〔一　般　論　文〕

Generic Submissions in Japan from a Global Generic Player's Perspective

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Summary：Japan, with the highest life expectancy in the world, is an aging society and its health insurance system is increasingly burdened by this demographic development. As the Japanese government seeks to maintain a healthy economic outlook, it must also adopt policies that continue to restrict overall health expenditures. One approach is to increase the use of low cost generics.
The Japanese government, indeed, is committed to increase generics volume share to over 30% by 2012, and is implementing a number of pro-generic measures. As the result, its generic market, expected to grow significantly in the following years, is becoming a major focus for global players. However, despite the fact that Japan is a member of the ICH（International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use）it has restricted this harmonization process towards new and innovative drugs and has excluded generics to a very great extent.
In contrast, the other two ICH regions, USA and the European Union, are successfully applying current international standards to generics. Manufacturers from these countries struggle with a different regulatory system when they try to get their products approved for the Japanese market.
The following review summarizes major issues concerning the application files necessary to receive generic drug approval, and outlines the differences between the three major pharmaceutical markets in this respect.

Keywords：Generics, Drug Approval, Registration Dossiers, Stability, Analytics, Bioequivalence, Pharmacovigilance, Good Manufacturing Practice（GMP）

Introduction:

The Japanese pharmaceutical market is the second largest individual market after the USA and with sales of more than 60 billion USD per year constitutes approximately 10 % of the world market.

Japan's society is growing old; according to the United Nations Populations Division the proportion of elderly people aged at least 65 years was 19.9 % in 2005 and is expected to rise to 36.0 % by 2050, —— thanks to an average lifespan of 82 years, the highest in the world. This demographic development is putting pressure on Japan's healthcare system, and price cuts are one approach of the Japanese government to trim ballooning healthcare expenditures. Another very recent approach is the implementation of policies to push the use of low cost generics, including generics substitution promoted at pharmacies and flat-fee payment system（DPC-Diagnosis Procedure Combination）promoted at acute hospitals.

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So for the pharmaceutical industry confidence is growing that the Japanese generic market is about to grow significantly in the next future, fuelled by the dual pressure of blockbusters coming off patent and the national healthcare system's demands for lower costs.

But Japan's pharmaceutical market is also opening up to a much greater extent than the time prior to the revision and enforcement of the new Pharmaceutical Affairs Law in 2005. With the removal of the obligation to manufacture locally, Japan's generic market has also become increasingly attractive for global players. However, a strong and advanced domestic manufacturing industry in combination with a different and unique regulatory system make the Japanese market a difficult and long-term prospect for such companies.

In addition, a considerable proportion of the data generated for generic submissions in other highly industrialized countries are often inadequate for Japan, or have to be significantly supplemented because requirements are not yet harmonized.

This article aims to provide an overview, and compares the most important requirements for marketing approvals of non-new chemical entities (generics) in Japan with those in the European Union (EU) and the United States of America (USA).

1. Submission Format and European Application Procedures

In 1990, representatives of the three most important pharmaceutical markets Japan, the EU and the USA founded the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the 3 regions to discuss scientific and technical aspects of product registration. As such, the Common Technical Document (CTD) was agreed as the structure for application dossiers designated by the tripartite agreement to be used across Europe, Japan, and the United States from July 2003 onwards.

The CTD consists of five modules and is meanwhile accepted in countries outside the ICH region (USA, EU, and Japan) as well. CTD-structured application files are applicable in the USA and Europe for both new chemical entities (NCE) and generic submissions. Japan enables the use of the CTD only for new and innovative drugs. CTD Module 3 that includes chemical and pharmaceutical data can even be submitted in the English language. Modules 1 and 2 have to be filed in Japanese. However, one big difference to both other regions is that Japan does not allow the CTD format for generic drug approval applications. These need to be filed in the former Japanese format and have to be entirely translated because the Japanese language is here mandatory for all parts. A different language in combination with a different format makes application for and maintenance of approvals a cost intensive and elaborate process for overseas manufacturers. Submission files have not only to be transferred into Japanese language, but also into the Japanese manner of expression.

It is probably unnecessary to mention that drug approval applications in the USA and the multilingual EU can be filed in the English language. English is also accepted for national drug approval applications at the authorities of the single European member states (except for Module 1 in some European member states).

The application for drug approval in the EU is unique and complex due to its multinational nature. However the legal situation is meanwhile homogeneous as European regulations have been transferred into national law by all member states. EU regulations, directives and EMEA / ICH guidelines are equally applicable no matter which kind of application is used.

