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REVEIW ARTICLE

Marketing Aspects of Biotechnological Products in Developed ICH Region – A Comparison

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ABSTRACT

Biotechnology products have different registration requirements than of allopathic drugs. They need to be deeply evaluated in case of safety and efficacy. Japan is the country which demands special requirements for registration of biotechnological products. Where as in Europe centralize procedure is mandatory for marketing of biotechnological products.

KEYWORDS

Biotechnological products, comparison

INTRODUCTION

For the present work two basic regions of ICH are selected and those are japan and European Union (centralized procedure). One of the biggest hurdles for the Japanese government is the "drug lag" problem, whereby many new innovative medicinal drugs do not reach the Japanese market until several years after the United States (US) and Europe (EU). This delay is caused due to the obligation to perform clinical bridging studies in Japan hand since clinical data obtained in non- Japanese trials such as EU and US studies cannot solely be used to obtain market approval in Japan. On the other hand there are long review periods for clinical trial applications and marketing applications. To minimize this "drug lag" the Japanese government is encouraging pharmaceutical companies to conduct simultaneous clinical development and include Japan in global clinical trials.

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Pharmaceutical companies also want to develop medicinal products more or less in parallel in the major markets of the US, EU and Japan even this aspect is driven by more commercial considerations.

The present work focusing on the comparison of the centralized procedure (CP) in the EU and the new drug application procedure in Japan (J-NDA). Centralized procedure was chosen since it's the mandatory procedure in the EU for biotechnology products. Special requirements which have to be taken into consideration when dealing with biotechnology products are included.

Registration Procedures

European Centralized Procedure

General Information

Medicinal products can only be placed on the market in the European Union when a marketing authorization has been issued either by the competent authority of a Member State for its own territory or when an authorization has been granted for the entire Community. This

so called Community authorization can be achieved via the centralized procedure (CP) and is valid for the entire Community which means that the medicinal product may be marketed in all Member States.

Pre-Submission Activities

Before submission of a Marketing Authorization Application (MAA) several activities have to be performed in advance.

Pre-submission Meeting – Scientific Advice

It is also advisable to perform a pre-submission meeting with the EMEA to obtain procedural and regulatory advice from the EMEA. Usual timeframe for this meeting is 6-7 months before submission. During such meetings the table of content, issues with invented names, plans for inspections, timetable and possible other open issues can be discussed. The type of procedures (simplified or standard) will be determined on a case-by-case basis 70-day timetable will usually apply. Depending on the nature of the request, this timeframe may be shortened to 40 days.

Team Members

From the authority side an EMEA Product Team will be established. The product team consists of a product team leader (PTL) and product team members. The team is responsible for handling all procedural aspects of the application, both in the pre- and post-authorization stage. They are responsible to perform the administrative validation of a MAA. They are managing the timeframe of the procedure to ensure it remains within the legal limits and coordinates the assessment reports (AR). The PTL is the primary contact point for the applicant and ensures that the applicant will be informed about all issues relating to the application.

Approval Procedure

The EMEA publishes well in advance the program of scheduled CHMP meetings and the respective times to submit new applications. A new MAA can be submitted each month at a defined submission deadline except for April. The procedural timetable shows the timeline for validation, preliminary assessment report of the rapporteur, schedule for the comments of the CHMP members and the timeline for the list of outstanding issues. The standard timetable for the evaluation of a MAA submitted via CP.

Table 1: Standard Timetable for the Evaluation of a MAA within the CP

Day	Action
-120/-180	Preparation of dossier Pre submission meeting Scientific Advice meeting
-16	Submission of a new MAA
-15	Validation by the EMEA
1	Start of procedure
80	Receipt of AR from rapporteur and co-rapporteur by EMEA, CHMP and applicant
100	Comments from CHMP to rapporteur and co-rapporteur
115	Receipt of draft list of questions (LoQ) from rapporteur and co-rapporteur by EMEA and CHMP
120	Plenary session of CHMP CHMP adopts LoQ and overall conclusion
Clock Stop	Up to 3 months (possible extension of 3 months per request)
121	Submission of the responses to LoQ
150	Receipt of joint response AR from rapporteur and co-rapporteur by EMEA, CHMP and applicant
170	Deadline for CHMPcomments

