Understanding the adoption of new drugs decided by several stakeholders in the South Korean market

Kyung-Bok Son

sonkyungbok@ewha.ac.kr

sonkyungbok@gmail.com

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- Regulatory approval and reimbursement decisions are necessary if new drugs are to become accessible in a timely manner
  - The process of regulatory approval and the establishment of reimbursement decisions varies across countries
    - In 1995, the European Union adopted the "Centralized Procedure" to evaluate new drugs and since then, has granted regulatory approval that is valid in all EU member states
    - However, each member state still individually manages its own pricing and reimbursement decision

Introduction

- The South Korean government adopted health technology assessments for reimbursement decisions concerning new medicines in 2006
  - A positive list system (PLS) was then introduced in 2007
  - There have been concerns about "delay in access to new medicines" since health technology assessments adopted in Korea

- To address these concerns, the government introduced a series of policies to reinforce access to new medicines
  - The government
    - introduced risk sharing agreements, which are similar to managed entry schemes in European countries ,
    - adopted a flexible incremental cost-effectiveness ratio (ICER) threshold in 2013,
    - and exemption from price negotiations between manufacturers and the NHIS and exemption from the health technology assessment for selected new medicines were newly introduced in 2015

- We are interested in the duration from regulatory approval to reimbursement decision for new drugs in the Korean market.
  - This topic is noteworthy because there are many decision points determined by various stakeholders, such as
    - manufacturers,
    - the Ministry of Food and Drug Safety (MFDS),
    - the Health Insurance Review and Assessment Service (HIRA),
    - the National Health Insurance Service,
    - and the Ministry of Health and Welfare (MOHW)

- Given these various players and processes, delays in access to medicines may occur at various points
  - Sometimes, a manufacturer may intentionally delay launching new medicines in the market even after regulatory approval, specifically in a low-price market,
  - while the pricing and reimbursement authority may cause a delay if the submitted dossiers are incomplete or do not contain enough information for decision making,

1. to analyze the duration between regulatory approval and reimbursement decision for new medicines

2. to evaluate various factors affecting the timely availability of new medicines

Model

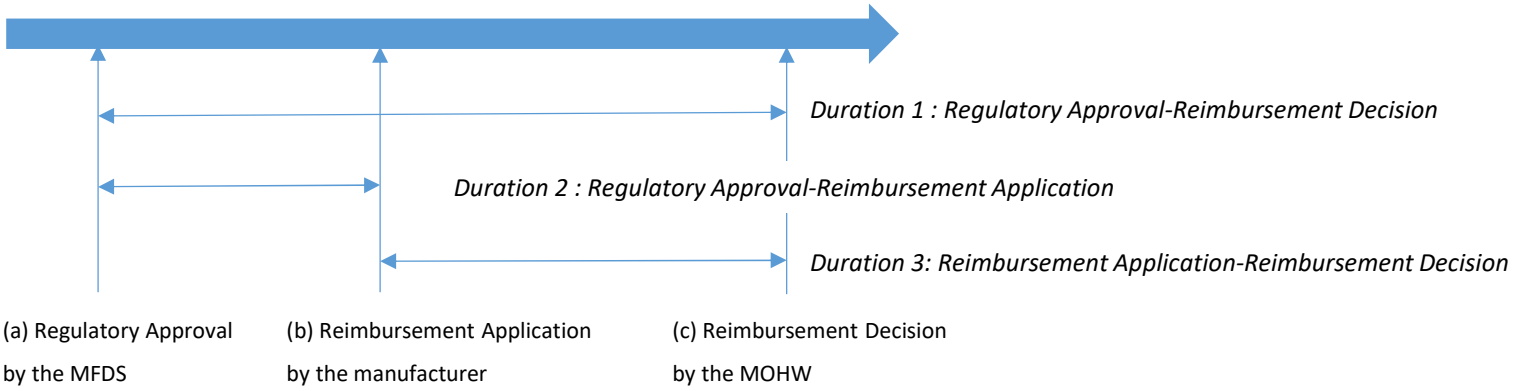
- selected several decision points

  - the MFDS approves new medicines,
  - a manufacturer decides whether to apply for reimbursement,
  - the HIRA reviews the submitted dossiers,
  - the NHIS negotiates the price with the manufacturers,
  - and the MOHW determines final reimbursement including price

