

Understanding the Japanese culture and approval process

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ABSTRACT

Gaining approval for a drug product in the West is a well-understood and documented process. Japanese approvals have often been more time consuming and, in the past, companies would often complete their "Western development" before thinking about Japan. However, as Japan is the second largest single pharmaceutical market, it is clearly an important part of the drug development process and needs to be considered in parallel with work targeted at the Western regulatory authorities.

An important factor in achieving success in Japan is to understand the culture as well as the regulatory environment and processes, both of which have changed considerably in the past few years. Gaining agreement with the regulatory authority on completing a full Phase III development within Japan or implementing ICH E5 to make use of foreign data is also an important step in the process.

This paper will look at working with Japanese colleagues to deliver a submission and the stages involved in the registration process. It will cover the interactions between the sponsor company and the Pharmaceutical and Medical Devices Agency. The concept of a bridging strategy to use foreign data will be introduced and some of the potential Japanese specific programming deliverables will be discussed.

INTRODUCTION

The FDA has many regulations and guidance for industry documents regarding submissions which are readily available on their website. Within the programming environment there are countless sources of information regarding Part 11 compliance. In Europe the approval processes (Mutual Recognition and Centralised) are also well understood. From a practical point of view, there are few differences a programmer would notice when producing outputs required for a submission to the FDA or within Europe (Item 11 for FDA being an obvious one).

However, when I first became involved in a Japanese submission team I found that there was little information available and I had to rely on Regulatory Affairs colleagues to explain the process at each stage. While programmers do not need to have an in depth understanding of the content of all the Japanese submission documents, having an overall understanding of the culture and approval process certainly helps, which is the aim of this paper.

JAPANESE CULTURE

The most obvious difference when working with Japanese colleagues is the language barrier. Although English is an essential subject from junior school in Japan and is also taught at high school and universities, they obviously aren't as comfortable at using it as Western people. As a result they can often appear to be rather direct and un-diplomatic but this is usually because they are trying to explain something as specifically as possible. In fact the opposite is true; they are generally very polite and quite shy. When asking a question to Japanese people, they may say "No!", "It's difficult" or "It's impossible" without any reason. This should not be taken as a sign of insolence. They are not as skilled at Western discussion style and will probably be wondering how to explain their problems as Japanese is a reflective language. Simply ask why, give them some time to think and they will explain the reason. Some private pre-schools have recently started teaching English because of the importance of the language. Hopefully, in future, Japanese colleagues will be more familiar with English and be comfortable using it more frequently in meetings. There are also cultural differences that you should be aware of such as nose blowing which, while not being earth shattering, should still be avoided if possible. There is no tipping in Japan and, generally, personal safety is quite high as there are low crime rates.

FEATURES OF THE MARKET

The Japanese pharmaceutical market is the second largest with annual sales of US \$58 billion, nearly 11% of the global market. However, the rate of growth is slower than the Western market at approximately 2% per year. The population of 127 million is rapidly ageing but generally wealthy and highly educated. All patients are covered by some form of private and/or public insurance which can cover up to 3rd degree relatives who do not live with you. Patients pay between 10 and 30% of costs depending on circumstances and can approach any GP or hospital directly who can prescribe and dispense medications. Multiple drug use is the norm and doctors get a fee for each treatment.

There is high use of recently approved drugs, although historically there has been low patient awareness of medical treatments.

BUSINESS IN JAPAN

Punctuality and use of the honorific title “-san” are very important when doing business in Japan. Business cards are valued as highly as a passport and exchanging these is an important ritual even internally within a company. You should always have a clean set of cards available and never deface any cards received; these should be taken to future meetings as a sign of respect. Generally there is a formal dress code but this may be more casual when they meet with Western colleagues. Japanese members of a group may not readily express opinions as there is still a sense of hierarchy and group orientation and, in general, they do not speculate. Social behavior is associated with the workplace and involves after hours group activities, which are an important aspect of working life. Working until late at night is normal in Japan. In meetings with Japanese colleagues, expect longer pauses in the conversation and cross check responses periodically.

