(very preliminary)

Science intensity of drugs launched in Japan and their performance

Junichi Nishimura (Gakushuin U.)
Sadao Nagaoka (Hitotsubashi U.)

March 2014

This research is a part of the ongoing research on “Science sources of innovation and its economic effects” supported by JST(Japan Science and Technology Agency).
We would like to thank for the excellent assistance by the RAs.

Function of science (1)

- Traditional view of technology development
  - Local search for solutions (Nelson and Winter, 1982)
  - Exploitation of existing knowledge (March, 1991)
  - Recombinations of existing components to develop smaller, incremental innovations (Henderson and Clark, 1990)

- Science in innovation process
  - Distant search for solutions (Nelson and Winter, 1982)
  - New perspectives and exploration of new knowledge
  - Science as a search capability (Fleming and Sorensen, 2004)

Function of science (2)

- Science and industrial innovation

A deeper understanding of the real world (Alkaersig, 2010)

Science in science-based industries such as the pharmaceutical industry (Gittelman, 2005; Pisano, 2006)

Few systematic studies on science underlying industrial innovation (Mansfield, 1995, 1998)

Disconnect between science and industrial innovation (Gittelman and Kogut, 2003; Pisano, 2006; D'este and Perkmann, 2010)

Science as the incentives and knowledge for drug development

- Incentives matter
  - Novelty of new drugs
  - Market size and price regulation
  - Time-bound patent protection
- Knowledge matters
  - Knowledge guiding drug discovery and clinical testing
  - Transferability of the data
- Science intensity of a drug would favorably affect both
  - The higher the science intensity, the more innovative

Aims of this study

- We assess how the Japanese market and institutions are friendly to the introduction of science-intensive new drugs by looking at
  - their JP launch timing, using the US launch timing as a benchmark, and
  - their post entry market or economic performance

- In order to do this, we develop the indicators of science intensity of new drugs at the level of NME (new molecular entity)

Measurement of science intensity

- Science literature cited by the inventors in the patents protecting a drug
  - The number of science or engineering literatures cited
  - The number of these literature listed by the WOS (*Web of Science*) database
  - The average frequency of the forward citations of the above WOS-listed literatures

- Science literature are cited both for describing the prior art and for describing the invention (e.g. method of the measuring its performance)

NME (new molecular entity) as a unit of analysis

- Aggregate data of all drugs for each NME (the sales and the backward citations to science literatures) for the study of post entry market performance.
  - Different uses of a NME (patents of use inventions)
  - Improvement or complement patents (e.g. patents on manufacturing process)
  - Sales by generic manufacturers as part of the performance

- This results in capturing more fully the contributions of science and the economic effects of new drugs

Conceptual framework (1): Drug launch in the US and Japan

- Simultaneous or sequencing decisions on clinical testing
  - Limited time of exclusivity → simultaneous launch
  - Duplications and high risk → sequencing

- Sequencing decisions
  - Learning on efficacy and safety: first in the country where the most knowledge can be gained and the cost is low
  - Complementary knowledge assets: first where the drug was discovered (help from an inventor etc.)
  - Market size: first in a high income and large country
  - Pricing: first in a high income country with free price

Conceptual framework (2): Drug launch in the US and Japan

- Higher novelty of drugs makes “learning”, “complementarity”, “market size” and “pricing” more important
  - In the context of the US vs. Japan, drugs with high science intensity makes the US launch precede that in Japan

- Assuming a given sequencing, the gap between the first launch and the second launch depends on
  - Transferability of the clinical research in the first country
  - High price of the follower country (reference pricing)
  - Complementary knowledge assets for clinical trials

Conceptual framework (3): Post entry performance

- Price dynamics
  - Drugs with high science intensity: less competition
  - More modest price decline

- Market share
  - Drugs with high science intensity: more innovative, price and/or quantity tend to be large
  - Market share increases with science intensity

- Life expectancy
  - Drugs with high science intensity: more innovative, new solution for unmet medical needs
  - Contribute to decrease death rates

Major findings

- Drugs with high science intensity are launched earlier in the US, controlling for the location of drug seeds, etc. The length of drag lag is longer for the drugs with larger price difference.

- Drugs with high science intensity experience significantly slower price decline and have high market shares: the quality of science exploited matters for post entry market performance.

