

Contemporary generic market in Japan – key conditions to successful evolution

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Summary

Japanese pharmaceutical market, world's 2nd largest in size, is traditionally renowned for its brands' domination and weakest generics share among major established economies. An in depth observation of published evidence in Japanese/English language provided closer insight into current trends in Japanese domestic legislation and pharmaceutical market development. Recent governmental interventions have resulted in significant expansion of generic medicines market size. Substantial savings due to generic substitution of brand name drugs have already been achieved and are likely to increase in future. Nationwide population aging threatening sustainable health care funding is contributing to the relevance of generic policy success. Serious long-term challenge to the modest Japanese generic manufacturing capacities will be posed by foreign pharmaceutical industries particularly the ones based in emerging BRIC economies.

KEY WORDS : Japan , generic medicines , pharmaceuticals market , industry , health policy , patent protection , bioequivalence , attitudes , drug information , prescribing , dispensing

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Introduction

Flourishing of pharmaceutical industry inventions in past decades worldwide brought about many essential improvements in health care quality, human longevity and welfare. Nevertheless, this was followed by rise in prosperity diseases and population aging [1]. The pace of health care spending growth in mature markets turned out to be twice faster than economic development [2]. These phenomena posed serious issues on sustainability of health care funding even among high income societies. Certainly the large portion of both in- and outpatient direct medical expenses, and the one mostly accessible to manipulation by public policy measures are drug acquisition costs [3]. An array of different policy instruments aimed at cost containment and providing affordable high quality medical care were developed. The originator pharmaceutical industry lawfully claim the right to get return on investment after the development of a novel medicine. In most countries major instrument to industry income protection was provided by means of a patent policy. In the next stage of governmental cost containment strategies, limiting of patent rights to innovative manufacturers was one of common measures. After the expiry of drug patents, market exclusivity is lost and in most markets the so called “generic” medicines manufacturers flood the market with much more affordable “copycat” medicines. The secret of their lower market prices lies in the absence of substantial research and development costs born by their senior competitors from brand drugs industry.

Brand name drugs industry has developed scale of strategies in order to limit sales erosion caused by the current wave of blockbuster drugs patents expiries worldwide. It is assessed that these losses to the brand industry will mount to the \$100 billion in the following few years. Recently published World Generics Market report, predicted sustainable market growth for 2008-2013 despite the worldwide economic crisis [4]. This prognosis turned out to be true. Current combined generic market size in major high income and emerging markets is assumed to be around \$77 billion [5]. Generic companies tend to become more innovative and are expanding their manufacturing bases. This is particularly the case with huge generic sectors of emerging markets of India, China and Russian Federation. [4]. It is gradually becoming obvious that BRIC countries due to their rapidly increasing welfare and expanding health insurance coverage will soon take the lead in terms of global uptake of generic medicines [5].

Generic Penetration and Off-Patent Drugs in Japan

In 2004, the US Department of Commerce gave the following short assessment of the Japanese generic market;

The generic share of the Japanese pharmaceutical market is small, at about 7 percent. Three factors have limited the use of generic drugs in Japan: 1) doctors are brand conscious and uncertain of the quality of generic drugs; 2) pharmacists are not allowed to substitute generic drugs; and 3) because of NHI, patients are not sensitive to the cost of drugs.⁹¹ In April 2004, generic drug prices were listed on the NHI price list at 70 percent (decreased from 80 percent) of the price of the original drug unless another generic has already been listed [101].

In any developed country, originator drugs enjoy monopoly while they are protected by patents and other complex regulatory system governing drugs, but there seems to be a wide variation among the countries in what happens to the markets after their patents expire. In the U.S., for example, when a patent on a brand drug expires, generic drugs enter the market, and immediately start replacing the brand drug. In fact, in two years, generics take most of the market away from the brand drug [6].

In contrast, in Japan, at least prior to 2006, “cases where patent expiration had led to market erosion by generics have been rare” [102]. For example, Mevalotin TM lost only 1.5% in 2003 in sales in spite of the launch of 23 generic versions in the year. Likewise, Gaster oral TM lost only 5.2% and 4.4% in sales, in 2002 and 2003, respectively [7]. More systematically analyzing 2002-2005 Japanese micro-data, Iizuka (2012) reported that “Generic shares increase gradually, but in most cases, they remain below 25 percent within one year after generic entry. ...” [8]. We should add that even this 25 percent generic share has a considerable upward-bias, as Iizuka has selected only the NCEs for his analysis that gave him sufficient number of observations. In fact, using IMS Japan data, Kasuya & Nishimura showed that, during 1996-2004 period, the combined market share of “long-listed drugs”, or unprotected brand drugs, remained almost constant at 80%, indicating that the generics penetration into the market used to flatten out at around 20%. According to yet another IMS Japan data, to grab just a 10% share of the market away from the branded drugs, the generics introduced in 2004 took almost 30 months, those introduced in 2005 took 38 months, and those introduced in 2006 took 32 months.

Since 2006, however, the speed of penetration of new generics seems to have accelerated considerably; on average, the same IMS data shows that, to take the same 10% share, generics introduced in 2007 took 24 months,

those introduced in 2008 took 18 months, but those introduced in 2009 and in 2010 took only 9 months. For example, generics for Norvasc TM (introduced in 2008) took only 3 months to take 12% of the market, and in three years they took 40% of the market. Recently, the acceleration continues for new generics; the generics for Lipitor TM, introduced in November 2011, took 18% of the market in just 3 months. In contrast, however, the generics for Aricept introduced at the same time, took only 7 % of the market in the same period of time, with the more aggressive price-cutting strategy and the existence of usage and process patents on the part of Aricept accounting for the slower penetration.

