Comparison of marketing authorization procedures for biotechnological products in the European Union (centralized procedure) and in Japan (J-NDA)

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List of Abbreviations

AR	Assessment Report
BSE	Bovine spongiform encephalopathy
CHMP	Committee for Human Medicinal Products
COMP	Committee for Orphan Medicinal Products
CP	Centralized Procedure
CTD	Common Technical Document
DNA	Deoxyribonucleic acid
EMEA	European Medicines Agency
EPAR	European Public Assessment Report
EP	European Pharmacopeia
EU	European Union
FUM	Follow-up Measure
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference for Harmonization
JAN	Japanese accepted name for pharmaceuticals
J-NDA	Japan New Drug Application
JP	Japanese Pharmacopeia
LoQ	List of question
MAA	Marketing Authorization Application
MCB	Master Cell Bank
MHLW	Ministry of Health, Labour and Welfare
NDA	New Drug Application
OPSR	Organization for Pharmaceutical Safety and Research
PFSB	Pharmaceutical and Food Safety Bureau
PAL	Pharmaceutical Affairs Law
PL	Package Leaflet
PMDA	Pharmaceuticals and Medical Device Agency
PTL	Product Team Leader
Q&A	Question and Answer
QOS	Quality Overall Summary
SAWP	Scientific Advice Working Party

SPC	Summary of Product Characteristics
US	United States
USP	United States Pharmacopeia
WCB	Working Cell Bank

1 Introduction

Japan is the second largest pharmaceutical market behind the United States and a highly developed country. It has about 130 million people, wealthy and highly educated with a rapidly increasing proportion of elderly people. The disease pattern is similar to the rest of the world with some differences in medical practice. It has been discovered that Japanese people are using multiple drugs with an especially high use of recently approved drugs. The patient awareness is now similar to that in the Western countries. Medicinal products represent over 20% of healthcare costs with about almost 50% in elderly patients. Therefore Japan becomes more and more attractive for the pharmaceutical industry.

Japan's Pharmaceutical and Medical Devices Agency (PMDA) has set itself the challenging task of expediting patient access to novel therapies while ensuring these meet international standards of safety, efficacy and quality. One of the biggest hurdles for the 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 can not 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. 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.

Once the clinical development program is finished and all data are compiled the dossier has to be created to be filed with the respective authorities. To simplify the general life cycle management a harmonized dossier approach would be of advantage. A harmonized dossier is easier to handle since the same document can be used for all countries. It also facilitates the compliance of the documentation, increases the supply flexibility and facilitates the communication between external and internal regulatory communication units. Once the marketing authorization is granted variations (clinical or quality based) or extension applications update of one dossier is faster than different dossiers.

Nevertheless it's not always possible to harmonize the complete dossier due to regional requirements not only for Module 1. Especially for Non-ICH countries the drug substance part of the dossier needs to be revised to eliminate confidential information. Since Module 2 in Japan contains more information compared to Module 2 documents of EU and US it's advisable to update the whole Module 2 section with the respective information.

The present master thesis is 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.

2 Registration Procedures

2.1 European Centralized Procedure

2.1.1 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 (1). The CP is mandatory for medicinal products which have been developed by means of biotechnological processes e.g. monoclonal antibodies and medicinal products containing a new active substance for which the therapeutic indication is in the treatment of e.g cancer. Optional can the procedure be used for other innovative medicinal products, medicinal products constituting a significant therapeutic scientific or technical innovation and medicinal product of community interest (1, 2, 3).

2.1.2 Pre-submission Activities

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

General

In case of any doubt if the medicinal product falls under the scope of a centralized procedure confirmation of eligibility should be requested by the applicant up to 18 months before the submission (3, 4). About 6 to 7 months before the submission the EMEA should be notified of the intention to submit an MAA (1, 5). The proposed invented name for the medicinal product should be submitted at the earliest 12 months and at the latest 4-6 months prior the planned submission date of the marketing authorization. The so called Name Review Group (NRG) will discuss the proposal taking into consideration the relevant objections and comments received on grounds of safety concerns (6).

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. (1, 5).