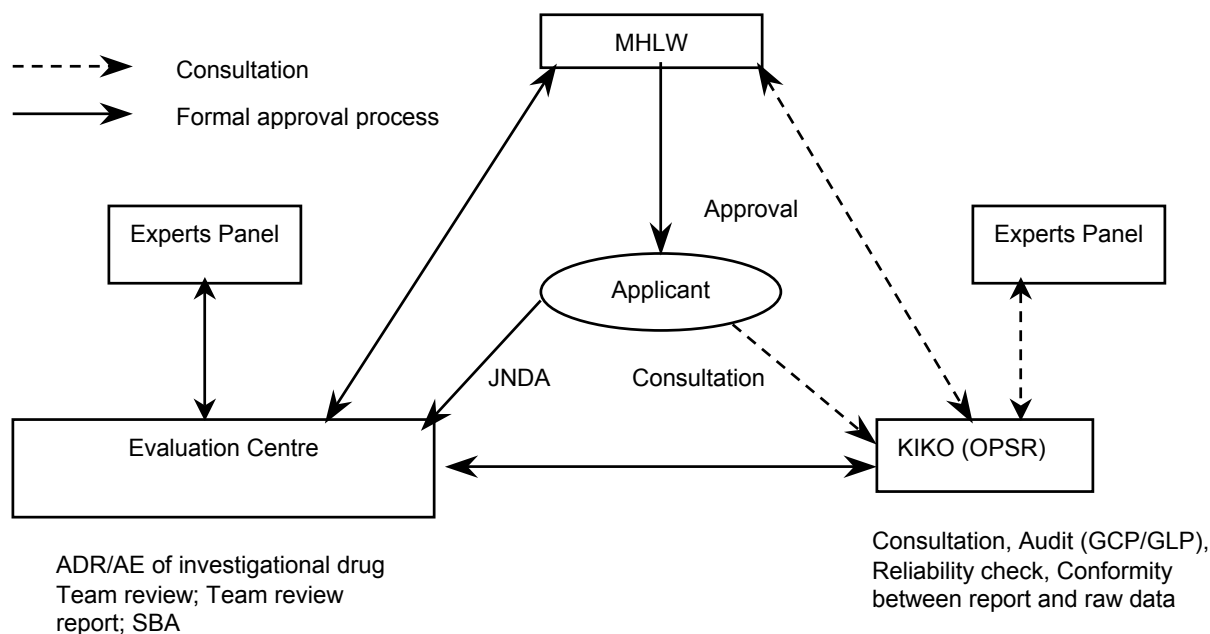
Due to the language barrier, translators will often be used in meetings and allowances have to be made for this. Verbal communication should be clear, with only one person talking at a time, and time allowed for translation. Some Japanese employees who don't have many opportunities to work with global colleagues can be hesitant at expressing their opinion even if they are comfortable with the English language so don't assume they don't have anything to contribute. Written documents and e-mail will be useful to confirm any discussion points, agreed points, requests, etc. During a conversation they might miss the meaning of the discussion, especially when there is a difficult issue to resolve so this type of confirmation will be useful to avoid any misunderstanding.

REGULATORY ENVIRONMENT

The regulatory environment in Japan has been changing considerably over recent years. Pricing controls have been introduced to curb the rise in healthcare expenditure and, just as there has been in the West, concerns over safety in the 1990's have naturally led to a more cautious approach as well as new laws and guidelines. The HIV infected blood scandal concerned the continued use of non heat-treated blood samples after heat-treated samples became available. Over 1000 Japanese patients with haemophilia are thought to have contracted HIV after being exposed to infected blood products. Another scandal involved Sorivudine, an antiviral agent, which was approved for use in Japan in September 1993. Within a few weeks 18 cancer patients who were also receiving 5-FU died as a result of a drug interaction and Sorivudine was withdrawn from the market within a month.