There are in principle four different ways to apply for drug approval in the EU:

a) The national procedure: application for drug approval in only one single member state.
b) The mutual recognition procedure (MRP): recognition of one national approval of a so-called reference member state (RMS) by the national authorities of other so-called concerned member states (CMS), resulting in approvals in more than one member state.
c) The decentralized procedure (DCP): simultaneous submission of identical application dossiers in different member states. The national authority of one reference member state (RMS) reviews the dossier; the other member states (CMS) recognize the RMS assessment and issue approvals as well.
d) The centralized procedure (CP): the drug approval application is submitted at the European Medicines Evaluation Agency (EMEA). This approval is valid throughout the EU.

The CP is mandatory for drug approval applications of medicinal products containing a new active substance for which the therapeutic indication is the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorder, diabetes and (with effect from 20 May 2008 on) auto-immune diseases and other immune dysfunctions and viral diseases[1].

Further the CP is mandatory for medicinal products developed by means of one of the following biotechnological processes[1]:

- recombinant DNA technology
- controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells
- hybridoma and monoclonal antibody methods

Generic applications of medicinal products authorized via the centralized procedure may be authorized via the centralized procedure. Alternatively, they may be authorized by the competent authorities of the Member States through a national, mutual recognition procedure or decentralized procedure.

However similar biological ("biosimilar") medicinal products which are developed by means of any of the above mentioned biotechnological processes have to be authorized via the centralized procedure[1].

2. Guidelines

ICH Expert Working Groups (EWG) are made up of representatives from regulatory authorities as well as experts from the pharmaceutical industry and academia of the three ICH regions. The EWG discuss technical and scientific aspects as well as testing procedures required to ensure the assessment of drugs for human use. In stepwise approaches, guidelines in the main topics quality, efficacy and safety are established as draft versions, which are, in further steps of comment and discussion, brought to final versions. The final versions are then passed on for national regulatory implementation and are brought into effect in the USA, EU or Japan like any other regional guideline.

ICH guidelines reflect the state of the art of their topics and therefore are respected and applied in many other countries as well. In addition, each of the ICH regions implements its own guidelines with scopes not covered by the tripartite guidelines or going beyond. In the EU and USA the relevant ICH quality guidelines apply to both innovative, new drugs and generics, whereas Japan considers data generated in accordance with these guidelines as insufficient or inappropriate for generic application files, but accepts them also for new and innovative drugs. On the other hand, the Japanese guidelines for generic submissions are not harmonized with ICH guidelines. Therefore it is often difficult for foreign manufacturers to find guidance which applies specifically to generics so they have the tendency to submit ICH conform data. From a western scientific point of view, it would be much clearer if the quality standards were compliant with ICH guidelines when the Japanese government tries to emphasize their equality with originals.

3. Good Manufacturing Practice (GMP)

The competent authorities of the EU, the Food and Drug Administration (FDA) of the USA and recently also the Pharmaceutical and Medicinal Devices Agency (PMDA) of Japan require pre-approval inspections to provide evidence that the active pharmaceutical ingredient (API) and Drug Product (Finished Dosage Form or FDF) manufacturing sites comply with current GMP principles.

In the US, the applicant principally agrees with the submission of a marketing authorization application (MAA) to an inspection by the FDA. If no GMP-inspection of all involved parties including contract research organizations (CRO) has been performed in the last two years, pre-approval inspections will be required. The MAA includes only an internal confirmation that current GMP- requirements have been met. In the US, process validation is not necessary for submission, but is done on the first three production batches. In the EU, process validation is required. However, the amount of data submitted in the dossier will depend to a certain extent on the nature and complexity of the product and the active ingredient, and the complexity, type and stage of development of the manufacturing process[2].

All three regions require an import license, which aims at getting information about the manufacturing site and the drug product. In Japan, this procedure is known as "Accreditation of Foreign Manufacturers of Pharmaceuticals" and is significantly more wide-ranging.

In Japan, there are two GMP requirements that have to be fulfilled: so-called GMP Hard, which refers to the structure and facilities of the manufacturing site, and GMP Soft, with focus on the manufacturing process of the relevant drug product and quality assurance aspects of the manufacturing environment[3,4].

The precondition for a marketing approval is that API and FDF manufacturers as well as packagers have received "Accreditation of Foreign Manufacturers of Pharmaceuticals". This means proving that any manufacturing sites involved in the production of the active pharmaceutical ingredient (API) or drug product comply with GMP Hard[3]. Accreditation is granted for drug manufacturing categories such as manufacturing of general drugs, sterile drugs, radiopharmaceuticals or packaging and requires the submission of information on site, facilities, manufacturing equipment and staff. It also requires personal information on the site manager.

