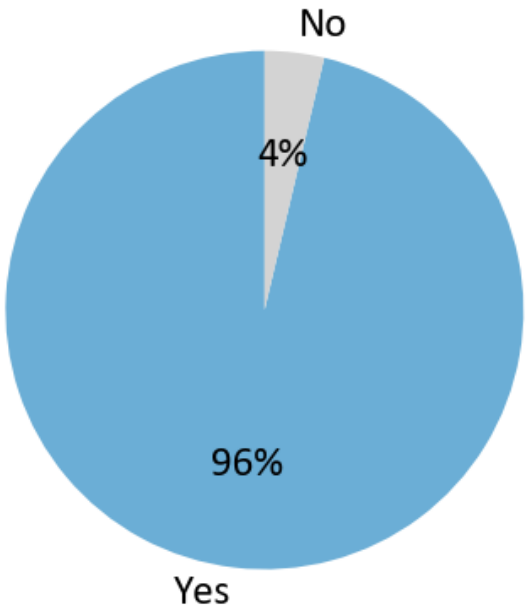
- **Study Period**: January–March 2025
- **Participants**: Regulatory experts and academic researchers from China, Japan, South Korea, and Singapore
- **Objective**: To assess the structure, content, accessibility, and regulatory applications of real-world data (RWD) databases across four Asian countries
- **Structure**
  - **Section 1: Demographics and General Information**
    - Information on the respondent's affiliation, country, and experience with RWD
  - **Section 2: Access and Characteristics of RWD Databases**
    - Structured information on database type, data elements, accessibility, and ownership
  - **Section 3: RWD Application for Regulatory Decision-Making**
    - Actual use cases, regulatory purposes, and challenges in applying RWD
  - **Section 4: Additional Comments**
    - Open-ended suggestions for improving RWD use in regulatory science

Database Access (DIA survey, ongoing)

Accessibility and Governance

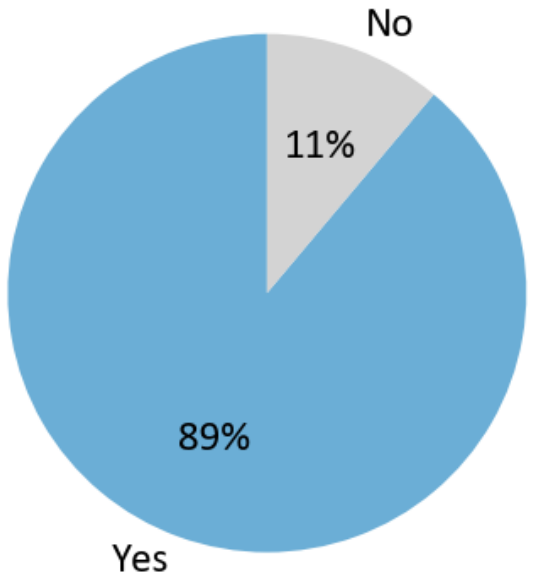
- **Real-World Databases Accessible to Government, Academic, and Industry Sectors**
  - While government and academic institutions have high levels of access (96% and 89%), only 48% of databases are accessible to the industry sector.
  - Limited industry access may constrain the generation and regulatory use of real-world evidence.

Government Access



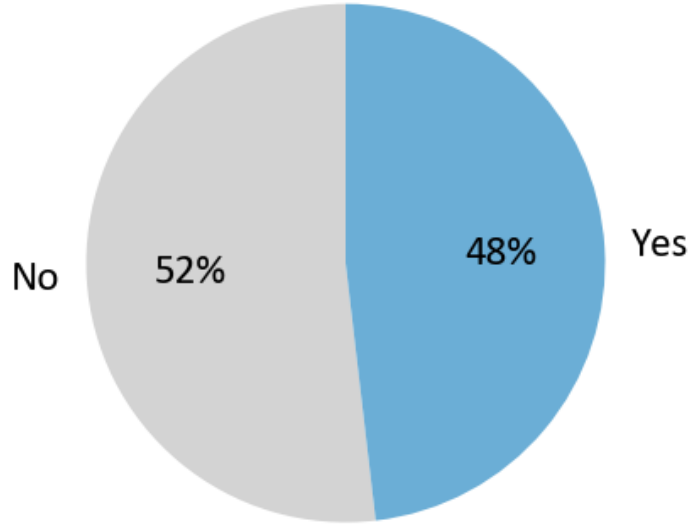
No access : 1 out of 27 (4%)

Academic Access



No access : 3 out of 27 (11%)

Industry Access



No access : 14 out of 27 (52%)

Trends in regulatory science in South Korea

South Korea

- Regulatory authorities such as the Ministry of Food and Drug Safety (MFDS) are actively encouraging pharmaceutical companies to explore RWD-utilizing research.
- **Act on Regulatory Science Innovation for Supporting Food and Drug Safety and Commercialization(2023)**
  - It aims to contribute to the safe and healthy life of the people by reasonably performing safety management of food and drug based on regulatory science for the safe use and rapid commercialization.