In addition scientific advice meetings can be performed. Scientific advices are dealing with scientific issues. Regulatory aspects are handled separately by the EMEA. Scientific advice should contain prospective questions concerning quality, preclinical and clinical aspects. Such scientific advice meeting can be used to discuss e.g. comparability studies, the strategy to present clinical studies and the proposed indication. It should be noted that any advice given is not binding for the EMEA or the

applicant with regard to any future MAA of the product. However the CHMP would have to provide argumentation during the evaluation of the MAA when questioning the design of studies performed following the provision of scientific advice (1).

The type of procedures (simplified or standard) will be determined on a case-by-case basis A 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.

For each scientific evaluation a rapporteur and co-rapporteur will be appointed. The appointment is made on the basis of objective criteria, which will ensure the provision of objective scientific opinions and will allow the use of the best available expertise on the relevant scientific area. The applicant does not have any influence nevertheless the applicant may provide preferences (1, 7).Once the rapporteur and co-rapporteur are nominated a meeting should be performed to present the data and familiarize the assessor with the filing strategy. An open and pro-active discussion should be performed to establish a good cooperation and working relationship with the rapporteur and co-rapporteur (8).

2.1.3 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 applicant provides a complete dossier to the EMEA, rapporteur and co-rapporteur in parallel. In case of an eCTD the EMEA does not need a paper copy anymore (from 1. July 2008). It depends on the nation of the rapporteur and co-rapporteur if paper copies of the whole dossier or only Module 1 and 2 need to be submitted (9).

Once a new MAA is submitted the EMEA performs a validation procedure. During the validation period the completeness of the dossier is verified. After successful validation the EMEA will inform the applicant of the positive outcome and the dossier needs to be provided to the CHMP members and alternates. In addition a timetable will be provided showing the timelines for the review period (1, 10). Table 1 shows 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

After 80 day the applicant is provided with the preliminary AR which reflects only the rapporteur's and co-rapporteur's opinion but not of the CHMP. Nevertheless this preliminary AR provides about 80% of the outstanding issues which need to be solved by the applicant.

It may be necessary to perform inspections in connection with a MAA. These inspections should be carried out within the 210 days review period. These could be Good Manufacturing Practice (GMP) inspections which verify the compliance with GMP at the manufacturing and quality control sites. Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) inspections are performed as a routine surveillance but are not necessary for all applications. The outcome of the inspections is usually requested for adoption by CHMP at day 90 or at latest by day 120 (1).

2.1.4 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 (1).

It might be necessary to establish post-authorization follow-up measures (FUMs) and make post approval commitments. The EMEA will inform the marketing authorization holder about any specific obligation and FUMs. Realistic timelines should be fixed to fulfill such FUMs and commitments (11).

2.2 Japan New Drug Application (J-NDA) Procedure

2.2.1 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).

In April 2004 a new independent administrative organization, the Pharmaceutical and Medical Devices Agency (PMDA, SOGO-KIKO) was established through the integration of different pharmaceutical institutes. Appendix 1 depicts the organization of the PMDA. The PMDA provides consultation concerning clinical trials of new drugs and conducts approval reviews of a new drug application (NDA). Therefore they perform GCP compliance review (document review and GCP inspections) as well as

GMP inspections. They handle all activities from preclinical stage to approvals and post-marketing surveillance. With the establishment of the PMDA a faster accessibility to better/more effective and safer drugs for the public should be ensured.

The pharmaceutical administration in Japan consists of various laws and regulations of which the Pharmaceutical Affairs Law (PAL) is a fundamental one consisting of 11 chapters and 91 articles.

Various regulations apply to the development, manufacture, import, marketing and proper use of drugs exists. Some of the main regulations affecting pharmaceuticals are listed below:

- Quality standards and government standards e.g. Japanese Pharmacopeia (JP)
- Classification of drugs e.g. biological products and specified biological products
- Concerning marketing approvals e.g. revision in April 2005
- GMP status e.g. GMP certificate as prerequisite to obtain a manufacturing business license
- Accreditation of overseas manufacturers e.g. accreditation is required to export medicinal products from overseas to Japan
- GLP and GCP standards
- Good Quality Practice (GQP) on marketed products
- Good Vigilance Practice (GVP) on marketed products
- etc.

2.2.2 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).