Comparing the two best-selling branded drugs for hyperlipidemia can make the contrast between the pre-2006 and post-2006 markets. Generics for Mevalotin (Pravastatin) introduced in 2002 took one year to capture 8% of the market, almost 2 years to capture 20%, according to Iizuka's data (2012) [8], and almost 9 years to capture 50% (JMIRI 2011), but, generics for Lipitor introduced in late 2011 took only 3 months to capture 18%, almost six times the speed at least in the initial phase. With the increase in the penetration speed in the initial stage, the long-term ceilings for generic penetration seem to be shifting upwards too. For example, using the MEDIAS data from MHLW during the period of April 2007 to December 2009, Shimura et al (2012) [9] estimated the logistic function for generics in six therapeutic categories, and predicted a ceiling of 16 % for Norvasc, introduced in 2008. In fact, the generics' share for Norvasc exceeded 40% in three years. Clearly the stable ceilings of 20% are moving upward.

Analytical Framework

Containing rising pharmaceutical expenditure has been a key policy priority for OECD countries [10], and most governments have been trying to promote the use of lower cost generic competitors of off-patent drugs, expecting a substantial relief to health care and pharmaceutical budget problems. However, for the generic promotion policies to achieve this goal, a number of conditions must be met: patients though cost-sharing must be price sensitive, doctors and pharmacists must have incentives to prescribe or dispense cheaper drugs, and several generics, qualified as substitutable for the originator, must be available in the market [103]. Even among the three countries (Germany, UK and US) that succeeded in promoting the use of generics during the 1989-1997 period, not all of them had been successful in controlling the pharmaceutical expenditures [11].

From an analytical point of view, public policies to promote generics cover both supply-side and the demand-side of health care economies [12]. Supply-side policies consist of two distinct sets of regulations; patent

policies and pricing policies. In the first group, Bolar-type regulatory interventions to improve availability of generic medicines and economic incentives for fast penetration of generic medicines are to be included. In the second group are regulations on the reimbursement prices of originator drugs and generics (e.g. reference pricing).

There are two-tiers in the demand-side of drugs; proxy demand and patient demand. Policies on the proxy demand either regulate or provide economic incentives to prescribing physicians and dispensing pharmacists. Increasingly, pharmacists have become the target of financial incentives [13]. Policies on patient-demand include reference-pricing and differential co-pays for generic medicines [12], but the policies to improve the acceptance of generics by patients should be included here.

Chronology of Japanese Government policies promoting generic medicines

During the last three decades, Japan has been consistently characterized by a significantly higher spending for pharmaceuticals, more than 20 % of total health expenditure [14, 104] compared to other 12-14 % in developed countries [15].

In most major economies, generics account for at least one half of volume market share [16]. Some recent assessments of utilization of generics in unprotected market, in terms of unit consumption, generics account for 71 % in UK, 75 % in Germany and even 89 % in the US [105]. Almost all OECD mature markets far exceed Japanese fraction of 25.3% in volume of the total pharmaceutical market share in the first quarter of 2012 [17], while total value of generic sales remains at 8.8 % in 2011 [106].

Low Patented Drug Prices and High Generic Drug Prices

It has been often pointed out that the relative prices of generic drugs in Japan are high, compared to other developed countries. In the US, when patent expires, several generic competitors enter, and it is common for generic prices to fall to 20 % of initial branded drug price [107]. In contrast, in Japan, they usually start at 70 % and decrease downwards rather slowly through the course of years [18].

In contrast, at least in the last 10 years, in Japan, the branded drugs have been given low prices, and generics have been given high prices. A systematic comparison of prices of 54 molecules by the US Department of Commerce, across the ten OECD countries, revealed that the average price of patented drugs in Japan was only

0.33 times of the price in US in standard unit (Fig.3 in p.15), but the average price of generics in Japan was 2.2 times of the US price in standard unit (Fig.9 in p.22) [108]. Thus the relative price of generics is almost seven times of the US relative price in these 54 molecules group. More recently, a comparison of the prices of 13 block-buster patented drugs among Japan, US and Europe(UK, Germany, and France) using 2008 IMS Health Data shows that US price was at 269.1, Europe(UK, Germany, and France) at 155.1 with Japan at 100 [109]. So the prices of block-buster drugs were even lower in 2008, probably as a result of “Repricing for Market Expansion” Rule of MHLW. The 1996 rule has adjusted the prices of such drugs downward by up to 25%, if the market for the drug has expanded more than twice the original expectation and the total annual sale exceeded 15 billion yen.

Pricing Rules for the First Generics in the early 1990’s

Up to twenty years ago, in Japan, the first generic entrants had been given the same list prices (reimbursement price) as branded drugs. In 1994, however, MHLW lowered the prices of first generics to 90% of branded drugs, in exchange for shortening the approval cycle for generics from once in two years to every year (in July). Subsequently, the first entrant prices were lowered to 80% in 1996 and then to 70% in 2004. In 2012, they were further reduced to 60%, if more than 10 generic drugs are to be listed simultaneously, as in the cases of block-buster drugs coming out of patent protection. For later entrants, the minimum prices of the existing generics have been given.

Once approved, however, the generic manufacturers had to struggle to find wholesalers most of whom had strong vested interest in the branded drugs, and, the wholesalers had to struggle to find clients for generics of uncertain quality produced by unknown firms. Given the same reimbursement prices, manufacturers of generics had to ship their products at much lower prices to wholesalers, who in turn had to give deeper discounts to cash-starved hospitals or clinics. Starting 1991, however, giving deep discounts would have automatically reduced their list prices under the new price regulations of MHLW, as “every 2 years, the government revises the reimbursement price downward based on a survey on actual manufacturer prices plus an allowance margin (15 percent in 1992)” [19].