On the other hand, GMP compliance review for the product seeking approval must be passed by proving that manufacturing processes comply with the principles of GMP Soft[4] and the relevant manufacturing facilities with GMP Hard[3]. Detailed information on the equipment, facilities, the manufacturing process, quality assurance organization, and staff has to be provided. Further, the applicant must submit batch records and validation data of three commercial batches. Since 2008, the PMDA has started conducting on-site inspections. However, for capacity reasons it is at the PMDA's discretion whether such on-site inspections are executed.

The application for marketing approval signals also in Japan that the applicant is in principal prepared for an on-site inspection. However, documents proving that the production processes comply with GMP Hard and GMP Soft respectively have to be submitted in any case.

4. Test methods and specifications of API and FDF

In the EU and USA, generic products are seen as individual drug products with their own individual pharmaceutical development. In the EU, API source and composition may be different from the originator, so that impurity and stability testing are to be self-supporting and do not need assessment by taking the originator drug product as benchmark. In the USA, this applies to all drug products except injectables, where the composition may differ with regard to buffers and preservatives only. Setting specifica-

tions and developing suitable analytical methods follows the same rules as for new chemical entities in both regions.

USA: The specifications of the United States Pharmacopoeia (USP) are mandatory. Test methods can be different, but if so, cross validation with the USP method is necessary. In case of uncertainties, the USP-method is always the relevant and binding method. Generally, ICH guidelines are applicable in the US, however sometimes there are discrepancies, e.g. stability requirements are less restrictive in the US: assay for non-compendial drugs is not as strictly limited as in Europe or Japan —— it is usually 90-110 %.

EU: The quality of the generic drug product must be examined and proved in the same way as for new and innovative drug products. If specification and analytical methods of the European Pharmacopoeia (EP) are available for the active pharmaceutical ingredient (API), they have to be respected unless it is proven that the applicant's own method is equal or superior. In this case, cross validation is necessary. The corresponding ICH guidelines are taken into account (e.g. ICH Q1A, Q2, Q3A/B/C and Q6A).

Japan: The situation in Japan is different. For instance, PMSB/ELD Notification No. 568[5] should also be applied to non-new ethical drugs[6]. In its "important notices", the notification itself explicitly allows test procedures other than those specified in the JP when those procedures are specified in the European Pharmacopoeia (EP) and/or the United States Pharmacopoeia (USP). In principle, this could be interpreted as meaning that test procedures of the EP and/or USP can be used for generics in Japan. However, regulatory reality demonstrates that this is only partly true:

a) Compendial drug substances or drug products:

For drug development indeed any suitable validated method other than those listed in the JP can be used, although the tests must follow the principle of so-called "actual measurement values" (AMV). This means that three specimens of each of three batches of a drug substance or drug product have to be analyzed. However, for batch analysis of registration batches and post approval release JP methods have to be used to prove compliance with FDF and API quality with the specification given in the JP. In this case, the marketing approval applicant knows the mandatory methods and specifications when the data for the submission file are generated.

b) Non-compendial drug substances or drug products:

The situation becomes more complicated in cases of a non-compendial API or FDF. Again, for drug development any suitable validated method can be used, although the principle of "actual measurement values" must be followed. However, via deficiency letters the PMDA requests the applicant to apply those methods for registration batch analysis and post-approval release, which were developed by the originator about a decade ago (re-examination period plus review time is at least 9 years). Further, the PMDA requests that specifications of API and FDF are adjusted to the specification of the originator product.

In this case, both the mandatory methods and the specification are unforeseeable and the manufacturer has to adapt the release procedure for Japan at short notice. From a scientific point of view, this procedure might appear unsatisfactory, because the self-developed methods have to be exchanged for a methodology and specification which is in principle intellectual property of the originator and hence not publicly available in advance. Still the authority communicates it, although very late, and requests their use for future FDF and API release.

5. Drug Master File (DMF):

The drug master file system protects intellectual property and facilitates review work by allowing a DMF holder other than the drug approval applicant to submit confidential information concerning e.g. manufacturing methods of materials used in the

production of the drug product separately from the application file of the drug manufacturer.

The DMF principle is equal for all three regions: the DMF needs to be CTD structured and consists of a closed and an open part. The open part is disclosed to both the drug approval applicant and the authority, whereas the closed part comprises confidential information and is revealed exclusively to the authority for review purposes in connection with a corresponding drug approval application (the FDA accepts DMFs also without corresponding drug application). A so-called letter of access (LoA) issued and signed by the master file holder provides evidence that the drug approval applicant has the permission to refer to the DMF.