Model

- and subdivided the duration into
- regulatory approval–reimbursement application and

  reimbursement application–reimbursement decision



Model

- We applied an event history model for a statistical estimation of the duration

  - Kaplan-Meier survival estimates as a univariate tool and
  - the proportional hazards model for a multivariate approach to determine the relative impact of the specific factors on various durations

    - Data management and analysis were performed using R statistical software (version 3.4.1). Statistical significance was defined as p-values less than 0.05

Model

- In our model, we included five discrete factors:
  - manufacturing type,
    - import, locally manufactured, locally developed and manufactured;
  - product type,
    - chemicals and biologics;
  - the Anatomical Therapeutic Chemical Classification (ATC)
  - clinical effectiveness of the medicine as decided by the PBC,
    - improved, similar/noninferior, and others;
  - and the period,
    - before 2014, after 2014

- Building upon the definition by the MFDS, we defined new medicines based on their active ingredient
  - We selected new medicines designated by the MFDS between 2007 and 2016 for this study
    - Note that the new PLS system was introduced in 2007
  - The data set used in this study was obtained from publicly available information prepared by the MFDS.

Data source_2

- We retrieved documents from the PBC posted on the HIRA website to collect information on reimbursement decisions
  - We found information on reimbursement recommendations by the PBC and the date when the application was reviewed
  - It should be noted that manufacturers can decide whether to apply for reimbursement under the PLS
    - Thus, we excluded new medicines that have not had applications made for reimbursement.

New medicines applied for a reimbursement decision

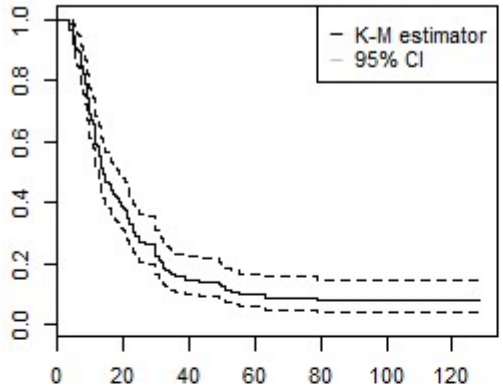
		2007-2013 First period	2014-2016 Second period
Reimbursement	yes	75	42
	no	10	1
Duration [1),2)] (right censored)	approval_reimbursement decision	29.24, (28.56)	13.40, (9.66)
	approval_reimbursement trial	10.85, (9.32)	8.60, (6.77)
	reimbursement trial_ reimbursement decision	18.39, (25.33)	4.79, (5.73)
Duration (reimbursed drugs only)	approval_reimbursement decision	20.61, (14.82)	12.83, (9.04)
	approval_reimbursement trial	9.95, (8.77)	8.50, (6.82)
	reimbursement trial_ reimbursement decision	10.66, (10.34)	4.33, (4.92)
Product types	chemicals	74	35
	biologics	11	8
Manufacturing types	import	68	36
	local manufacturing	11	2
	local development and manufacturing	6	5
ATC	ATC J or L	29	21
	others	56	22
Clinical effectiveness	improved	27	15
	similar/non-inferior	26	18
	others	32	10

1) unit: months

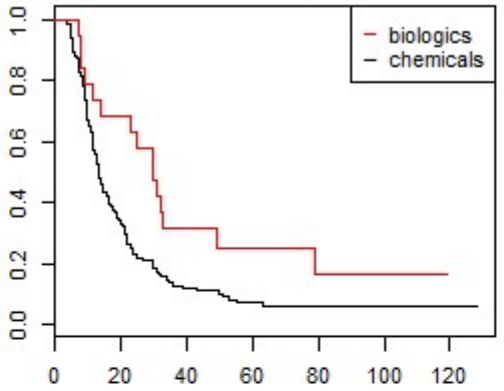
2) mean (standard deviation)