STRUCTURE OF THE “OLD” REVIEW SYSTEM

Until recently, reviews and related operations for pharmaceutical medications were handled by two organisations. The Pharmaceuticals and Medical Devices Evaluation Center (PMDEC) was the main product review body comprising of 8-10 specialists while the Organisation for Pharmaceutical Safety and Research (OPSR or KIKO) was an independent consultation body. The PMDEC and KIKO worked closely together and both made use of “experts”, which would often comprise the same people. The Ministry of Health, Labour and Welfare (MHLW) supervised PMDEC and KIKO and granted approval.

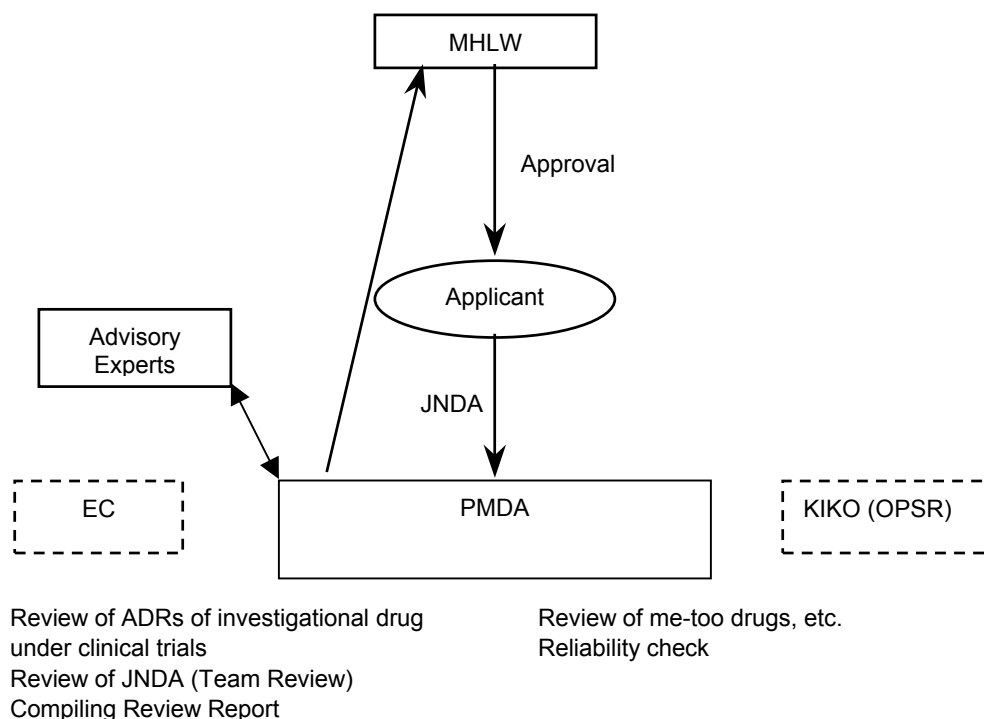


Use of the KIKO advisory committee prior to submission was encouraged by the MHLW. This could comprise up to 6

consultations lasting 2-3 hours, for which the sponsor company was charged a fee, although 20-minute informal pre-consultation meetings were also available for free. Some of the time points for these meetings were pre Phase I, post Phase II (essential for discussing bridging strategy) and pre-JNDA (essential for guidance on the suitability, inclusion and presentation of clinical data).

STRUCTURE OF THE “NEW” REVIEW SYSTEM

As part of the reforms that have been ongoing recently, the PMDEC and KIKO, along with the Japanese Association for the Advancement of Medical Equipment (JAAME), were merged in April 2004 to form the Pharmaceuticals and Medical Devices Agency (PMDA).



The PMDA now handles the whole process from clinical study stage, providing “face to face” advice, through the approval phase and is also responsible for post marketing safety measures. As part of the merger of the previous organisations, the MHLW set the PMDA a series of mid term targets, although these do not include the “clock stop” time when the applicant is responding to instructions. This will be achieved by increasing their review staff, paid for by increased consultation fees (from around 8m yen to 17m yen per JNDA), but should help to speed the introduction of safe medications to the market, benefiting both patients and the pharmaceutical industry.