Price Floors for Generics (1990-2001) and “Low-Priced Drugs” Regime (2002-)

The price regulation introduced in 1991 would have forced most of the generics out of the market in a short period time. This would have eroded what little confidence the physicians or the patients had in generics, as well as the cost-saving from their use for the health insurance programs. For this reason, between 1990 and 2002, the MHLW had given generics “price floors” under the special rule known as “1/2.5 rule for Generics”. More precisely, during this period, generics whose list prices would have fallen below ‘1/2.5’, or 40% of the brand in the same class under the normal price revision rules, were grouped together as “low priced items” and given a single list price equal to 40% of the branded drug in each class. As a result, distributors of generics could give discounts without worrying about the consequence on the next list price revision.

In 2002, however, the price floor policy was terminated, and, all the generic drugs whose prices would have fallen below 20 % of the branded drug were grouped together under their generic name as “low priced drugs”, and were given a single price at their weighted average. These changes reduced the prices of generics in the subsequent price revisions, and “it was not uncommon to see the generic prices fall to less than half of the introduction price after the first price revision” [7]. In 2004, generic prices were set between 15% to 70% of the prices of originator drugs, with the average estimated around 50% [7]. According to the 2007 Drug Price Survey, the average unit cost of generics in the year had fallen to around 35% of the unprotected branded drugs, as generics accounted for 18.7% in volume but only for 6.6% in sales value [110]. (This change, however, resulted in so many prices for hospitals and clinics to handle in reimbursement processing that, in 2012, price groupings of the generics whose prices fall between 20% and 30% of the brand drugs were put in place).

Price Adjustment for Long-Listed Drugs (Off-Patent Drugs)

Also, in 2002, the special price adjustment for “long-listed drugs” (meaning off-patent branded drugs) was applied for the first time. This adjustment was apparently introduced because the prices of best-selling branded drugs had not fallen much as much as MHLW had hoped in the first price revision following the generics’ entry. MHLW decided to reduce the price of the branded drugs by 4-6%, for once, in addition to the regular price revision. Since then, the same proportional cuts have been applied, except in 2006 when the rates were increased to 6-8%. Furthermore, starting 2006, further cuts (2% in 2006. 2.2% in 2010 and 0.86% in 2012) had been applied to the items that had already undergone the long-listed drugs adjustment. In 2012, there was a special reduction of 0.33% on generics as well. Moreover, in the next (2014) price revision, the special rule will take into account of the generic dispensing rates in the class [111].

Comprehensive Payment for Hospital Inpatient Services: DPC

In a seemingly unrelated development, in 2003, a new system of reimbursement for inpatient care called **Diagnosis Procedure Combination** (“DPC” system) was introduced in 82 leading hospitals throughout the country. It was a system of per-diem flat-rate reimbursement for inpatient care, designed primarily to remove the inefficiencies of fee-for-service system of the last few decades. Almost immediately, the management of these hospitals began asking physicians to substitute generics for brand-name internal drugs to cut costs [112].

Since then, the number of DPC hospitals grew in leaps and bounds: in 2006, the number of DPC hospitals reached 360, covering 180,000 beds, and, by 2012, the number of DPC hospitals exceeded 1,500, covering almost 480,000, or one half of all the beds of acute-care hospitals [113].

Economic Incentives and Changes in Prescription Forms

In 2002, a set of new economic incentives were introduced in the Japanese public health insurance system to encourage physicians to prescribe generic drugs. An additional 20 yen was given to both physicians for writing a prescription containing a generic drug, and to pharmacists for filling such a prescription. At the same time another 100 yen per prescription was to be given to pharmacists for filling a prescription by generic names. The impacts of these incentives were limited because generic substitution at the pharmacy had been prohibited [8] and generic names had not been widely used by physicians [114].

Then in 2006, the prescription format was changed to add a box for ‘generic substitution allowable’ and the physicians were asked to sign if they would authorize pharmacists to switch to available generics from the prescribed branded drugs [9, 115]. In spite of this change, in a July 2007 survey sponsored by the CSIMC, only 17.4% of surveyed prescription forms contained the physician’s signature permitting generic substitution, and only 8.2% of them actually resulted in a generic dispensing [16]. Overall, this format change pushed the generic penetration rate in volume from 15.4% in March 2006 to 16.1% in April 2008 [9].

Action Program of the Government (2007)

In 2007, as a part of the Economic and Fiscal Reform of 2007, the government set the goal to double the dispensing rate of generics in volume to 30% by 2012. Shortly after, MHW published a number of key problem

areas that had limited the utilization of generics in its “Action Program for Promotion of Easy-Mind Use of Follower Drugs”, and asked the generic manufacturers to solve them. They were stable supply, quality, and information.

In response to Action Program, Japan Generic Medicines Association (JGMA), on behalf of 43 member companies implemented the package of interventions. Secure stable supply: number of items out of stock at wholesaler was reduced almost to zero level and in the remaining cases, delivery time upon request was within the same day in 99.3 % of such events in 2008.

In terms of quality, dissolution tests and long-term storage tests were to be conducted. Dissolution tests were conducted on all generics for internal use approved prior to April 1997, covering 550 compounds and 5,500 drugs and, in 2008, 99 % of generic products nationwide were tested. The names of the products that have passed these tests are published by the government, which have been compiled into the Japanese “Orange Book” at PMRJ foundation site [116]. With respect to information provision, generic companies publicly announce detailed drug monographs of their products at their own web sites, and “Generic Drug Information Provision System” was initiated at the website of the Japan Society of Generic Medicines to provide the most up-to-date detailed information on generics to health care professionals upon demand [106].