Kaplan-Meier estimates_1

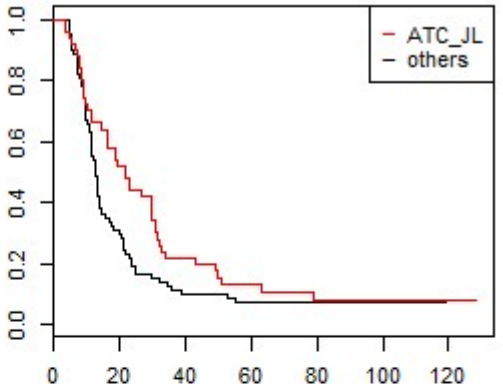
Approval-Decision



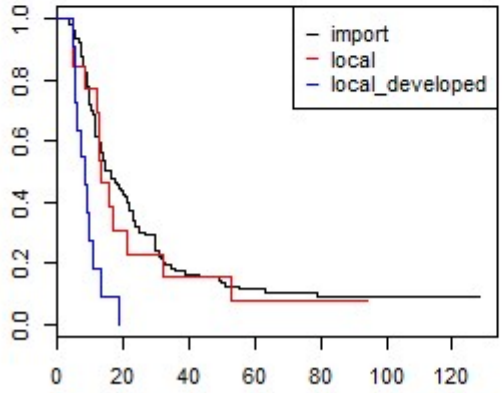
drug types



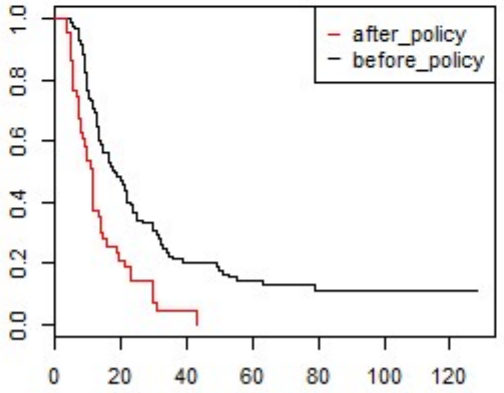
ATC classification



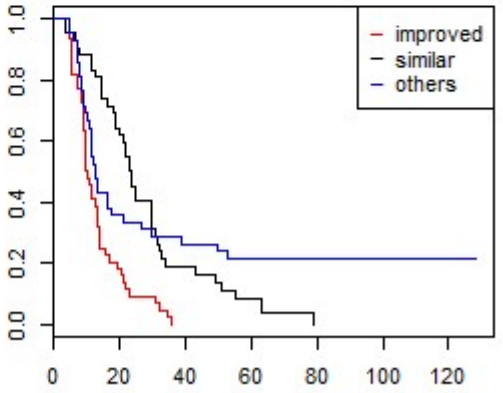
manufacturing



policy

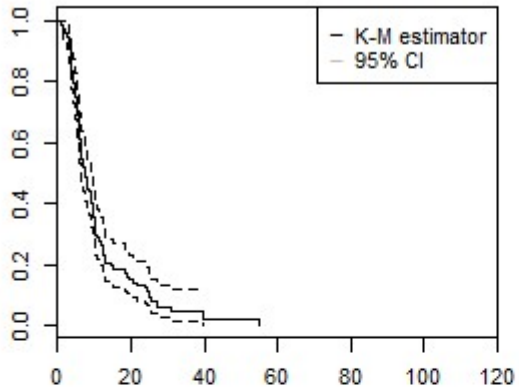


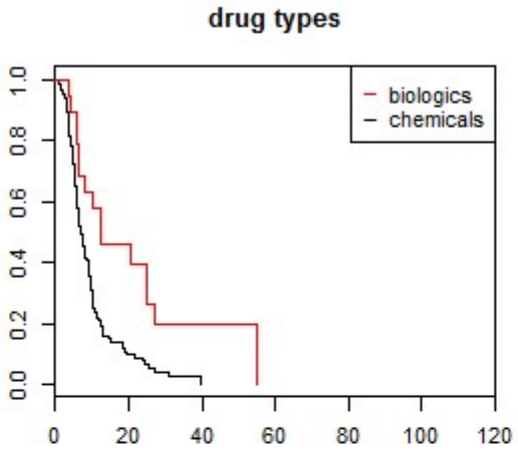