180	CHMP discussion and decision if "list of outstanding issues" and/or oral explanation by the applicant is needed
Clock Stop	Applicant should respond within 1 months
181	Restart of clock and oral explanation (if needed)
210	Final draft of English SPC, PL and labelling sent to rapporteur and EMEA
210	Adoption of CHMP opinion and CHMP AR
215	SPC, PL and labelling to be provided in 23 languages
229	Comments on SPC, PL and labelling to be provided to applicant
232	Required changes to SPC, PL and labelling to be provided by applicant
237	Implementation of changes
239	EMEA will compile the opinion in all languages and send final copy to EU commission
246	Provide packaging layout in English and "worst case" language and smallest package size
277	Commission Decision

Post Authorization Activities

The EMEA will prepare a "Summary of Opinion" together with the applicant which will be published on the EMEA website after the adoption of the CHMP Opinion. In addition the EMEA will publish the CHMP AR on the medicinal product which includes the reasons for its opinion in favor of granting authorization. This document is called the European Public Assessment Report (EPAR). The applicant will receive the EPAR and need to identify those issues which are considered to be commercially confidential. The agreed EPAR will be made public at the EMEA website after the Commission Decision.

Japan New Drug Application (J-NDA) Procedure

General Information

The Ministry of Health, Labor and Welfare (MHLW or Koseirodosho in Japanese) is in charge of the pharmaceutical regulatory affairs in Japan. Formal approvals and licenses are required to marketing drugs in Japan which are obtained from the MHLW. The MHLW was established in January 2001 as part of the government program for reorganizing government ministries. One of the 11 bureaus of the MHLW is the Pharmaceutical and Food Safety Bureau (PFSB). This bureau handles clinical studies, approval reviews and post-marketing safety measures[12].

Pre-submission Activities

Consultation Meetings

In Japanese culture it is uncommon to make decisions during consultation meetings based on information, which is exchanged in this same meeting by means of discussion or presentation. Usually, in Japan decisions are either made prior to a meeting based on available information or, alternatively, the final decision is taken after the meeting. In case the decision is taken prior to the meeting the outcome is then basically only explained during the meeting. Therefore it is recommended to provide a strategy which allows influencing the thinking of the PMDA prior to the meeting. Prior to the official consultation meeting pre-meetings are taking place to discuss the content of the dossier in advance for review[14].

Approval Procedure

The PAL's principle objective is to provide an approval system which ensures good quality, efficacy and safety of the medicinal products to

be marketed and used for healthcare in Japan[15, 16].

The approval review process consists of the following steps:

o J-NDA evaluation process

o Compliance Review (including GCP inspection)

o GMP inspection (can also be performed as paper audit)

Priority Review Designation

NDA approval reviews are normally processed in the order the application forms are received. For medicinal products considered to be especially important from a medical standpoint such as new drugs treating serious diseases and meeting especially high medical need, priority review can be granted (for orphan drugs priority review is automatically granted). Criteria for priority review are severity of the target indication (disease with important effect on patient's survival (fatal disease), progressive and irreversible disease with marked effect on daily life) and medical efficacy (no existing treatments available, superior to currently available therapies with regard to efficacy, safety and quality of life)

Accreditation

A foreign manufacturer who intends to export medicinal drugs into Japan is required to be accredited by the MHLW as an "Accredited Foreign Manufacturer". The applicant is required to submit an "Application for Accreditation" that is addressed to the minister and an "Application for Accreditation Examination" to the chief executive of the PMDA[16]. Among the documents which have to be attached to the accreditation application (all documents have to be translated into Japanese) is a medical certificate from a physician which indicates whether or not the applicant (e.g. the CEO of a company) has mental disorders or is addicted to narcotics, cannabis, opium or stimulant drugs.