Pharmacist’s New Discretion in Generic Substitution (2008)

In April 2008, the government changed the prescription format again, this time asking the physicians to sign if they who would refuse a switch to generics, and to give reasons for the refusal [9]. At the same time, MLHW asked physicians to cooperate to the switch by changing the regulation governing public insurance medication, and even removed the incentive fee of 20 yen introduced in 2002 for the physicians to indicate the obligatory nature of the cooperation. On the other hand, pharmacists were given new legal discretion to switch to less expensive, available generics within the same class, including the changes in drug formulation and specifications, requiring only the consent of the patients. In 2010, the prescription form was changed slightly so as to permit the pharmacists to substitute all the prescribed drugs by available generics if the physicians did not sign.

Financial Incentives for Pharmacies; Hurdle Policies for Generic Substitution (2008~)

In April 2008, pharmacies were offered a new increment in the dispensing fees of 20 yen, on every prescription they fill, regardless of branded or generic, if the pharmacies had dispensed generics in 30% or more of all the prescriptions during the past three months [9,117].

The new 'hurdle' policies substantially reduced the number of pharmacies below the hurdle [16]. In fact, by December 2008, only nine months after the change, 83.4% of pharmacies were above the critical 30% threshold [16]. The policy, however, provided no further incentives for the 'high-performing segments' (i.e., pharmacies with more than 50% dispensing rates) to increase their generic substitution further [16]. As a result, after the initial jump, the generic dispensing rate, in volume, advanced rather gradually from 16.1% in April 2008 to 18.7% in December 2009 [9].

In April 2010, the generic dispensation increment has undergone two major revisions. Firstly, the new hurdles were to be based on volume, i.e. the number of units of drugs dispensed, rather than the number of prescriptions. Secondly, to qualify for an increment of 60 yen, a pharmacy must dispense at least 20% of all the drugs in generics. But if the dispensing rate exceeds 25%, the increment is increased to 130 yen, and, if the dispensing rate exceeds 30%, the increment is increased to 170 yen [118]. The use of volume-based dispensing rate and the use of three threshold levels instead of one provided a continuous incentive even for the high performers to increase generic substitution [16]. At the same time, hospitals in which the number of generics used is more than 20% of all the drugs used were permitted to charge 300 yen in the first day for inpatients as well. As a result of these changes, in fiscal 2010, the share of the generics in volume jumped to 22.4% [119].

In April 2012, the threshold percentages of the dispensing rate and the sizes of increments were adjusted again (50 yen if dispensing rate exceeds 22%, 150 yen if dispensing rate exceeds 30%, and 190 yen if dispensing rate exceeds 35%). At the same time, however, the per-prescription incentive introduced in 2002 was terminated for the pharmacists as well. To reduce the pharmacy's cost of dispensing generics, MHLW made recommendation to the physicians to prescribe medicine by International Nonproprietary Name (INN) and offered a new incentive (20 yen) to comply. According to a private national survey of physicians conducted in June 2012, only two months after the change, already 30% of physicians prescribe by IIN, while 15% of them prescribed by brand names and prohibited generic substitution [120].

New Roadmap (2013)

In April 2013, the MHLW announced new “Roadmap to further promote the use of Generics”. The new target for generic dispensing rate is 60% by March 2018. Although the dispensing rate is volume-based, the new target ratio will be computed by excluding brand drugs that have no generic counterparts be excluded from the denominator. With this adjustment, 30% target in the Action Program of 2007 is equivalent to 52.5%, according to the MHLW.

Institutional Factors

Another key issue is traditionally weak separation of prescribing and dispensing among far eastern societies. Medicine used to be prepared and administered in doctor’s office in Japan as well. It was not until 1951 when, under the GHQ directives, the government tried to separate the prescription and dispensing, only to fail by the strong opposition of physician’s professional associations. In postwar Japan there were strong health policy initiatives to separate these two stages of medical services provision. Nevertheless these efforts remained quite unsuccessful for long decades due to strong opposition by physician’s professional associations. Even today approximately one third of all medicines dispensing takes place inside clinics and hospitals [121]. Such a vertically integrated doctors who prescribe and dispense drugs can earn a price-cost markup [8], or the difference between the government-set retail price and the lower wholesale price. This mark-up can distort the choices of doctors in several ways: to increase the use of drugs, to choose more profitable drugs.

Besides weak reward on investment for generics following market entry, due to lack of favoured first entrant policy deployed in other countries, substantial additional obstacle is slow administrative process. An average time from submission to marketing approval with the Japan Pharmaceuticals and Medical Devices Agency (PMDA) of 20 months in 2008, was by far the longest one compared to European Medicines Agency and Food and Drug Administration processing times [122].

Characteristics of Japanese Wholesale Market for Drugs

As we have explained above, the retail prices of all the drugs patients purchase in our public health insurance system are set by the MHLW. Most of the hospitals, clinics or drug stores purchase the drugs through wholesalers, and their purchase prices are not regulated.

For decades, it has been the practice of most drug manufacturers to designate only one wholesaler for each customer (hospital/pharmacy), presumably to minimize the logistics problems. This strategy has practically eliminated price competition in their own drugs, but the Fair Trade Commission, in charge of regulating monopolies in Japan, has not yet ruled such a practice per se as anti-competitive. Under the stringent price control regime of the last two decades, as reasonable zone factor has been reduced from 15% to 2%, manufacturers quickly noticed that it is in their best interest to minimize the price difference between the regulated retail prices and the wholesale prices. Using the overwhelming bargaining powers, the manufacturers have forced the wholesalers to practically abandon the wholesale margins, practically selling the drugs at manufacturer's shipping prices. In exchange, the manufacturers have given wholesalers barely enough "rebates" and "allowances" to survive, subject to the condition that the wholesalers report all transaction prices and quantities to them.