clinical effectiveness

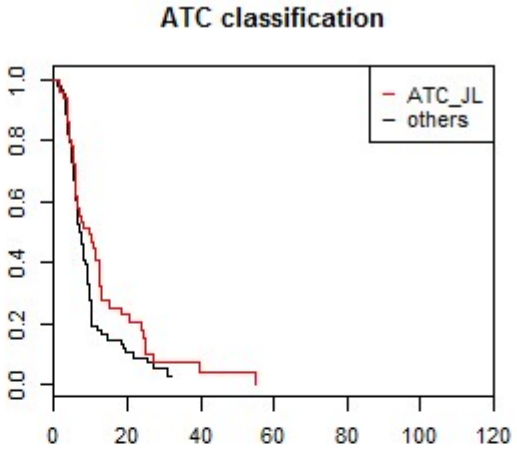


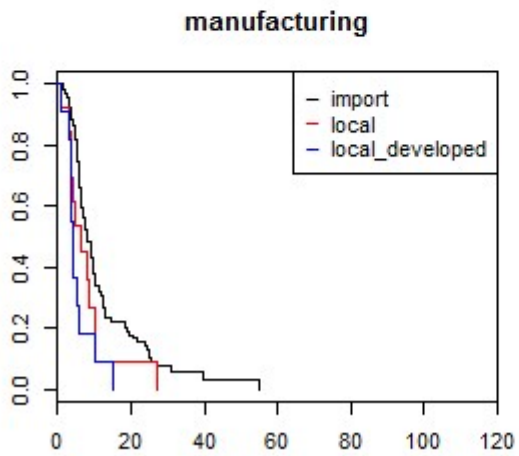
Kaplan-Meier estimates_2

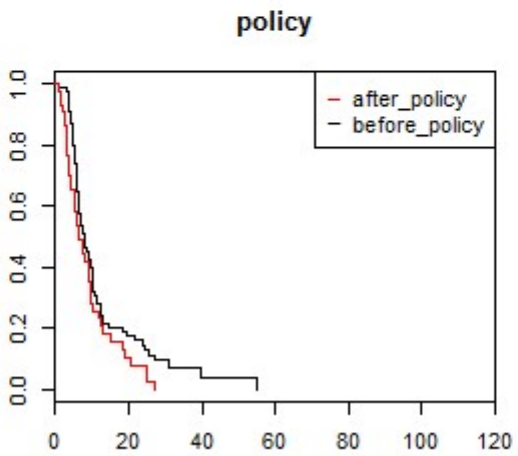
Approval-Trial

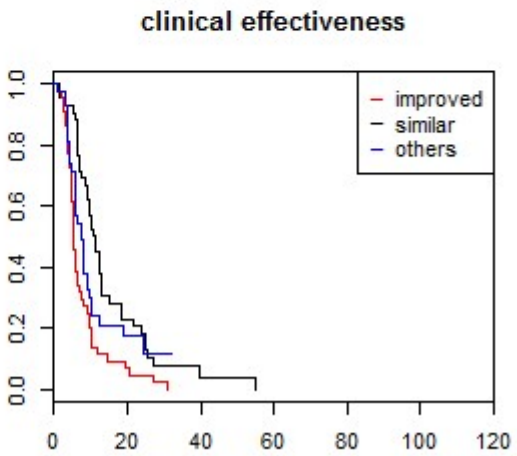






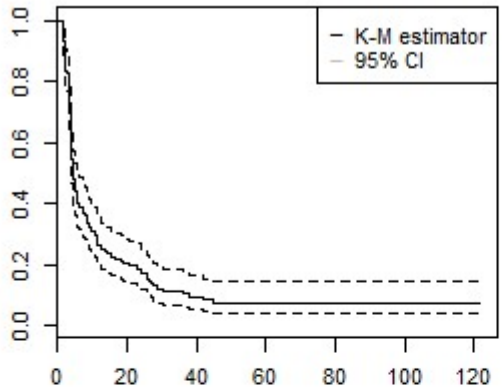


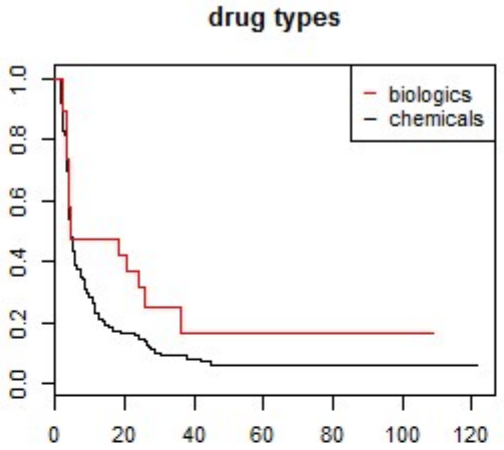