PMDA Review Targets

Review of Application	By 2007	By 2008
New Drug JNDA	70% in 12 months	80% in 12 months
Priority Review	50% in 6 months	50% in 6 months

USE OF FOREIGN DATA

Historically there have been concerns that ethnic factors may affect a drug’s safety, efficacy, dosage and dosing regimen in a new region. This has limited the acceptability of foreign data to support a drug submission and regulatory authorities have often requested all, or most of, the foreign data to be duplicated in their region. This would normally require either full-scale development in Japan or the inclusion of Japan in the global development. As a consequence there have been delays in being able to get new drugs to market and unnecessary waste in drug development resources.

INTERNATION CONFERENCE ON HARMONISATION GUIDELINE E5

In order to resolve the problems involved in using foreign data in support of a submission, ICH developed Guideline E5 "Ethnic factors in the acceptability of foreign clinical data" in 1998 which describes

- Characteristics of foreign data that will enable it to be extrapolated to a different population
- Ways to minimise the duplication of clinical data
- Use of bridging studies to help extrapolate foreign data
- Methods to characterise ethnic factor influences

ICH E5 was implemented in Japan from August 1998. Some of the characteristics of how sensitive a drug is to ethnic factors are:

- Linearity of Pharmacokinetics
- Pharmacodynamics curve for safety and efficacy
- Therapeutic dose range
- Metabolism
- Potential for protein binding
- Potential for drug-drug, drug-diet and drug-disease interactions
- Mode of action
- Potential for inappropriate use

A Clinical Data Package that meets all of the regulatory standards is defined as a Complete Clinical Data Package. Before extrapolation can be considered, the Complete Clinical Data Package should contain

- Adequate PK, PD, dose response, safety and efficacy data in the foreign region(s)
- Clinical studies establishing dose-response, safety and efficacy which should have been designed and conducted according to regulatory standards and have appropriate endpoints
- Characterisation of PK and PD in a relevant population

BRIDGING STUDIES

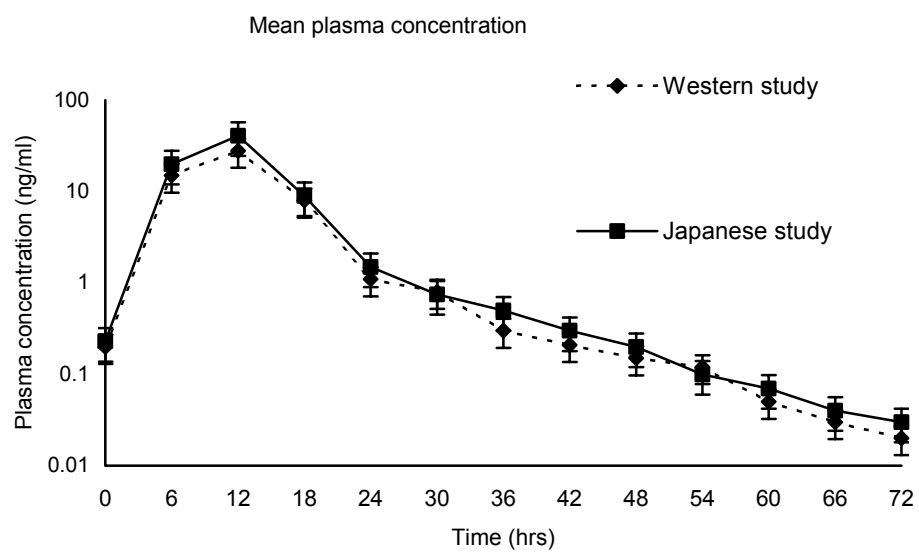
A bridging study is an additional study conducted in the new region to provide PK or safety, efficacy and dosing data in that region that will allow extrapolation of foreign clinical data to the new region. If the bridging study demonstrates similar dose response, safety and efficacy then the study 'bridges' the foreign data. Even if the bridging study shows that a different dose results in similar safety and efficacy to that generated in the foreign region, it is still possible to extrapolate the foreign data with appropriate dose adjustment.