All this time, the wholesale market for pharmaceuticals in Japan has been characterized by such peculiar trade practices as lump-sum bulk buying, delivery without price agreement, and murky rebate/allowance system [109]. Lump-sum bulk buying refers to a purchase of a large number of drugs by different manufacturers at a single price, and delivery without price agreement refers to shipping drugs with the understanding that the prices are to be settled many months later, most often at the end of fiscal year. Both are attempts by large hospitals or chain-store pharmacies to force price concessions either by masking price information from the manufacturers or bargaining hard to put pressures on the manufacturers to increase rebates or allowances. No wonder that for more than two decades MHLW and Japan Pharmaceutical Wholesalers Association (JPWA) have been trying to eliminate these practices through formal meetings, with little success [109].

The almost complete control of wholesaler by the manufacturers could explain why the branded drugs have been slow to lose their sales even after the drugs lost patent protection. The wholesalers, the sales agents of the branded drug manufacturers, had no incentive to reduce their marketing efforts of the branded drugs. The change in their behavior such as deeper discounts given by the wholesalers themselves could have come only

from the direct penetration of generics into their clients. But this was kept to a minimum too, because the physicians or pharmacists were reluctant to switch to the generics, mostly because of their concern over the unknown quality of the products made by unknown producers. In addition, patients or consumers were also reluctant to switch to cheaper generics as the elderly, who are heavy consumers of drugs and who should be most price-sensitive due to limited income, have been the beneficiary of very small out of pocket cost policies. To offset such a disadvantage, many generics producers and distributors resorted to deeper discounts and larger margins for a short-term gain, but under the strict price regulation, this strategy was not sustainable, and their threats were short-lived. In contrast, other producers developed their own MR forces, concentrated their marketing efforts on limited segments of the market, tried to establish their reputation in their products, and survived with the branded drugs.

Bioequivalence testing standards – Are they compliant between Japan and major ICH markets ?

There is large degree of consensus on pharmaceutical technology quality standards of generic medicines manufacturing today. It assumes that both speed and extent of drug absorption into the bloodstream following administration do not differ substantially between original reference preparation and a „copycat“ drug [20]. These criteria on so called „bioequivalence“ were widely adopted by the countries signatories of International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use [21]. Regardless of titanic historical efforts on reconciling international standards in pharmaceutical technology for comparability and quality assurance, recent methodological systematic review confirmed significant differences remaining [22]. Anyway the time showed that major regulatory bodies like US FDA, European EMA and Japanese PMDA may interpret these rules differently [21]. As a key pharmacokinetic parameter describing bioavailability of certain drug is considered „area under curve“ (AUC) reflecting drug blood concentration – time dynamics. Guidelines recommend as acceptable AUC values of last sampling in EU, from zero point to infinity in the US and from zero to last sampling in Japan(AUC_{all}) [23]. These apparently slight regulatory differences were proved to bear risk of occasional low ability of detection of unsatisfactory in vivo bioequivalence of generic preparations compared to brands. Comparative bioequivalence trial on ibuprofen tablet dissolution applying Japanese and US standards respectively, proved explicitly that there are relevant differences in terms of in vitro dissolution behavior of similar dosage forms [24]. An extensive local study compared in vivo human bioequivalence of 44 different generic drugs, tested by Towa Pharmaceutical Co. Ltd.

(Osaka, Japan). Authors succeeded to clearly recognize ratio AUC/dose as the key pharmacokinetic variable distinguishing medicines with high likelihood of bioequivalence [25].

Particularly sensitive issue is lack of generic medicines bioequivalence with brand name originals among the drugs with narrow therapeutical blood concentrations. In these cases even rather small inefficiency in delivering active substance from its pharmaceutical formulation can cause clinically significant consequences in terms of losing disease control. In case of epilepsies this issue was well studied in the literature [26]. Seizure occurrence due to generic drug introduction or even replacement of one brand with another „me too“ analogue, was described [27,28]. In other medical disorders, consequences of unsatisfactory bioequivalence of generic medicines can also lead to serious consequences such as cardiac arrhythmia worsening (antiarrhythmic drugs) or blood clotting accidents (oral anticoagulant drugs) potentially leading to vascular events such as stroke or infarction [29]. Among clinical conditions where slightly smaller bioavailability of generics could play significant role in terms of efficacy are certainly acute bacterial infections of surgical wounds and soft tissues acquired in hospital conditions. It was proven in Japanese setting that potency of vancomycin was 14.6 % and teicoplanin 17.3 % weaker compared to brand name products. It is worthy to notice that current Japanese regulations for registering generic product require evidence on bioequivalence in oral preparations, digestive absorption pharmacokinetic trial in particular, but such evidence is not mandatory submitted in parenteral formulations such as injections. Without clinical trials in humans, “in vitro” evidence is regarded satisfactory [30].

In vast majority of cases, due to similar or equal quality assessment criteria prior to marketing approval, generic drugs exhibit satisfactory bioequivalence as compared to their innovator counterparts. Nevertheless, some clinically unpredictable conditions treated with drugs of narrow therapeutic range, should be paid more attention in terms of BE evaluation, in order to avoid undesirable consequences of treatment protocol change.

Drug information insufficiency attributed to generic manufacturers

Numerous surveys in Japan conducted and published both by independent academic research cores or the authorities have reported that lack of confidence in generic medicines efficacy, safety and quality by health care professionals and similar public opinion were major determinants of low consumer demand [31]. Among the most common causes of insufficient substitution recommendation by physicians and pharmacists comes rather lower quantity and quality of information inside drug package insert compared to the originals [32, 33]. Iijima et

al have pointed out that evaluation of texts of generic drug package inserts could be used as a selection criteria to distinguish among plenty of generic manufacturers offering the same or similar active compounds in the market [34]. In another study the same research group noticed that this information insufficiency contributing to the lack of confidence in generic medicines both among health care professionals and patients as consumers [35]. An in-depth analysis of 14 different active ingredients each represented by at least 20 different commercially available products (327 product items) resulted in almost double higher quantity of information in favour of innovator products with ratio being even higher when single companies are compared [32].