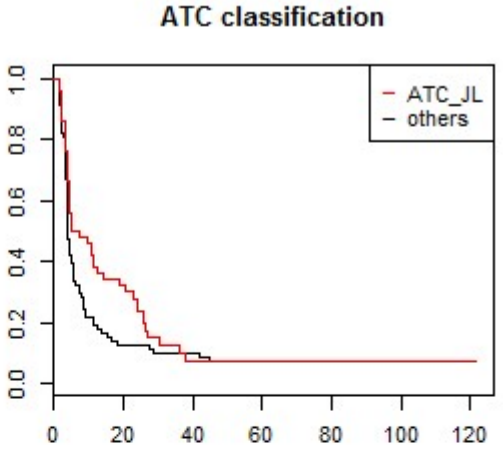


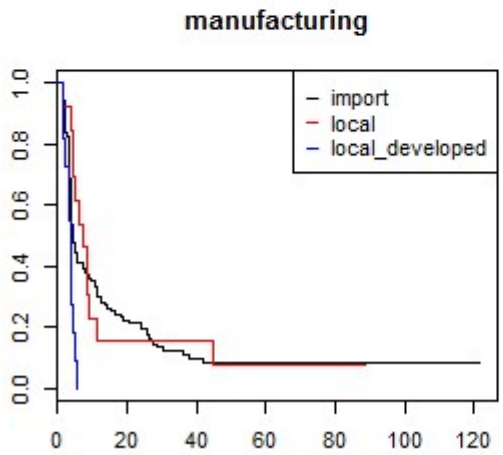
Kaplan-Meier estimates_3

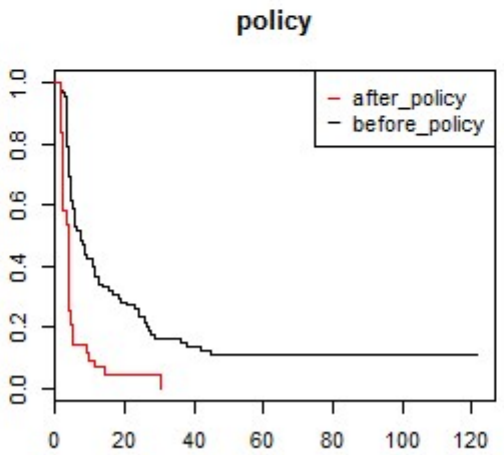
Trial-Decision

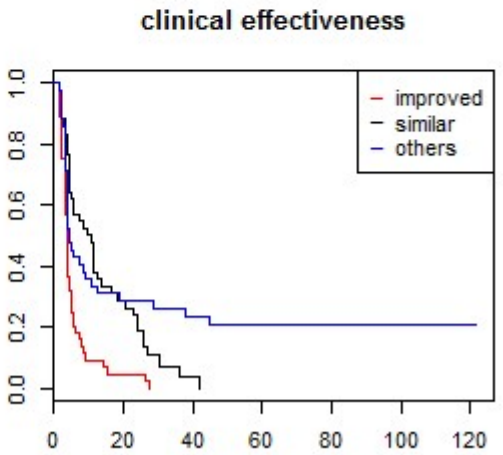












Cox proportional hazards model

Table 1 Results for the discrete factor effects and the linear effects from the Cox model with the duration as outcome