Bridging in Japan is mainly focussed on efficacy, containing a comparison of PK and dose response (see example plots 'PK comparison of Japanese and foreign data' and 'Dose response comparison of Japanese and foreign data'). Less emphasis is placed on a safety bridge in order to use the foreign data. However, long-term safety data in a reasonable number of Japanese patients is required.

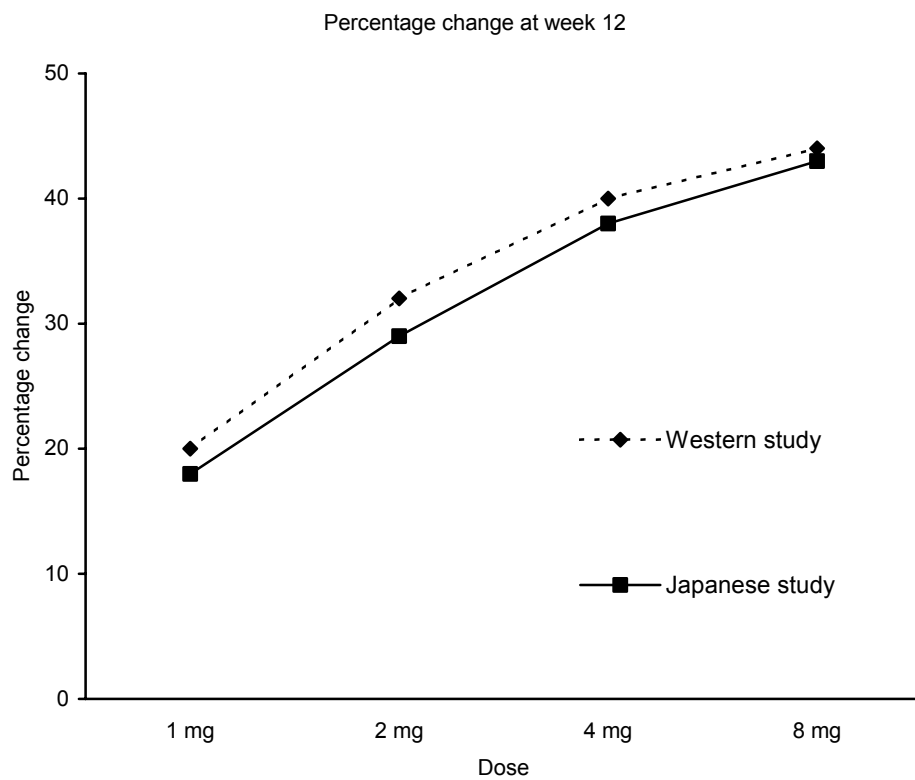
Depending on the results of the PK and PD comparisons, various scenarios may arise with differing consequences for your bridging strategy:

RESULT OBSERVED	CONSEQUENCE
Same efficacy Same PK	No dosage issues
2 * efficacy 2 * PK	Use half the dose in Japan
Same efficacy Different PK	Need more investigation and explanation
Different efficacy Same PK	Need more investigation and explanation

PK COMPARISON OF JAPANESE AND FOREIGN DATA



DOSE RESPONSE COMPARISON OF JAPANESE AND FOREIGN DATA



KEY FACTORS FOR A SUCCESSFUL BRIDGING STRATEGY

Some of the key factors for a successful bridging strategy in Japan are:

- Prospective bridging where a Japanese study is designed for bridging based on PMDA consultation. Retrospectively using a Japanese study that was not designed for bridging is difficult due to likely differences in study design, entry criteria, endpoints and medical practice between the study and the foreign study.
- Evaluation of the same primary endpoint in the studies to be bridged
- Successful demonstration of dose response in the Japanese and foreign study
- “Case by case” – make use of the consultations with PMDA to develop a strategy most suitable for the drug and indication
- A different dose does not preclude extrapolation of foreign data, providing the safety and efficacy profiles are similar and can be justified (e.g. by PK/PD data)
- For multiple indications, a bridging strategy for indication is required
- Bridging will not be established with PD or PK data only

Although there are obvious benefits to a successful bridging strategy, it does limit the experience that key opinion leaders will have with the product at the time of launch, one of the benefits of a full scale Japanese development. It should also be noted that the PMDA still have a conservative view of extrapolating data.