USA: The DMF procedure can be used for drug substance, drug substance intermediates and materials used in their preparation, primary packaging materials, certain excipients (e.g. colorants, flavors, and essences) and sterile validation information.

A DMF may be filed anytime before submission of the corresponding Abbreviated New Drug Application (ANDA, generics application) but review takes place only in connection with the ANDA referring to it. The DMF registrant can be any legal person, but an American- in-country agent announced and contracted by the registrant must make the submission. Mandatory DMF language is English.

EU: The Active Substances Master File (ASMF) procedure, commonly known as European Drug Master File (EDMF) procedure is used for drug substances only. The submission of an ASMF is only possible in connection with a corresponding drug approval application. The DMF holder can be any legal person. DMF language is English. There are two further master file procedure besides the ASMF, —— the Plasma Master File (PMF) and the Vaccine Antigen Master File (VAMF), which follow different rules, are differently applied and are not scope of this article.

Japan: In accordance with PFSB/ELD Notification No.0210004[7], several materials used for manufacturing pharmaceuticals can be registered by using the MF system:

1) Bulk pharmaceuticals, drug intermediates and drug substances (bulk items with special dosage forms)
2) New additives and premix additives with differing formula proportions
3) Medical device materials
4) Containers and packaging

The submission of a Master File is only possible in connection with a drug approval procedure. The DMF registrant can be any legal person, but a Japanese-speaking in-country agent announced and contracted by the registrant must make the submission. The function of the agent is to communicate with the authority, act on behalf of the applicant and represent his interests throughout the phases of the MF life cycle.

The information needed in the application form of a master file needs to be in the Japanese language. This includes among other data, the manufacturing process description, the specification, and the analytical methods as well as their validation. An English CTD Module 3 is allowed to be submitted as supplement in the English language.

6. Stability

Stability testing in the USA and the EU follows ICH guidelines. There is in principle no difference between stability testing of innovative and generic drug products.

Extrapolation is possible and means the practice of using a known data set to infer information about future data. Extrapolation to extend the shelf life beyond the period covered by long-term data can be proposed in the application, particularly if no significant change is observed at the accelerated condition. An extrapolation of stability data assumes that the same change pattern will occur beyond the period covered by long-term data, but the correctness of this assumption is critical. Thus, shelf life granted based on extrapolation should always be verified by

additional long-term stability data as soon as these data become available. The ICH system uses both short term testing under accelerated conditions and long-term testing under permanent conditions for estimating appropriate shelf lives for drugs [8].

EU and USA: As ICH principles allow bracketing and matrixing both regions accept stability testing of generics in accordance with ICH guideline Q1D [9]. Bracketing means that the design of a stability schedule is such that only samples on the extremes of certain design factors (e.g., strength, container size, and/or fill) are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested [9]. Matrixing means that the design of a stability schedule is such that a selected subset of the total number of possible samples for all factor combinations would be tested at a specified time point [9]. Both methods significantly reduce the number of samples and analyses needed for stability testing.

USA: For marketing authorization applications, the submission of stability data of one pilot batch and 3 months accelerated and long-term stability data are sufficient.

EU: For drug approval purposes, the submission of stability data of two pilot batches in case of a stable API and standard dosage form is required. In this case, 6 months accelerated and long-term stability data have to be submitted. Otherwise, three pilot batches (one batch can even be smaller), 6 months accelerated, and at least 9 months long-term stability data have to be provided. The amount of samples that have to be drawn is not regulated.

Japan: ICH stability guidelines are not applicable to generics. Stability testing has to be performed according to PAB/PCD Notification No. 43 [10].

As ICH stability-testing guidelines are not applicable, bracketing and matrixing are not easy to realize for generics, because wide-ranging additional data are required. However, extrapolation is very well possible: submission of 6 months testing data under accelerated stability conditions results in a shelf life of 3 years. The submission of long-term data to confirm the extrapolation is not required. This approach is doubtlessly convenient for drug development, but is it safe? Only recently, a PFSB/ELD notification [11] was enforced requesting the generation of permanent stability data as in-house confirmation for extrapolation in analogy to the ICH stability approach.