J-NDA Evaluation Process

With the agreement reached on the CTD guidelines of the ICH, new guidelines for preparation of approval application data were issued. Applications using the CTD format became obligatory for new products filed after July 2003 (electronic specifications for the CTD have been applied to application submitted in eCTD format since April 2005)[17].

Table 2: Timetable for the Evaluation of a J-NDA

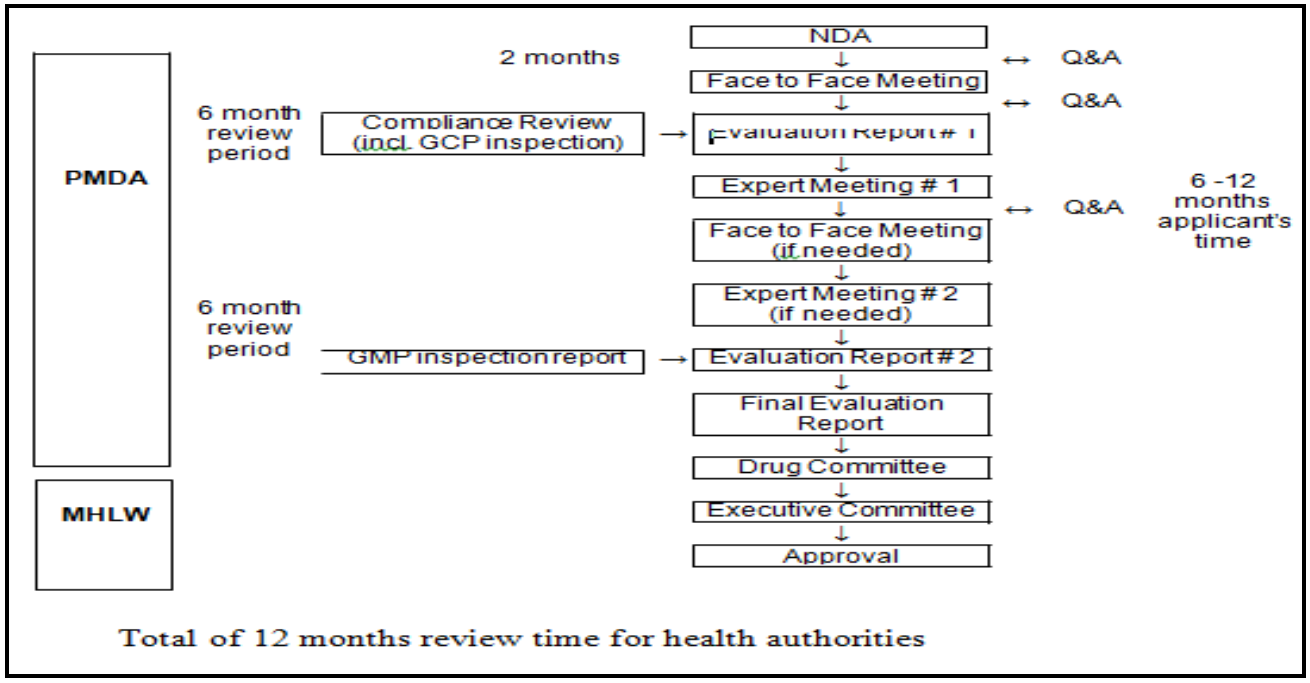

Table 3: Timetable for the Meetings at the PMDA and MHLW

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Expert M.	X	X	X	X	X	X	X	X	X	X	X	X
Drug Committee M.	X	X		X	X		X	X		X	X	
Exective Committee M.			X			X			X			X
Approval				X			X			X		

The evaluation process of the J-NDA is shown in Table 2.

Post Authorisation Activities

Information concerning the new drug approval prepared form the review data (final evaluation report) is placed on the website of the PMDA so that accurate information concerning the quality, efficacy and safety obtained during the approval review process is supplied to the medical institutions. The PMDA request the applicant to provide a masking proposal of the evaluation report and a masking proposal for the data that summarizes non-clinical and clinical results. Masking of quality data is not necessary since they are not included in such publication report. Information related to the quality of the medicinal product is provided in the information to the doctors. The summary data should be published within 3 months after approval at the latest[18].