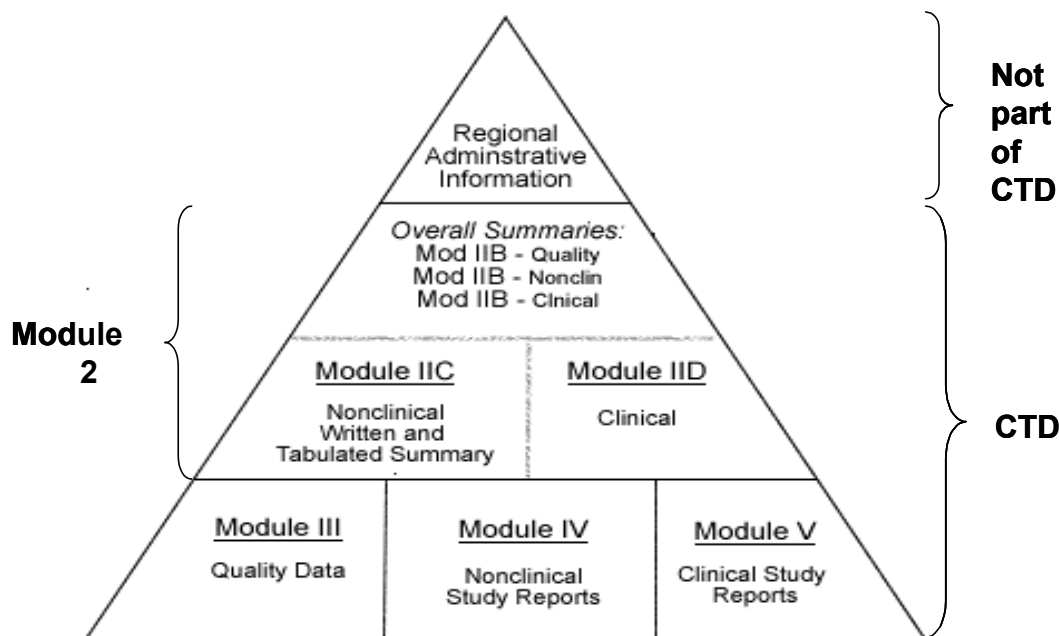
COMMON TECHNICAL DOCUMENT (CTD)

CTD format for submissions was formally adopted in Japan on 21st June 2001 (notification number 899) and it's use became mandatory on 1st July 2003.

Pre-CTD, the Gaiyo was a summary document forming part of the submission containing approximately 200-300 pages and contained 7 sections:

- Origin or background of Discovery – A
- C&P General (B), Stability (C)
- Preclinical (toxicity, pharmacology, kinetics) – D, E and F
- Clinical (kinetics, efficacy) – F and G

The SAS® output produced by the programming team would be used in section G.



Modules 2 to 5 of an NDA dossier must be submitted in CTD format. Module 2 replaces the Gaiyo and must be written in Japanese. The interpretation of the clinical data should focus on the Japanese component of the global program, with the bridging study providing a link to the foreign safety and efficacy data, which will be included in sections 2.5 (clinical overview) and 2.7 (clinical summary). Module 5 can be written in English and must cover

- Efficacy from studies considered pivotal to the submission
- AEs and SAEs from all studies

- Cases of abnormal laboratory test results
- Figures showing laboratory test changes

Foreign data should be used as appropriate.