In 2005 the activities of the PMDA consultation meeting were evaluated to review the timelines of such meetings. New shorter timelines were determined which were again revised in 2008. The timeline for the new procedure and the comparison to the old procedure for consultation meetings are provided in Appendix 2 and 3.

2.2.3 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:

- J-NDA evaluation process
- Compliance Review (including GCP inspection)
- 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)

Products of priority review are given priority at each stage of the review process as much as possible. The process of the MHLW could therefore be shortened from 12 months to 6 months which results in a total of 12 – 18 months approval period. When a drug product subject to priority review is approved this fact is made public (12-15).

Accreditation

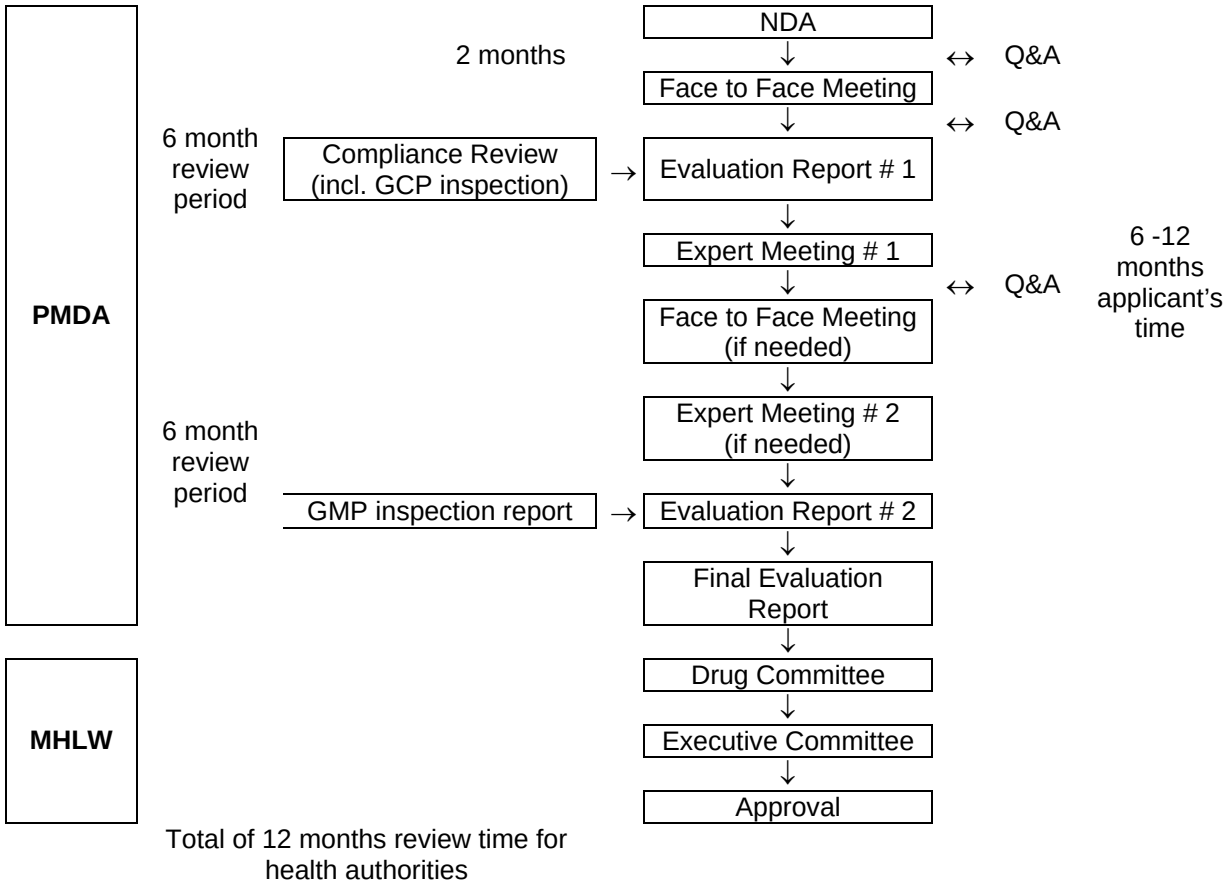
A foreign manufacturer who intends to export medicinal drugs into Japan is required to be accredited by the MHLW as an "Accredited Foreign Manufacturer". The applicant is required to submit an "Application for Accreditation" that is addressed to the minister and an "Application for Accreditation Examination" 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.