Ministry of Food and Drug Safety, 2024 project keyword is 'Regulatory Science Innovation Act and Human Resource Training'

Park Yoon-joo, Director of the Korea Food and Drug Safety Evaluation Service, "We will add value to innovative products through global regulation and talent training"

The Ministry of Food and Drug Safety plans to develop domestic bio-health regulatory science by nurturing human resources along with the 'Regulatory Science and Innovation Act on Safety and Commercialization Support for Food and Drugs' next year.

Park Yoon-joo, director of the Food and Drug Safety Evaluation Service of the Ministry of Food and Drug Safety, said this in a keynote lecture under the theme of 'MFDS's Strategic Plan for Advancing Regulatory Science' at the 2023 Fall Conference of the Korea Federation of Regulatory Science (hereinafter referred to as the Regulatory Science Society) on the 8th. The conference was held under the theme of 'Recent Changes in Bio-Health Innovations and Challenges in Regulatory Science' at The K Hotel Seoul, Seocho-gu, Seoul.

The Regulatory Science and Innovation Act was amended by the Ministry of Food and Drug Safety on August 16 to establish a legal basis for the launch of domestic regulatory science, such as regulatory science concepts, food and drug safety management, regulatory science research, commercialization support, and professional training.

In order to provide more professional support to the pharmaceutical industry, which is developing rapidly under the existing promotion law, details such as △food and drug safety management, regulatory science research, △regulatory consistency review, △ commercialization support, △ professional manpower training, △ public-private cooperation promotion and international cooperation have been added.

Director Park Yoon-ju explained about the Regulatory Science and Innovation Act, "The purpose of the Act is to lead a safe and healthy life for the people by rationally carrying out safety principles based on regulatory science for the safe use and rapid commercialization of food and medicine."

First of all, the MFDS will conduct regulatory science research and development projects. According to Director Park, unlike R&D by other ministries that support product-based technologies for the purpose of industry promotion, regulatory science R&D is characterized by a strong public nature, such as the development of safety standards and specifications and safety and effectiveness evaluation technologies.

The MFDS R&D field is broad from product licensing to production, distribution, and consumption. Director Park condensed the key strategies of MFDS's regulatory science R&D into four categories: △Standards and specifications for food and drugs, △Risk assessment technology for human exposure to hazardous substances, △ Safety and effectiveness evaluation technology for medical products, and △Test and analysis technology for food and drugs.

http://m.yakup.com/news/index.html?mode=view&nid=288343

Trends in regulatory science in South Korea

- **Act on Regulatory Science Innovation for Supporting Food and Drug Safety and Commercialization(2023)**

Productization Support

- **BRIDGE Project(2023~)**
  - Standardize domestic regulations to global standards
  - R&D coordination
  - Consultation with regulatory experts
  - ✓ **R&D coordination**
    From the planning stage of the study, review the product classification, regulatory target, and evaluation technology necessity.

Regulatory Science R&D

- **Focus on publicity**
  - Development of safety standards
  - Safety and effectiveness evaluation technologies
- **Research strategy(2024)**
  - Standards & Specifications of food and drug
  - Risk Assessment Skill for human exposure to hazardous substances
  - Technology for evaluating the Drug's Safety & Efficacy
  - Technology for Testing & Analyzing food and drug

Human Resources Development Project

- Operate **Regulatory Science Human Resources Development Universities(2021~)** in eight areas, including food, drug, and medical devices.
- **Cultivate expertise** with overall knowledge of regulatory science and research capabilities related to drug evaluation.

⇒ **Our current participation in guideline development ensures that practical considerations and sector expertise are incorporated into future frameworks.**

THANK YOU

성균관대학교
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SUNG KYUN KWAN UNIVERSITY(SKKU)