For sJNDAs you can use a mixed format i.e. cross-reference to a pre-CTD submission. Unlike the US and EU, CTD format will not be required in Japan for generics or OTC products. To date there have been 72 J-CTD submissions

- 27 for new chemical entities
- 4 were e-CTDs

The key focus has been on Module 2, especially clinical and quality issues. CTD format for submissions will be required for

- NCEs
- Biological products
- New dosage forms or doses
- New routes of administration
- New indications

Feedback from the MHLW indicates

- The CTD is about a standardised format, not content
- Content should be easily understandable, focused on the Japanese data and facilitate Japanese review
- Module 2 will be disclosed to the public in the same manner as the Gaiyo it replaces. CMC information is protected, however, the critical overviews for S & E and the summary documents will be released

PAEDIATRICS

As with other agencies, MHLW are keen to see the pharmaceutical industry consider paediatric developments. Incentives for this are in place, with up to an additional 4 years exclusivity and there is evidence to suggest that companies are beginning to take advantage of this incentive.

JNDA TEAM

The JNDA team should comprise of functional representatives from Japan and the West, core clinical members will be a physician, project manager and a statistician. A programming representative may be included as an extended member if they are in a different skill group to statisticians. Commercial will normally have input to the team as well. From a resource point of view, having a dedicated team assigned to the JNDA will help if this is running in parallel to the Western development as running three major submissions will be too much for one team. Leaders of both the Western and Japanese members of the JNDA team should be identified but there should also be an overall lead and this will normally be the Japanese lead member.

Hopefully, most of the time there will be good agreement within the JNDA team but it is important to have a mechanism in place to resolve issues that the team cannot agree on rather than waiting until an issue arises. If a separate team has been created for the JNDA, it is important to have good links to the team managing the EU and US submissions to ensure consistency in the key messages.

PLANNING THE SUBMISSION

Planning for JNDA submissions has changed over the past few years. Historically, companies would ensure their "Western Development" was complete before thinking about gaining approval in Japan. Even today, it can be difficult to encourage teams to think about Japan at the same time as the West.

"We don't have enough resource ..."

"We have to focus on the US/EU ..."

"We don't know if we can do that in Japan"

"We need to move quickly and Japan will just hold us back"

Given that Japan is potentially the second biggest market for a new medication, companies really should plan to develop the JNDA at the same time as the Western submissions. Most multinational companies should have development templates that factor Japan into the global planning process. The JNDA timings should be based around the key decision points and/or formal PMDA meetings and sufficient resource will need to be put in place if parallel development is to take place.

Face to face meetings are important, videoconference and teleconference meetings help but they do have limitations. The key clinical sections should be scoped out before discussing the detail. The JNDA team needs to understand the commercial and medical positioning of the product in Japan. With more and more companies adopting a bridging

strategy, the use of Western data as pivotal in Japan is becoming widespread. The impact this has on the submission package needs to be considered, as it will be much larger as the requirements for Western certificates increases and the bridging strategy needs to be included.

SAS OUTPUTS

Even if there is a large foreign database and a successful bridging study supporting a JNDA, there are additional tables that have to be generated by programming and/or statistics. These “G-tables” are a regulatory requirement and are traditionally where the key data in the submission are taken from and used for the Japanese Patient Information (JPI). G-tables are produced for both efficacy and safety data and studies considered pivotal in Japan will be used in the efficacy tables, irrespective of the trial design and patient population. This can result in pooling of data that would be considered inappropriate for a US/EU submission. The data will also be cut in various inappropriate ways.

When discussing the format of the G-tables (or any other data requested during the consultations and review process) it is worth remembering that Japanese colleagues may also feel that the requested format for presenting the data is inappropriate and meaningless. Even though these may take considerable time and resource to prepare, without them the submission or approval cannot go ahead as the authorities will not readily change their stance.