The application should be submitted at latest when the NDA is submitted. The accreditation process takes about 5 months. The accreditation needs to be renewed every 5 years.

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). The evaluation process of the J-NDA is shown in Table 2 (see also Appendix 4).

Table 2 Timetable for the Evaluation of a J-NDA



The standard processing period by the MHLW is about 12 months. The applicant normally needs another 6 -12 months to respond to the inquiries (Question and Answer session: Q&A) which sums up to a maximum period of about 18 - 24 months from the application to the approval. Marketing approval can not be obtained without accreditation approval and GMP inspection report.

There is a defined timetable for the various meetings at the authorities as depicted in Table 3.

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		

Pharmaceutical manufacturers outside Japan can apply directly under their own name for marketing approval. Nevertheless they have to identify a licensed manufacturer (e.g. subsidiary company) who will release and distribute the medicinal product to the Japanese market (see Appendix 5).

2.2.4 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).

2.3 Biotechnological Products

From a regulatory perspective biological medicinal products are distinguished from conventional medicinal products. Per definition biological medicinal product is a product, which active substance is a biological substance (29). The biological substance is produced or extracted from a biological source. Therefore biological medicinal products are complex therapeutics, e.g. antibodies. Since biological products are manufactured utilizing the biosynthesis process of organisms, the molecular structures of such products may not be uniform and the biological activities maybe influenced by changes in higher structures, which are hardly identified by physicochemical methods for analysis. It is therefore considered that the influences of manufacturing method change on quality, safety and efficacy should be evaluated in a different manner in biological drugs as compared to usual chemical drugs. Furthermore biological drugs include various types such as proteins, glycopeptides, polypeptides and their derivatives, and they are controlled in various ways. For complete product characterization a determination of its quality a combination of physicochemical and biological tests together with the production process and its control is required. Furthermore essential viral safety requirements are necessary. If raw materials derived from animals, especially bovine derived, are used actions have to be taken to control the source and manufacture of such materials.

In principle the same definitions, requirements and safety precautions apply in Europe and Japan for biological products. In addition Japan has established further measurements to minimize the risk using products of biological origin.

According to PAL biological products are classified into “bio-derived products” and “specified bio-derived products” which are using raw materials from humans or other organisms that require special precautions in terms of public health and safety measures (19, 20). “Specified bio-derived products” are defined as products with higher theoretical or actual risk of infection, e.g. blood products. “Bio-derived products” are products, such as antibodies, produced in human cells or animal cells including manufacturing steps such as viral inactivation and removal steps which confirm the absence of viral pathogens.

When applying for a J-NDA for a biological product the applicant has to submit data for product designation review to define the classification of the biological product as listed above. For each component used in the manufacturing process from human or animal origin a special form has to be completed. This form lists the category of the human- or animal-derived material (e.g. human blood-derived component, ruminant-derived component, animal-derived component), the purpose of use (e.g. active pharmaceutical ingredient, host cell, cell culture component, excipient), a description of screening/controlling the humans / animals as origin of raw material (e.g. manufacturing process of the raw material including viral safety measurements, certificate of the origin from the supplier).

Standards for biological ingredients have been established to ensure the quality, efficacy and safety of pharmaceutical products e.g. the US was removed from the list of countries of origin of raw materials originating from cows and other ruminants that can be used as raw materials for drugs. Since bovine spongiform encephalitis (BSE) occurred pharmaceutical companies have been requested to undertake voluntary inspections and make adjustments in the approval documentation to ensure quality of and take safety measures for pharmaceutical products manufactured using raw materials of bovine origin. As a preventive measure in keeping with international trends to enhance safety measures for drugs using bovine-derived raw materials several notification and revisions concerning bovine-derived raw materials that require precautions were issued, latest in Sept. 2007 (21-23).

When bio-derived components are used in the manufacturing process a risk assessment has to be made taking into account the risk of such components such as medium components (24). In addition if bovine derived materials sourced from US are included as raw material in the manufacturing process a detailed explanation has to be provided why no different source is available and if there is any possibility to remove this material or switch to a different source. If possible detailed timelines should be provided (see Appendix 7).