Variable		Model 1 (approval decision)			Model 2 (approval trial)			Model 3 (trial decision)			Model 3_1 (trial decision)		
		Coefficient	Standard Error	p-value	Coefficient	Standard Error	p-value	Coefficient	Standard Error	p-value	Coefficient	Standard Error	p-value
Manufacturing types	locally manufactured (Ref. import)	-0.097	0.317	0.760	0.208	0.326	0.523	-0.276	0.320	0.388	-0.305	0.320	0.340
	locally developed and manufactured	1.064'	0.349	0.002	0.784'	0.338	0.020	0.349	0.355	0.325	0.287	0.356	0.420
Product types	biologics (Ref. chemicals)	-0.650'	0.295	0.027	-0.787'	0.310	0.011	-0.316	0.292	0.279	-0.194	0.299	0.515
Clinical effectiveness	improved (Ref. similar/non-inferior)	-0.597'	0.253	0.018	-0.687'	0.265	0.009	-0.443'	0.259	0.087	-0.338	0.264	0.199
	uncertain/others	-0.716'	0.252	0.004	-0.320	0.240	0.183	-0.679'	0.263	0.009	-0.609'	0.265	0.021
ATC	ATC J or L (Ref. others)	-0.468	0.231	0.042	-0.010	0.242	0.968	-0.520'	0.221	0.018	-0.481	0.217	0.026
Period	the second period (Ref. the first)	1.005'	0.223	0.000	0.513'	0.212	0.015	1.041'	0.221	0.000	0.987'	0.221	0.000
Duration	approval_trial										-0.024'	0.015	0.099

Summary of findings

- First, a series of policies that were introduced to reinforce access to medicines after 2014 was effective in improving the timely availability of new medicines
  - Specifically, the second period shortened all durations in the models, including approval–decision, approval–application, and application–decision
  - This result indicates that policies led manufacturers to apply for reimbursement earlier, and the authorities, including the HIRA, the NHIS, and the MOHW, to more promptly offer a favorable decision

Summary of findings

- Second, biologics (reference chemicals), improved medicines and medicines that are uncertain from the perspective of clinical effectiveness (reference similar medicines), and medicines belonging to ATC J or L (reference other classifications) presented significant delays in the duration between regulatory approval and reimbursement decision (or in model 1)

Summary of findings

- However, different patterns were presented in models 2 and 3
  - For instance, biologics and improved medicines experienced delays in the duration between regulatory approval and reimbursement trial
    - This result indicates that these factors influenced the manufacturer's strategic decision on applying for the reimbursement trial
    - In other words, manufacturer may unintentionally or intentionally delay the application due to either preparing the dossiers submitted to the HIRA or to strategically considering that Korea is a low-price market and external referencing price in other markets
  - However, uncertain drugs from the perspective of clinical effectiveness and ATC J or L delayed the duration between reimbursement trial and reimbursement decision
    - These factors require the HIRA to prolong the time taken to evaluate the submitted dossiers and to make a favorable decision
    - Sometimes, the NHIS might need more time to negotiate the final price of these new medicines

Summary of findings

- Third, medicines that were developed and manufactured in the local market were adopted promptly.
  - Specifically, this factor significantly decreased the duration between regulatory approval and the reimbursement trial. However, the duration between the reimbursement trial and the decision was not significantly shortened by this factor

Study limitations

- First, there is a possible limitation in our methodology
  - Because of the unavailability of information on the reimbursement application date, we used the date of the PBC appraisal as a proxy for the reimbursement application date
- Second, this study noted the first trial for reimbursement application
  - Therefore, if a manufacturer produces additional data on clinical effectiveness, the clinical effectiveness of the drug may change over time
  - In addition, there were several cases in which the PBC reviews on the clinical effectiveness of the drug were ambiguous or incomplete
  - To address these problems, the author and other person independently evaluate the information in the PBC reviews and reached a consensus on the clinical effectiveness

Conclusion

- The duration between regulatory approval and reimbursement decision has decreased, and the main cause of the delay has changed
  - For instance, the proportion of reimbursement trial–reimbursement decision in the total duration was 62.9% (18.39 months out of 29.24 months) in the first period, while the proportion of regulatory approval–reimbursement trial in the total duration was 64.2% (8.6 months out of 13.40 months) in the second period
- A series of policies to reinforce access to medicines after 2014 has been effective for the timely availability of new medicines, including both prompt reimbursement application decided by manufacturers and timely review process by the authorities

Thank you