SUMMARY AND DISCUSSION

Due to the harmonization of regulatory requirements (ICH) the registration procedures in the EU and Japan can be summarized in pre-submission activities, submission and review procedures and post-submission activities which finally result in marketing approval for medicinal products. EMEA as well as PMDA provide detail guidance to achieve a positive outcome once a marketing application is submitted. Table 5 lists the main steps and timelines for CP and J-NDA. As shown above the CP takes about 1 year whereas the J-NDA takes about 6 months longer (priority review). There is no defined time table for J-NDA available and due to multiple Q&A sessions the review period is extended. After scientific evaluation by EMEA or PMDA, respectively the final approval will be granted by the EU Commission or MHLW. In summary timelines given for the European CP are more stringent compared to the J-NDA procedure which ultimately leads to shorter timelines for the CP compared to the J-NDA procedure. Guidelines on preparation of the dossier are available for EU as well as for Japan. Unfortunately not all guidelines in Japan are available in English.

CONCLUSION

The following items have been identified to be critical for a successful filing:

Western Culture meets Asian culture

It has to be clear from beginning that there are culture differences between Europeans and Japanese which have to be respected and differences have to overcome. Therefore it is essential to establish a good working cooperation from the beginning based on trust and commitment.

Language Barrier

Most European are not native English speaking persons. For Japanese the English language is even more difficult since a translation from English to Japanese cannot be performed one to one. It is essential to either work with well English speaking people (European as well as Japanese side) or to identify interpreters /

Table 5: Comparison CP and J-NDA

Step	**CP**	**J-NDA**
Pre-submission meeting	Advice on regulatory and procedural topics Briefing package to be provided Advice can be also in writing	Advice on content and specific topics Briefing package to be provided Pre-pre-meetings can take place Q&A session Confirmation of scientific advice
	6 – 7 months before submission 2 months (70 day) procedure	5 months procedure
Approval Procedure	12 – 15 months (incl. 2-6 months clock stop)	24 months (priority review about 18 months) (incl. 6-12 months Q&A session)
	Defined timelines during review	No defined timelines during review (multiple Q&A sessions) Partial response to minimize delay is accepted for priority review
Add. activities	GMP inspection	GMP inspection
	-	Accreditation application
	-	Priority review designation
Post authorization activities	Publication report (EPAR)	Publication report (EPAR)
Step	**CP**	**J-NDA**
Pre-submission meeting	Advice on regulatory and procedural topics Briefing package to be provided Advice can be also in writing	Advice on content and specific topics Briefing package to be provided Pre-pre-meetings can take place Q&A session Confirmation of scientific advice
	6 – 7 months before submission 2 months (70 day) procedure	5 months procedure

Approval Procedure	12 – 15 months (incl. 2-6 months clock stop)	24 months (priority review about 18 months) (incl. 6-12 months Q&A session)
	Defined timelines during review	No defined timelines during review (multiple Q&A sessions) Partial response to minimize delay is accepted for priority review
Add. activities	GMP inspection	GMP inspection
	-	Accreditation application
	-	Priority review designation
Post authorization activities	Publication report (EPAR)	Publication report (EPAR)

translators which also know the pharmaceutical business and technical terms.

Meetings

To build a good relationship face to face meetings between the respective persons on both sites (Europe and Japan) need to be established on a regular basis. In addition regular telephone conferences to discuss open points and clarify any issues should be performed.

Japanese Requirements

Special Japanese requirements and Japanese style have to be identified from the beginning to be introduced in the preparation of the dossier. It is important to adhere to these styles since the PMDA reviewers are used to Japanese dossiers. The review process may be simplified since the PMDA reviewers are pleased.

Internal Review Process

The internal review process between European and Japanese has to be established in an early period to avoid lengthy discussions on open issues or misunderstandings which could have been clarified by early reviews.

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