Objectively lower drug information quantity and quality compared to innovator products could be self-explanatory. Innovator industry invests heavily into new promising chemical compounds development [36]. Therefore most of data originating from an expensive and time consuming preclinical and clinical research trials, belong to the sponsor of research projects. This ownership of data on particular drug's pharmacokinetics, pharmacodynamics, safety profile, dosage regimens should be regarded the source of relative paucity of evidence listed inside generic drug package. This issue was partially resolved in Japan by allowing to generic manufacturers during the last years of market exclusivity, to prepare an abbreviated submission for marketing approval while using published clinical data acquired by innovator pharmaceutical industry [123].

It should be also noted that generics are commonly approved for indications and in dosage regimens authorized for respective brands in their first ever approval. Post-marketing experience in large numbers of patients outside strictly controlled clinical study setting and MHLW reevaluation conclusions frequently lead to revised dosage regimens and/or indications. It is important that generics approvals so far still do not follow these updates in Japan. This rule ultimately creates diversity of preparations and dosage forms which makes clinician's decision on substitution even more uneasy and delicate [30].

Patent protection and market exclusivity rights to original drugs manufacturers in Japan

Intellectual property legislature was historically developed worldwide in order to protect rights and income arising from either personal creativity and inventions or industrial scale innovations outsourcing from systematic investment of resources into technological development [37]. Pharmaceutical industry was no exception although patent protection rights were interpreted in a vast array of ways across different jurisdictions [38]. Keeping in mind profit dependency on such patents, this issue became a hot spot of struggle between different pharmaceutical manufacturers. Innovator of new, therapeutically promising chemical compound commonly

registers the patent for 20 years duration in the early stage of its preclinical development. Until it reaches the marketing approval stage on average 10-13 years of both in vitro and clinical testing will take place. The remaining time proved to be insufficient for most manufacturers to realize satisfactory return on investment. Therefore Japanese regulations allow patentees to apply for additional 5 years of patent extension in selected cases [123].

Originator industry is regarded essential for the society in terms of improving quality of health care and bringing substantial scientific and technological advances through discovering new treatments for previously incurable diseases [39]. It is argued by some health policy think tanks that long term benefit outsourcing from innovator product development actually bring much higher societal welfare compared to short term savings due to generic medicines consumption [124]. Therefore governmental policy makers decided to further help to the brand industry by introducing the so-called “extension of effective market exclusivity” for the patent holders in a period after the expiry of the patent [38]. The success of this legislature solution was obvious in many countries. Broad patents are known to favour business interests of the patentees and limiting the manoeuvring room to generic competitors. Another advantage of such protection is its impact on generating serious research and development investment by major companies [125]. The adverse effect of such policy was loose control of profit driven industry. There is a sensitive balance between protecting public interest in terms of affordable quality health care and providing pharmaceutical industry with proper return on investment reward [18].

The historical beginning of patent protection on novel medicines is 1967 when market exclusivity was introduced in Japan in relation to new drug approval in order to encourage domestic industry development [18]. After thorough consideration, Japanese national healthcare strategy since 1990s was to implement narrow patent policy which tended to support technological instead of essential innovation [40]. Such approach brought the blossoming of vast variety of “me too” synthetic analogues of the existing drugs invented elsewhere and pharmaceutical forms at the expense of rather modest contribution in terms of novel treatment discoveries [41]. An interesting point for comparison between major economies is chronological order of introducing such legislature changes. In the US it was introduced by Waxman-Hatch Act in 1984, in Japan since 1988 and in the EU by “supplementary protection certificates” which were introduced in 1993 [42].

Policy of several consecutive governments in Japan in terms of regulatory data protection was aimed to establish strong market exclusivity protection of innovating pharmaceutical products. This is evident in article 14-4. of

Japan's Pharmaceutical Affairs Law which has established the so called "re-evaluation period" on safety and efficacy of approved drugs. Currently depending on the drug class it can range 6 - 10 years. An average duration of this period of 8 years was actually a compromise between Japan Pharmaceutical Manufacturers Association (JPMA) and Japan Generic Pharmaceutical Manufacturers Association (JGPMA) submitted as a joint proposal to the MHLW [43]. Before re-evaluation of patented brands, it is essentially requested from generic firms to provide their own data on clinical efficacy, adverse events and quality. This is simply unaffordable for rather small and medium Japanese generic firms and forces them to fill in marketing approval request only after re-evaluation is done. So, this strategy brought with it substantial post-patent market exclusivity to the brand industry [126].

Surprisingly, series of legal rulings made by Nagoya, Osaka and Tokyo prefectural Courts, reacting to patent infringement suits filed by brand industry against generic competitors, decided that clinical trials of stage II and III for generic medicines before patent expiry date do not represent patent infringement [44]. The development on the opposite side was Intellectual Property High Court of Japan ruling on suit filed by Taiyo Yakuin Co. Ltd against Astellas Pharma in 2007. Japanese patentee after 5 years from base patent expiry had registered another patent on the crystal form of certain blockbuster antibiotic compound. This decision was a remarkable one pointing out to the vigorous patenting of pharmaceutical forms of the off-patent drugs by their innovating producers in order to slow down price erosion and loss of revenues [45].