TABLE G1 – EFFICACY

The efficacy table only contains studies considered pivotal to the submission and appears in JNDA as one very wide table. In order to produce these, SAS tables have to be split by study or pool and parameter grouping. The primary endpoint is summarised by several parameters

- Demographic e.g. age, sex, race
- Concurrent diseases
- Concomitant medications of interest
- Treatment regime

The table below shows an example of the structure of Table G1. All pivotal Western studies will be included and columns for all Japanese studies, Japanese total and Grand total will also be required.

Characteristic		Western study 1			Western study 2			Western total		
		N	Mean	SD	N	Mean	SD	N	Mean	SD
Sex	Male									
	Female									
Age	< 18									
	18 - <=49									
	50 - <65									
	>=65									
Race	Caucasian									
	Black									
	Etc									
Etc										
Baseline Efficacy Value	Group 1									
	Group 2									
	Etc									
Medical History	History 1									
	History 2									
	Etc									
Concomitant Medication	Medication									
	Medication									
	etc									
Dose	1 mg									
	2 mg									
	Etc									
Treatment Duration	< 6 weeks									
	6<= - < 24 weeks									
	24<= - <52 weeks									
	Etc									

TABLE G2 – SAFETY

Again, several SAS tables will be required to populate one wide published table and the data will be included in the JPI (the Japanese equivalent of the Core Data Sheet). Treatment emergent and drug related treatment emergent adverse events are summarised by patient pool (Japanese, Western, All) and individually for each study included.

The table below shows an example of the structure of Table G2. All Western studies will be included and columns for all Japanese studies, Japanese total and Grand total will also be required.

		Western study 1		Western study 2		Western total	
Safety population		N=		N=		N=	
Causality		ADR	AE	ADR	AE	ADR	AE
Patients with ADR/AE		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Number of ADRs/AEs		N	N	N	N	N	N
System Organ Class 1	Preferred Term 1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Preferred Term 1	N (%)	Etc				
	Etc						
System Organ Class 2	Preferred Term 1						
	Preferred Term 1						
	Etc						
Etc							

PATIENT LISTINGS

The patient listings are an appendix to Module 2 of the NDA and are produced for pivotal studies only. Numerous sources of data are compiled into an extremely wide published listing. As these need to be translated for the submission, the format used to output the listing is less important. One way to avoid splitting the listing over several SAS listings is to produce a dataset which “looks like” a SAS listing and exporting out to a Microsoft Excel® file. Obviously, you will need to ensure that all the Excel files produced are an accurate reflection of the data, e.g. the correct formats have been exported.

There are three patient listings required for each pivotal study:

- Patient information
- AEs
- Abnormal laboratory data

The data types used in the patient information listings includes

- Demography
- ADRs
- Concomitant medications
- Dosing
- Medical history
- Efficacy
- Reason for withdrawal

The patient AE listings includes

- Demography
- Concomitant medications
- Medical history
- AE information (MedDRA terms, onset date, dose at onset, duration, causality assessment)

The information required for the abnormal laboratory data listings includes

- Demography
- Concomitant medications
- Medical history

- All results, timings and doses for the laboratory parameter classed as abnormal

CONCLUSION

The “JNDA” team needs to be identified as soon as possible and the leadership of this should be agreed and a process for issue resolution needs to be in place. The language barrier and other cultural differences can cause difficulties, for both Japanese and Western colleagues but understanding these issues from the start and gaining early agreement on the team structure and working arrangements can improve the co-operation within the team.

Gaining early agreement with PMDA on the development strategy with reference to bridging or further development in Japan is key to delivering a submission package. The data should be evaluated from a Japanese perspective rather than merely translating the key messages from FDA and/or EU submission packages and commenting on the bridging studies.

With the right resources in place, use of the consultation processes and effective planning, Japanese developments can run in parallel to those in the West.

GLOSSARY OF TERMS SPECIFIC TO JAPAN

PMDA	Pharmaceutical and Medical Devices Agency
MHLW	Ministry of Health, Labour and Welfare
PMDEC / EC	Pharmaceuticals and Medical Devices Evaluation Center
OPSR / KIKO	Organisation for Pharmaceutical Safety and Research
JPI	Japanese Patient Information

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