- Drugs with high science intensity improve life expectancy whereas those with low science intensity do not

Data sources on drugs (NMEs)

- *IMS.JPM, Japan*
  - Panel data at the NME-dosage level between 1995 and 2010 (1737 NMEs)
  - Information on sales, price, launched year, therapeutic fields (Anatomical Therapeutic Classification, ATC)

- "*Sanei Report*"
  - Drugs sold in Japan in 2001, the sales value of which exceed 1 billion yen per year (880 NMEs)
  - Information on patents which protect these drugs

- *REDBOOK ONLINE, US*
  - Panel data at the NME-dosage level since launched year

Data construction

- Matching between *IMS.JPM* and *REDBOOK ONLINE*
  - Population: 646 NMEs launched in Japan between 1989 and 2011
  - Matched: 198 NMEs at the NME-dosage level
  - The observations to compare the launch timing between the US and Japan

- Matching between *IMS.JPM* and *Sanei Report*
  - Population: 1737 NMEs listed in *IMS.JPM*
  - Matched: 629 NMEs
  - The observations to assess post entry performance in Japan

Empirical models (1): Drug launch in the US and Japan

- Two models of estimations
  - Probit model accounting for whether Japan led the launch or not (1: lead by Japan and 0: lead by the US)
  - OLS explaining the difference of the launch years (focus on the sample where the US led)

- Independent variables and expected signs (Probit)
  - Science intensity of the drug －
  - Location of seeds Japan: ＋ and US: －
  - Controls: product patent, therapeutic fields, 2000s dummy

Fig. 1 Launch years (US vs. Japan)

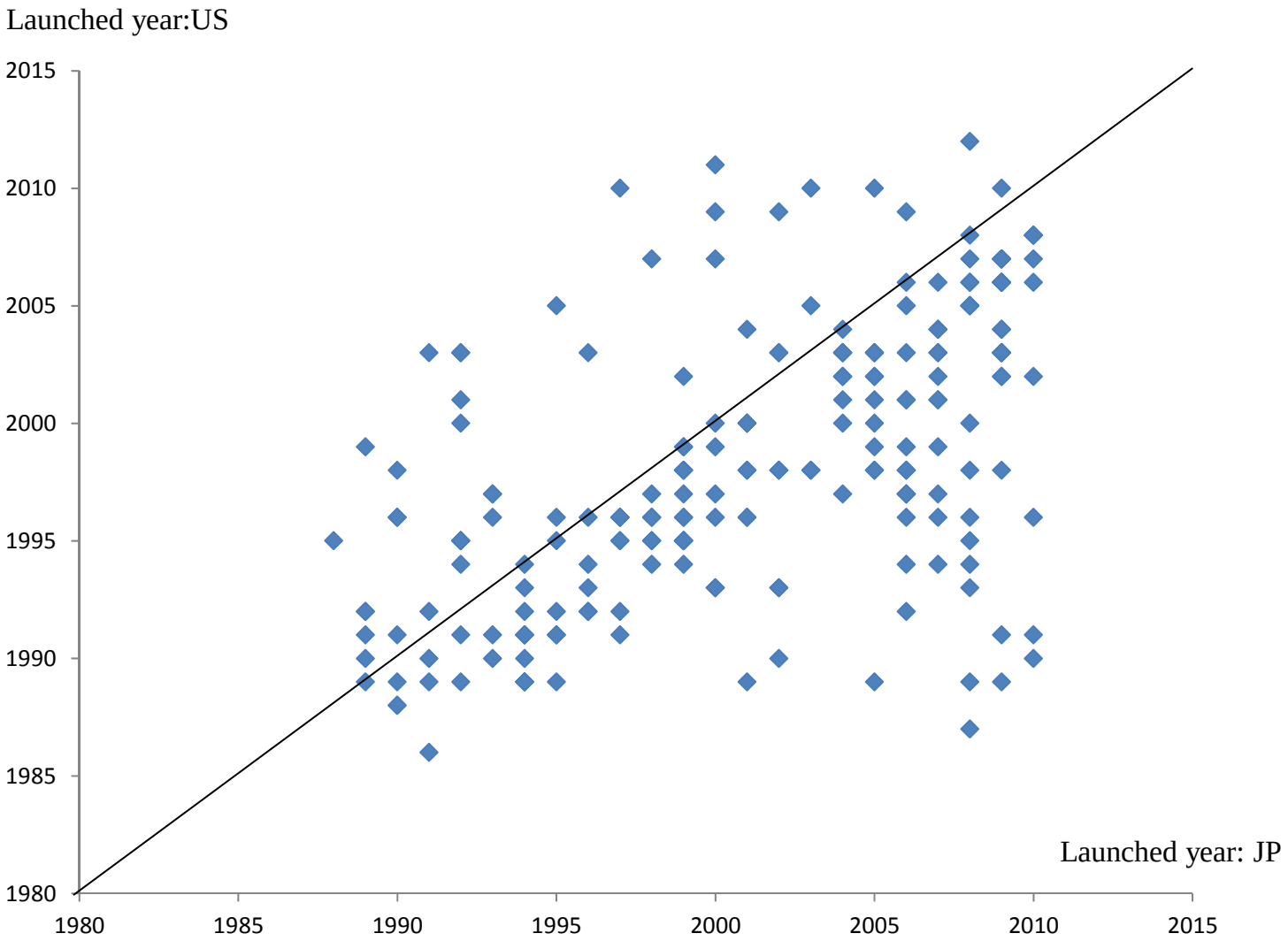

Table 1 Probit (marginal effect)