The Japanese guideline requests AMV (actual measurement values) for drug development. So also for stability, three samples of each of three pilot batches of AMVs have to be provided at every testing time. This means a 50 % increase in sample numbers when compared with ICH requirements and even more when additional sample reduction due to bracketing and matrixing is taken into account. Here it seems that more sampling and testing does not necessarily provide a higher level of safety, where extrapolation without confirmation by real time stability data is the critical step. It remains an open question as to why the shelf life of generics is determined less thoroughly than for new and innovative drugs.

In addition to the different number of requested samples also the conditions for accelerated and permanent stability testing are, although slightly, different. Nevertheless, incompliant data can not be used. Japan requires a range of ± 1℃ for accelerated conditions whereas ICH accepts ± 2℃. This means that stability studies for Japan need different settings for climate chambers. Table 1 shows parities and disparities between Japanese stability testing conditions required for generics and ICH conditions.

7. Bioequivalence (BE) studies

Within the frame of this article, it is not possible to summarize and compare the requirements for BE studies of all three regions for different dosage forms. In order not to go beyond the scope of this article, only general and most important aspects will be considered.

Table 1: Comparison of Japanese generic stability requirements and ICH conditions

	Japan (Generics)		ICH	
Storage conditions	General case (Room temperature)	Specified temperature	General case (Room temperature)	Storage in refrigerator
Accelerated Stability conditions	40°C ± 1°C, 75 ± 5% RH	(Specified storage temperature +15°C) ± 1°C, 75 ± 5% RH	40°C ± 2°C, 75 ± 5% RH	25°C ± 2°C, 60 ± 5% RH
Permanent Stability (PS) conditions	25°C ± 2°C, unspecified RH	Specified storage temperature ± 1°C, unspecified RH	25°C ± 2°C, 60% ± 5% RH	5°C ± 3°C, 60% ± 5% RH
AS Test Times	**4** in 6 months		3 in 6 months	
PS Test Times (months)	0, 3, 6, 9, 12, 18, 24, **30**, 36		0, 3, 6, 9, 12, 18, 24, 36, 48, 60	
Actual Measurement Values (3 batches, 3 samples / batch)	Yes		No	
Extrapolation of Shelf Life	Generally 36 months after 6 months AS		Extrapolation according to ICH Q1E	
Shelf life after real time testing	PS not required in case of AS Or: Not less than Originator		Shelf life = Time covered by PS data	
Extension: shelf life > 36 months	No regulatory action necessary		Variation with Review of PS Data	

With a BE study, the generic applicant refers to the clinical efficacy and safety data of a reference product (originator drug product). The originator's clinical study data are intellectual property and hence protected.

In the USA, data exclusivity is 5 years and can be extended for 3 years if studies for a new indication are provided.

In the EU, data protection is 8 years, but the product can be marketed only 10 years after approval date of the reference product. Prolongation of data protection in the EU is one year for a new indication.

In Japan, the reexamination period (corresponding to data protection or data exclusivity resp.) is eight years and is extended up to two years if study data for a further indication are submitted and approved.

In all three regions, the relevant authorities have implemented the "good clinical practice" guideline of the ICH (ICH GCP), which was finalized and recommended for adoption in 1996. Japan set the Japanese version (J-GCP) into effect in 1997 and revised it in 2006.

Good Clinical practice (GCP) is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials. It assures that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial subjects are protected. This standard consequently applies to all studies performed for marketing approval of drugs in the ICH region.

However, there are some minor formal differences between the agreed English ICH-GCP and the implemented Japanese J-GCP version.

The principle of generic or abbreviated new drug applications (ANDA) is that safety and efficacy stud-

ies need not to be repeated when the data protection period has expired and the applicant is able to prove that his product is bioequivalent to the reference product.

According to D.J. Birkett[12], two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent and their bioavailability (rate and extent of availability) after administration in the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, can be expected to be essentially the same. Pharmaceutical equivalence implies the same amount of the same active substance(s), in the same dosage form, for the same route of administration and meeting the same or comparable standards[12].

Bioequivalence is usually shown with clinical bioequivalence trials (in vivo BE studies) and comparative dissolution testing (in vitro BE testing).

a) Comparative dissolution testing (in vitro BE testing)

Comparative dissolution testing (in vitro BE study) is required to show that both the original (reference) and generic (test) formulation show similar dissolution profiles in certain aqueous solutions, which simulate physiological conditions regarding pH and temperature.

Due to the complexity of the tests with regard to poorly soluble active ingredients and/or delayed or modified release formulations, only immediate release (IR) oral dosage forms with readily soluble active ingredients will briefly be outlined here.

The principle is that at certain intervals the dissolution grade of the formulations is compared.