Another sensitive issue in terms of generic producer's competitiveness is the timing of clinical bioequivalence testing relative to the brand patent expiry date. These manufacturers generally need to provide firm evidence in bioavailability of their product to the reference original drug in human subjects. Since recently it was allowed by Japanese authorities, that these time consuming efforts take place before the brand patent expiry. This allowed for timely submission of data to the Ministry of Health, Wealth and Labour and shortening of generic entry lag [42].

The key impulse for generic entry planning for manufacturers should be regarded market size of its brand name counterpart and timing of patent expiry [42]. The larger the market size of an originator compound and shorter delay of generic entry following patent expiry, the bigger profit margins should be expected. More successful drugs are likely to face harsher generic competition upon losing market exclusivity protection. Other, less successful drugs will likely keep their revenue stream intact, attracting less competitors [42]. (Therefore in less

regulated markets such as the US, sales erosions in the first years following patent expiry are usually sudden and huge [46]. On the opposite side there are public health gains in terms of access to affordable medicines to the broad layers of the community which increase proportionally [105]. In Japan timing of market entrance is also important because it was proven that generics following the first one more than a quarter could not establish market supremacy. Nevertheless local generic profit harvest is much more equalized among competitors compared to the Western communities [9].

Attitudes on generic medicines prescription and dispensing

There have been numerous research efforts worldwide aimed at assessing both public [47] and professional opinion on the use of generic medicines. Majority of published evidence worldwide suggests that physicians either remained neutral or slightly supportive towards prescribing generics or substituting brand name drugs with generics. Quite a unique feature of overall Japanese market of goods and services is characterized by a designer-brand led culture. It is well known that local consumers have rather strong confidence in traditional, preferably domestic brands and this applies to the medical services and medicines too [122]. Recent local studies have approved that general public awareness on generic drugs is significant and gradually rising in Japan [48]. Nevertheless, the major cause of weak patient confidence was lack of knowledge on copycat medicines because their attending physician did not prescribe such drug nor has explained the presence of alternatives to the brand name products in the market. Most local psychometric studies indicate that Japanese clinicians are actually not well informed on strict quality and bioequivalence criteria deployed by the Japan Pharmaceuticals and Medical Devices Agency (PMDA) prior to marketing approvals of generic products [122].

One of the less known features of the elderly population was patient's obvious lack of knowledge on true prices of medicines and actual market prices of common drugs before governmental subsidies [48]. These circumstances can lead to well described phenomena of consumer induced demand for goods in scenario where it is effectively quite affordable for the ordinary citizen due to heavy reimbursement policy [49]. Lack of knowledge on individual harmful consequences of drugs overuse and avoidable societal cost could be corrected by public educational campaigns initiated by the authorities.

It is interesting to notice that Kobayashi E et al after an extensive survey, reported that 55.6 % of community pharmacists very rarely or never dispense generic drugs. As the most common obstacles to the wider implementation of generic prescribing and dispensing are stated common health professional's attitudes of poor

quality and therapeutic unreliability. Quite unexpectedly another finding was reported – clear contrast between rather supportive attitude of pharmacists towards generics use and their behavior in everyday practice heavily neglecting recommendation of generics to the patients. Besides aforementioned reasons, lack of stocked generics in pharmacies and modest market availability of generic replacement for only 43.7 % of brand name medicines were listed among contributing factors [50].

Expert commentary

Dedication of Japanese authorities to the goal of increasing generic medicines market share both in terms of volume and value, to at least comparable level to that of other OECD economies, has attracted attention from abroad. World's leading generic manufacturers both from high income Western economies and BRIC emerging markets have responded to the Japanese challenge [45]. Local business adapted by merging of several major Japanese generic companies with their counterparts from overseas in order to achieve more efficient market access. A large scale example of such strategies was recent Daiichi Sankyo fusion with one of the globally leading, India based, Ranbaxy industries. Recommendations for foreign companies planning market expansion in Japanese pharmaceuticals market to find a local industry partner was present for a long course of years [122]. Historical experience of overseas companies simply proved that likelihood of success is far higher if foreign company does not act alone. There are a few reasons for this peculiarity but certainly the major one relies in consumer confidence into traditional domestic manufacturers. This is applicable to the pharmaceutical sales as well. The stakes at the local market are high. Thanks to the approaching blockbuster patent cliff worldwide, some \$17 billion value of prescription drugs in Japan are going off patent in 2011-2015 time span. Largest local generic company Sawai Pharmaceuticals achieved only \$770 million in revenues 2010 [127].

World's leading, Israeli based, generic company, Teva Pharmaceutical Industries was present in the local market for a number of years and is likely to retain its stronghold and secure future earnings by expanding its businesses. It recently established joint venture Teva-Kowa Pharma Limited aiming to manufacture locally high quality generic medicines and reach target sales of US\$1 billion until 2015 [128]. US based generic manufacturers Mylan Inc. (acting in Japan joined with Pfizer Inc. since 2012) and Hospira Inc , Swiss based Novartis subsidiary Sandoz and Iceland based Actavis all made either acquisitions of smaller Japanese firms or strategic investment moves in the local market in recent years [122].

Past decade brought with itself a challenging new chapter with the advent of large generic companies based in the major emerging economies. Political pressures from abroad accumulated and led to establishing of Indian-Japanese free trade agreement in 2011. Local authorities finally decided to allow marketing of Indian products under the condition that they obey the principles of Good Manufacturing Practice. Among major India based, generics companies first Ranbaxy, and afterwards Dr Reddy's, Zydus Cadilla, Cipla Ltd. and active ingredients producers Dishman Pharmaceuticals, Suven Lifesciences and Ind-Swift Labs, have all been searching opportunities in the local market by capital investment either through merging or acquisitions of local Japanese firms such as Nikkei and others [129, 130]. There are also some promising signs of similar Sino-Japanese agreements in the foreseeable future [17].