	early_launched_japan		
	(1)	(2)	(3)
number_paper	−0.006***		
	0.002		
number_wos_paper		−0.010**	−0.010**
		0.004	*0.005*
number_wos_citation			0.000
			0.000
seeds_japan_dummy	0.177*	0.164*	0.164*
	0.105	*0.103*	*0.100*
seeds_us_dummy	−0.135	−0.159*	−0.159*
	0.082	*0.081*	*0.081*
substance_pat_dummy	0.004	−0.004	−0.004
	0.105	*0.106*	*0.106*
launched_2000s_dummy	0.053	0.036	0.036
	0.098	*0.097*	*0.097*
atc_class_dummy	yes	yes	yes
N	131	131	131

Findings (1)

- Drugs with high science intensity are launched in the US first
- Location of seeds have expected signs

Difference in the launch lag (OLS)

- Independent variables and expected signs
  - Science intensity of the drug ＋
  - Initial price difference (Japan/US) －
  - Location of seeds Japan: － and US: ＋
  - Controls: product patent, therapeutic fields, 2000s dummy

- Reference pricing
  - Reference pricing makes pricing endogenous to sequencing (if the US is launched first, the reference pricing is used so that the price difference becomes smaller)

Table 2 Drug lag
(Launch year in Japan – US>=0, OLS)

	difference_launched_year (Japan－US＞0)		
	(4)	(5)	(6)
number_paper	0.005		
	0.014		
number_wos_paper		－0.015	－0.023
		0.023	*0.020*
number_wos_citation			0.001
			0.001
diff_initial_price	－0.008**	－0.008**	－0.007*
	0.040	*0.003*	*0.004*
seeds_japan_dummy	－0.566	－0.566	－0.604
	1.148	*1.141*	*1.151*
seeds_us_dummy	1.683**	1.812**	1.806**
	0.861	*0.869*	*0.868*
substance_pat_dummy	－0.878	－0.772	－0.805
	1.303	*1.258*	*1.265*
launched_2000s_dummy	－2.271***	－2.064***	－2.196***
	0.740	*0.731*	*0.743*
atc_class_dummy	yes	yes	yes
constant	4.267***	4.335***	4.471***
	1.571	*1.555*	*1.557*
N	114	114	114

Findings (2)

- No significant association between science intensity and the length of launch lag: 1) no significant difference in transferability of the knowledge in clinical trials from the US to Japan, 2) two conflicting effects
- Price difference matters significantly: higher Japanese price accelerates the introduction
- Location of seeds (especially the US seeds) does matter
- 2000s dummy is strongly negative and significant (two years reduction): reflect the changes in regulatory behaviors

Empirical models (2): Post entry market performance

- Panel data (NME by year): market share, price change
- The focal independent variable
  - Science intensity of drugs
- Controls
  - Age of NME (plus its square)
  - Therapeutic fields and year dummies
  - Product (or substance) patent dummy
  - Firm dummy

Table 3 Science intensity, market share, and price decline

	market_share			price_decline_rate		
	（1）	（2）	（3）	（4）	（5）	（6）
dummy_paper	0.0448*** *0.0042*			−0.0470*** *0.0133*		
ln (number_paper)		0.0209*** *0.0018*			−0.0118*** *0.0041*	
ln (number_wos_paper)			0.0242*** *0.0042*			−0.0064 *0.0076*
ln (number_wos_citation)			0.0042*** *0.0009*			−0.0027** *0.0009*
passed_year	0.0033*** *0.0005*	0.0035*** *0.0005*	0.0027*** *0.0005*	0.0031*** *0.0008*	0.0029*** *0.0007*	0.0033*** *0.0005*
(passed_year)^2	−0.0000*** *0.0000*	−0.0000*** *0.0000*	−0.0000*** *0.0000*	−0.0001*** *0.0000*	−0.0001*** *0.0000*	−0.0001*** *0.0000*
atc_class_dummy	yes	yes	yes	yes	yes	yes
year_dummy	yes	yes	yes	yes	yes	yes
substance_pat_dummy	0.0165*** *0.0039*	0.0190*** *0.0039*	0.0217*** *0.0042*	-0.0117 *0.0091*	0.0005 *0.0110*	−0.0128 *0.0082*
firm_dummy	yes	yes	yes	yes	yes	yes
constant	0.0016 *0.0104*	−0.0336*** *0.0114*	−0.0399*** *0.0138*	−0.0389 *0.0304*	−0.0299 *0.1556*	−0.0299 *0.0359*
N	8808	8808	8808	5872	5872	5872