The USA require that BE batches (test and reference batch) are compared in three different media, covering the physiological range in case a bio waiver is submitted or in case of a delayed release formulation[13]. 12 units (e.g. tablets) per medium are examined. In combination with a clinical BE study the relevant dissolution conditions given in the USP or the FDA's "Dissolution Tests for Reference Listed NDA Drug Products" might be sufficient, but the guideline explicitly states that testing in additional media might be requested if scientifically justified. If the product is neither listed in the USP nor in the "FDA list" testing in three buffers is mandatory[14]. This usually leads to the approach that companies prepare comparative dissolution testing data in named three buffers from the beginning on to prevent problems.

In the EU, immediate release formulations should be tested in vitro under various conditions (media, pH, apparatus, and agitation). Testing conditions providing the most suitable discrimination should be chosen for comparable dissolution testing of reference and test batch. 12 units are usually examined.

Japan requires dissolution profiles generally in four different media. In contrast to the EP and the USP, the Bioequivalence Guideline[15] clearly defines further procedures in case of poorly soluble APIs. In addition dissolution behavior has to be tested with a higher paddle rotation speed in one medium which shows superior discrimination.

For all three regions one of the pre-conditions to be allowed to prove bioequivalence with only one (usually the higher) strength is that all strengths dissolve in a similar manner (see also Table 2).

Japan additionally requires that out of three originator drug product batches, one batch showing intermediate dissolution behavior is defined as the reference batch. However, three originator batches are sometimes not simultaneously on the Japanese market.

Special for Japan is the requirement that in case a specific and significant difference in dissolution is observed between the test and reference products at a neutral pH, subjects with achlorhydria should be recruited into the bioequivalence study because the two drug products may show a large difference in bioavailability depending on the gastric acidity level. This requirement is a precaution reflecting the relatively high incidence of achlorhydria in the Japanese population.

b）Requirements and conditions for in vivo BE study（IR capsules / tablets）:

All three regions observe the principle of the so-called "Bolar-Provision". The Bolar Provision allows a party other than the patent holder to manufacture samples and conduct clinical trials for drug approval purposes before patent expiry. The Bolar Provision enables generic producers to market and manufacture their drugs as soon as the patent has expired.

The required studies are quite similar for all three regions（Table 2）. For the USA, normally an additional fed study is required, with the exception of the following cases:

- The label states explicitly that the drug should be taken on an empty stomach
- There is no statement about the effect of food on absorption or administration
- The drug is a BCS class 1 product（see below）

EU and USA: The biopharmaceutics classification system（BCS）allows biowaiver（bioequivalence study waiver）for rapid dissolving immediate-release（IR）products of Class I drugs（high solubility and high permeability）.

All three regions allow BE studies with only one（preferably the higher）strength if for all strengths the manufacturer and/or manufacturing process are same, the dissolution profiles comply with the regulatory requirements（are similar）, and the formulations are proportional. Japan defines by its BE guideline several levels of dose proportionality: Level A（exactly proportional）, B, C, and D. For level E,

Table 2: Conditions and requirements for BE studies in the USA, the EU and Japan

	USA	EU	Japan
Required study	Single dose, non-replicate, fasting Single dose, non-replicate, in most cases fed	Single dose, fasting	Single dose, non-replicate, fasting
Biowaiver (BCS)	Yes BCS I	Yes possible for BCS I	No
Required strengths for BE study	Highest strength when: – same manufacturer – same dosage form – appropriate *in vitro* dissolution – proportionally similar	1 strength when: – same manufacturer and process – same qualitative composition – similar dissolution – linear pharmacokinetic – proportional formulations	Highest strength when: – same manufacturer/process – same qualitative composition – appropriate *in vitro* dissolution – proportionality: (different levels defined)
Number of studies	1 (Pivotal)	1 (Pivotal)	2 (Preliminary and pivotal)
Number of subjects	≥ 12	≥ 12	Not regulated
Study population	Representative of the general population (age, sex, race)	Normal BMI, Non-smokers or moderate smokers (less than 10 cigarettes / day), no history of alcohol or drug abuse, could belong to either sex	Healthy adult volunteers, belong to men in general
Study location	Not restricted to the US	Not restricted to the EU	Japan
Age of subjects	≥ 18	18 - 55	≥ 20
Study design	crossover	crossover	crossover
Acceptance range	80-125% (AUC, Cmax)	80-125% (AUC, Cmax) Range can be widened when justified to 75-133%	80-125% (AUC, Cmax)

new studies are mandatory. However, Japan does not require linear pharmacokinetics (PK) in this respect.