Profit driven brand industry development has been leading to the significant gaps in progress with novel therapeutic solutions. Well known areas of less rewarding development are orphan drugs for rare diseases and acute conditions such as infections. Generic manufacturers too are following the same logic. Blockbuster with a large market size and shorter presence is likely to attract fierce generic competition while old drugs with small market size remain for long years without any generic alternatives [9]. Expanding domestic generic producers will need higher volume of market share to make their business profitable and running in the surrounding with continually decreasing prices. [31]. Responsible authorities should also consider the policy solutions to attract generic competitors into less saturated areas such as antibiotic manufacturing. The success in providing affordable copycat medicines to treat not only chronic but also acute conditions could bring substantial long term savings to the national health system.

Five-year view

Spreading utilization of generic medicines among general community will contribute to achieve highest attainable public health with available resources. Unfortunately, advertising efforts by competing brand name manufacturers were made to discredit generics even by financing and disseminating false "evidence" on their suspicious safety and/or efficiency. In spite of such market access competition, local Japanese clinical trial tested therapeutic equivalence of originator vs copycat calcium channel blocker manidipine hydrochloride in hypertensive patients. Authors reported absence of patient compliance, safety and efficacy within cohort of patients switching from brand to generic compound [51]. The sceptic's objections to the quality of generic medicines were excellently addressed in two meta-analysis papers by Kesselheim AS et al [52, 53]. In a well

designed systematic reviews of high methodological validity it was proved for both essential cardiovascular medicines and anticonvulsants that there is no statistically significant difference between originator compounds and generics in terms of either bioequivalence or clinical efficiency.

Japanese generics market has passed a long way since the complete refusal of adopting generics prescription and dispensation up to the current decent level of generics uptake. Policy makers are well aware that current difficulties in health care funding and trend of population aging are likely to continue for many decades to come. Aforementioned circumstances lay ground for possibility of substantial savings in Japanese domestic health care market by implementing medicines substitution as in other branches of medicine [54]. Such trend would be compliant to mainstream of Japanese official policy of promoting generic drugs use and prescription [123]. Further favourable attitude and promoting campaigns initiated by Ministry of Health, Labor and Welfare are likely to bring even more savings in future. Major components of „Program to Promote Use of Generic Drugs in Japan“ published March 2012 by MHLW are providing generics of reliable quality, supply and information provision, medical fee calculation based on quantity of generic dispensing and dissemination of data on generics availability from the insurers to the patients [106]. Experiences of other mature markets seems not to report negative impact of generic substitution to the overall quality of medical care. The shape of pharmaceutical market change in Japan is highly promising but the dynamics of such change appears insufficient. Further efforts should be invested. There are few remaining policy means available to promote substitution of brand name drugs with their generic counterparts to be extended in Japan: strengthening financial incentives to promote prescribing by attending physicians and dispensing by pharmacists ; strengthening financial incentives to the patients (establishing higher pricing differential compared to brands at the NHI list); popular campaigns aimed at public opinion to embrace generics as reliable, high quality affordable medicines ; education efforts and guidelines development targeted to convince healthcare professionals of pharmaceutical quality of copycat preparations, in terms of their efficacy, safety and bioequivalence and ultimately electronic supervision and feedback over their prescribing and dispensing practice. Most of the measures proposed by this study are demand-side oriented and some have already been in place in Japan in the course of past 15 years. Due to rather gradual, stage-by-stage approach they had weaker impact compared to earlier implementation by the US, Canada and Australia in 1980s and the EU in 1990s. In less regulated mature markets common feature of policy success is sudden price erosion upon patent expiry and fierce generic competition on the supply side. Outside of improving and hospitable regulatory framework for generic drugs in Japan, insufficient domestic industry

capacities to meet rising demand and provide continuous supply could be regarded as the second most important obstacle towards successful development. Ultimately, in favour of long term sustainable universal health care funding in Japan, policy makers shall be forced to shift large part of brand industry revenue stream towards generic businesses. Both Japanese domestic, foreign owned and mixed generic firms will have to expand their manufacturing base, enlarge research and development investment and advertising campaigns in order to meet rising market expectation in decades to come.

Key Issues

*This systematic review of published evidence in English and Japanese language was undertaken in order to fill in current gap in knowledge on fresh new developments and consequences of past health policy measures in Japanese market of generic medicines.

*Authors believe that an effort aimed at encompassing the contemporary big picture in generic market evolution could be useful viewpoint for the pharmaceutical industry leaders but also pose new challenging research questions for the academic community.

*Years of targeted interventions of Japanese government have resulted in significant expansion of generic medicines prescription and market size in terms of unit consumption.

*Health policy measures targeted at attending physicians and pharmacists, supporting generic substitution of brand name drugs, bear certain peculiarity due to traditional lack of separation between prescription and dispensing of medicines in the Far East region of Asia.

*These cost containment efforts nationwide are likely to bring substantial savings essential for financing the unmet population needs in the long run.

*Anticipated impact of generic substitution to the quality of medical services will be rather acceptable opposing conventional attitude on unreliable quality and safety of copycat medicines embraced by Japanese consumers.

*Having in mind far reaching consequences of population aging for sustainable health care funding and rising role of the emerging markets generic manufacturers in Japan it is likely that national generic sector will expand further.

*Few large scale mergers of domestic with overseas generic companies, together with more receptive attitude of local policy makers and health care professionals will keep attracting substantial foreign investment in this industry branch.

*Although presence of generic manufacturers from established, mature economies in Japan is substantial, companies based in emerging BRIC countries are most likely to pose serious long term challenge to the national industry.

*Trends noticed through the past two decades implicate that Japanese pharmaceutical market has the potential to actually become one of the globally competitive generic industry hubs in the future.

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