Findings (3)

- Drugs with high science intensity experiences significantly slower price decline and have high market shares
- The quality of science exploited also matters for both these performances
- Product patent is associated with high market share but not with slow price decline (product patent itself may not prevent intra-NME competition)

Empirical models (3): Post entry economic performance

- Panel data (therapeutic fields by year): mean age at the death (*WHO Mortality Database*)

- The focal independent variables
  - Stock of NMEs with high science intensity
  - Stock of NMEs with low science intensity

- Controls
  - Therapeutic field dummies
  - Year dummies

Table 4 Science intensity and life expectancy

Mean age at deaths	(1)	(2)	(3)
(Science intensive NME stock) t	0.078***		
	0.029		
(Not science intensive NME stock) t	0.008		
	0.045		
(Science intensive NME stock) t-1		0.112**	
		0.046	
(Not science intensive NME stock) t-1		0.010	
		0.813	
(Science intensive NME stock) t-2			0.125**
			0.061
(Not science intensive NME stock) t-2			0.023
			0.054
year dummies	yes	yes	yes
therapeutic dummies	yes	yes	yes
Number of observations	165	154	143
R-squared	0.877	0.877	0.870

Findings (4)

- Stock of science-intensive drugs improves life expectancy whereas stock of non science-intensive drugs does not: Around one-quarter of launched drugs only decrease the death rates

- It seems to take several years for new drugs to be widely used by physicians

Conclusions (preliminary)

- The US tends to lead the launch of the drugs with high science intensity
- Price regulation accounts for the length of the launch lag in Japan
- At the same time, the Japanese market significantly rewards drugs with high science intensity and only the drugs with high science intensity have the effects of significantly reducing the death rates.

- More work to be done
  - Introducing the data on the initiations of the clinical research (Pharma projects)
  - Assessing why science intensity matters for drug launch: “ Learning on efficacy and safety of new drug ” , “Market size” and “Reference pricing ” .
  - Endogeneity of price on the sequencing decision of drug launches with respect to (data on types of price regulations) and truncation problem of drug launch (hazard model)
  - More name and dosage matching between the US and Japanese drugs
  - Improving science intensity measures
  - Incorporating the temporal effects of patent expirations

App. Table 1 Descriptive statistics (1)

Variable	Definition	Obs	Mean	Std. Dev.
early_launched_japan	Equal to one if a drug was launched earlier in Japan	131	0.2	0.4
difference_launched_year	Launched year in Japan －launched year in the US	131	3.0	5.7
number_paper	Number of scientific papers which drug patents cite	131	13.6	23.5
number_wos_paper	Number of scientific papers which drug patents cite (from Web of Science)	131	6.1	13.2
number_wos_citation	Average number of forward citations of WOS-listed scientific paper	131	219	776
diff_initial_price	Initial price in Japan divide by initial price in the US	131	1.0	1.2
seeds_japan_dummy	Equal to one if a drug seed was developed in Japan	131	0.2	0.4
seeds_us_dummy	Equal to one if a drug seed was developed in Japan	131	0.4	0.5
substance_pat_dummy	Equal to one if a drug has at least a substance patent	131	0.8	0.4
launched_2000s	Equal to one if a drug was launched in the 2000s	131	0.4	0.5

App. Table 2 Descriptive statistics (2)

Variables	Definition	Obs	Mean	Std. Dev.
market_share	Market share of a drug	8808	0.1	0.1
price_decline_rate	Rate of drug price decline	5872	0.1	0.3
dummy_paper	Equal to one if drug patents at least cite a scientific paper	8808	0.3	0.5
number_paper	Number of scientific papers which drug patents cites	8808	5.7	22.2
number_wos_paper	Number of scientific papers which drug patents cites (from Web of Science)	8808	2.7	12.3
number_wos_citation	Number of forward citations of WOS paper	8808	186.6	1719.4
passed_year	Number of years since a drug was launched	8808	19.7	15.3
substance_pat_dummy	Equal to one if a drug has at least a substance patent	8808	0.4	0.5

App. Table 3 Descriptive statistics (3)

Variable	Definition	Obs	Mean	Std. Dev.
Mean age at the death	Mean age at the death by therapeutic fields	165	76.3	4.3
Science intensive NME stock	NME stock with high science inteisity by therapeutic fields	165	12.4	9.2
Not science intensive NME stock	NME stock with low science intensity by therapeutic fields	165	29.0	20.9