In the EU and USA, one study with at least 12 subjects is in principle sufficient to show bioequivalence. In Japan, a preliminary study should be conducted before the pivotal study is performed. However if BE can be shown with a preliminary study alone; the second pivotal study is not required.

The study population is generally representative for the population in the region, with some restrictions concerning drug abuse and body mass index (BMI) in Europe. The ages of the recruited subjects are given in Table 2 for ordinary drugs. However, study population age may vary with medication (e.g. drugs for elderly patients).

The acceptance range for BE is 80 – 125 % for Cmax (maximum plasma drug concentration) and AUC (total area under the plasma drug concentration-time curve). In Europe the acceptance range may be widened to 75 – 133 % when justified.

The requirements for BE studies in the ICH region are, when compared, not strikingly different. The most crucial disparity is the fact that studies for Japan require subjects with standard Japanese lifestyle habits (dietary habits, way of living, etc.). For a study performed with a Japanese study population living abroad evidence must be provided that results are the same as if the study had been performed in Japan. The analysis of Japanese plasma samples can be done in any other country. As a consequence of study location, most of the data are generated in Japanese and have to be back-translated for analysis and for archiving in the data bases of multinational concerns.

8. Pharmacovigilance

All of the three regions have elaborated and agreed on the ICH safety data management guidelines E2A – E2E. The pharmacovigilance or post-authorization (post-marketing) surveillance systems follow in principle this common approach, but procedures and formal aspects vary. Overall pharmacovigilance provisions do not distinguish between innovative drugs and generics.

The following overview outlines only the most important items and principles.

USA:

The FDA requires pre- and post authorization safety reports per 21 CFR Part 312.32.

Pharmacovigilance in Clinical Trials:

The sponsor is responsible for notifying the FDA and all participating investigators in a written Investigational New Drug (IND) safety report of:

c) Any adverse experience associated with the use of the drug that is both serious and unexpected; or

d) Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The sponsor is required to notify the FDA as soon as possible but in no case later than 15 calendar days after the sponsor's initial receipt of the information and regarding any unexpected fatal or life threatening experience in no case later than 7 calendar days after initial receipt.

Pharmacovigilance Post Authorization:

All Marketing Authorization Holders (MAH) of approved New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs) have to establish and maintain records and make reports to the FDA of all serious, unexpected adverse drug experiences (cases) associated with the use of their drug products. Expedited reporting (i.e. submission to FDA in no case later than 15 days after receipt) applies to all domestic cases classified as serious irrespective of whether categorized as expected or unexpected and to all foreign cases classified as serious and categorized as unexpected. In addition, annual line listings have to be submitted covering all reports received by the MAH.

EU:

The pharmacovigilance regulations were upgraded and amended in 2005.

Pharmacovigilance in Clinical Trials:

The sponsor has to submit expedited reports to the competent authority in case of suspected unexpected serious adverse reactions (SUSARs) occurring in the EU with the following reporting requirements:

a) Fatal or life-threatening adverse reactions: Reporting is required within seven days, —— a follow-up report within additional eight days.
b) Other suspected unexpected serious adverse reactions: reporting is required within 15 days.
c) SUSARs occurring in non-EU countries where they involve products for which clinical trials are being conducted in the EU require expedited reporting, in accordance with the periods given above.

Non-expedited reports are required by the sponsor by means of annual and/or final reports in case of:

– serious expected adverse reactions
– serious adverse reactions not considered to be related to the study product (expected or unexpected)
– Non-serious adverse drug reactions (expected or unexpected)

The sponsor has to keep records of all adverse events reported to him by the investigator(s). Such records must be submitted to the competent authority if so requested.

Pharmacovigilance Post Authorization:

The MAH is required to submit expedited reports in the following cases:

– Serious adverse reactions, either spontaneously or through non-interventional post-authorisation studies, must be reported immediately and in no case later than 15 calendar days from receipt.
– Reports of overdose, abuse or misuse that lead to serious adverse reactions
– Reports of lack of efficacy if the product used is e.g. a contraceptive, a vaccine, or a medicinal product used for the treatment of life threatening diseases
– Reports of any suspected transmission of an infectious agent via a medicinal product

Non-expedited reports:

Non-serious adverse reactions from EU and non-EU countries do not normally need to be reported on an expedited basis but may require inclusion in periodic safety update reports.

Japan:

Pre- and post-marketing surveillance is stipulated by the Pharmaceutical Affairs Law (PAL).

Pharmacovigilance in Clinical Trials:

Expedited reports (in no case later than 7 days) are required from the sponsor in case of the following unexpected adverse reactions during clinical trial or unexpected averse reactions with the same product elsewhere, or trial elsewhere with a product having similar ingredients:

– Fatal or life threatening adverse reactions
– Unexpected infection suspected to be caused by use of the investigational drug

Expedited reports of following exemplary serious adverse events suspected to be caused by the trial drug (not later than 15 days) are required by the sponsor:

– Inpatient hospitalization or prolongation of hospitalization
– Persistent or significant disability or cases which might result in disability
– Congenital diseases or abnormalities in the next generation

Details for reporting of adverse events are given in PFSB/ELD Notification No. 0921001: "Implementation of the Standards for the Conduct of Clinical Trials of Medicinal Products" (GCP), 21 Sep 2006[16].

Pharmacovigilance Post-Marketing:

Adverse events committing the MAH to expedited reporting within 15 days of occurrence —— mandatory under provisions of Enforcement Regulations of PAL, Article 253 —— are unexpected serious events like:

– Unexpected death or life-threatening adverse reactions
– Unexpected persistent or significant disability or

cases which might result in disability
- Unexpected inpatient hospitalization or prolongation of hospitalization
- Unexpected congenital diseases or abnormalities in the next generation

Adverse events committing the MAH to reporting within 30 days of occurrence —— mandatory under provisions of Enforcement Regulations of PAL, Article 253 —— are expected serious events like:
- Expected life-threatening adverse reactions
- Expected persistent or significant disability or cases which might result in disability
- Expected inpatient hospitalization or prolongation of hospitalization
- Expected congenital diseases or abnormalities in the next generation

All unexpected adverse events (except death and disability) require periodical reporting (annually for generics).

The post marketing re-examination system of Japan is generally applicable to new drugs and is only in very exceptional cases applied to generics. It is therefore not considered to be within the scope of this article.

9. Other aspects:

a) Some authorities of EU member states request samples of the drug product which is under review in all or some of the member states for demonstration purposes.

The FDA requires a sample availability statement, which has to be submitted for both API and FDF samples.

In Japan, samples are not requested.

b) Raw data: The FDA requires the submission of master batch records and executed batch records of all strengths.

The EU usually does not require any raw data, except in some deficiency letters where a very detailed answer is requested.

In Japan, the situation is different. Raw data (HPLC print outs, etc.) of all analytics necessary to compile the data for the submission file have to be submitted. In case of non-English records, translations are necessary. The assemblage of raw data should not be underestimated. A major complication in this respect is the GMP requirement that laboratory records should be written in native languages to prevent errors. An optional way out are bilingual records in those laboratories generating data submitted in Japan to save translation costs.

c) Manufacturing process description: In Europe and the US, the manufacturing process is described on a comparatively brief basis. A flowchart with a narrative description is adequate. In Europe, details concerning equipment and facilities are not given and descriptions are held general to trim workload in case of slight variations. This is a mutual approach of both the manufacturer and the authority.

For Japan, the production process needs to be particularized and equipment details have to be given. The narrative is instructive and allows, in combination with equipment and facility details from the GMP compliance file, a complete and detailed reproduction of the process.

Conclusion:

Although every ICH region has its own requirements, the application of the tripartite guidelines and submission format is of significant help to facilitate the generation of data necessary for drug approval applications filed across Europe, the USA and Japan. Nevertheless, for generic drug approval in Japan, these guidelines are not applicable. Consequently, the assessment of shelf life and purity of generics in Japan follows different rules compared with innovative drugs. From a scientific point of view, there seems to be no reason why standards for originator drugs in this respect should not be applied to generics as well. With a number of pro-generic measures being implemented, the Japanese government attempts to push the use of generics. However, this

would probably have a better chance of success if chemical and pharmaceutical quality aspects for generics were assessed in the same way as originals. After all, generics also have their own, distinct compositions and their sources of ingredients and excipients may differ from those of the originator product. It is therefore no surprise when Japanese customers and health professionals, both known to be quality-conscious, prefer to use originals. However, it is important that patients have a safe alternative option to seek lower cost medicines with consultation to medical professionals. The government should also have an alternative to manage healthcare expenses while achieving the same medical outcome.

In the age of globalization, it would further be very much appreciated if requirements could become harmonized. In addition, the analytical workload necessary for generic approvals in Japan could be greatly reduced. However, even if all these technical hurdles were abolished in the near future, another hurdle remains cultural and linguistic differences for global generic players. At last but not least, I hope this summary somehow supports to establish a pro-generic system in the regulatory field in Japan which is consistent to the Japanese government's overall pro-generic measures.

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