3 Dossier Creation

3.1 General Information

The dossier has to be created according to the ICH guideline for Common Technical Documents (CTD) and follows the CTD structure. Therefore the dossier exists of Module 2 with the summary documents for quality, non-clinical and clinical, Module 3 including the quality data, Module 4 the non-clinical data and Module 5 the clinical data, respectively. In addition regional information e.g. labeling information is provided in Module 1.

In Japan Module 3, 4 and 5 can be submitted in English whereas Module 1 and 2 have to be translated into Japanese. Module 1 contains in Japan the so called “Application Approval Form” (AAF) listing product formulation, relevant manufacturing information, shelf life and storage condition as well as the specification and test methods. A detailed description is provided below (Section 3.3.1). After the Q&A session and the expert meeting Module 1 and Module 2 have to be revised accordingly and resubmitted.

The following sections are focusing on Module 1 and Module 2, especially on quality overall summary (QOS), and the main differences between the dossier to be submitted in the EU compared to Japan, since Module 3 is identical for the EU and Japan.

3.2 Content of Module 1 and Module 2 (QOS)

3.3.1 Module 1

EU-MAA

Module 1 contains general information such as the application form, labeling information, information on the expert, pharmacovigilance system and risk management plan. No information with regard to the manufacturing or process controls and specifications are given in this Module for an EU MAA (25, 26).

J-NDA

Module 1 contains the following information:

- NDA application form (including AAF and position paper for priority review, if applicable)
- Certificates (GLP, GCP statements, expert statements)
- Patent status information
- Discovery, research and development history
- Conditions of use in foreign countries (including labeling information)
- List of other drugs with similar pharmacological action

- Draft package insert
- Documentation of non-proprietary name
- Summary of data on designation e.g. powerful drug
- Draft protocol for post-marketing surveillance
- List of attached documents (Module 3, 4 and 5)
- Others:
    - Application form for accreditation and registration of foreign manufacturers
    - Application form for GMP inspection
    - List of laboratories conducting GLP studies
    - GCP compliance report
    - Application form for document review

Application Approval Form (AAF)

The AAF describes critical aspects of the drug. It is attached to the license upon approval. The “approved” items described are binding. They determine a regulatory commitment and are the basis of post-approval changes. Topics which are not mentioned in the AAF may be changed without regulatory consequence (15).

The AAF contains the following information:

- General information as required
    - e.g. name, dosage and administration, use or indication, storage method and shelf life, specifications and test methods, manufacturing facility, drug substance facility
- Information about ingredients and content
    - Composition: amount of excipients and specifications (JP)
    - Information if bovine derived raw material is used
- Specifications and test methods
    - Detailed description
    - List of reagents and solutions used
- Reference substance
    - Testing methods
    - Storage conditions

- Manufacturing methods
  - Preparation of gene constructs (including amino acid sequence)
  - Preparation of master cell bank
    - Method of preparation and in-process controls
    - Testing
    - Storage/Stability
    - Renewal criteria/method
  - Preparation of working cell bank
    - Method of preparation and in-process controls
    - Testing
    - Storage/Stability
    - Renewal criteria/method
  - Drug substance manufacturing step
    - Cell culture process
      - Culture media
      - Culturing steps (inoculums, flasks, bioreactor)
      - Process parameters or in-process controls
    - Harvest
      - Process parameters or in-process controls
    - Filtration, concentration
    - Purification
      - Virus removal and inactivation steps
      - Process parameters or in-process controls
    - Storage
  - Drug product manufacturing step
    - Filling
    - Packaging and labeling
    - In-process controls
    - Storage and shelf life
  - Manufacturing performed in Japan for local release
    - Packaging and labeling
    - In-process controls
    - Specifications and test methods
    - Storage

- Manufacturing facility
  - Drug substance manufacturer
  - Drug product manufacturer
  - External testing facilities

Information listed in the AAF should be a summary of the information in the QOS e.g. manufacturing description and in-process controls and test methods. The information is provided in special format as provided by the PMDA. Summary tables and figures should be included with very brief narratives of the information provided in the QOS. In the manufacturing description the items applicable to minor change notification or partial change application have to be highlighted. On the other hand, specifications and test methods in the AAF should be a copy of the description in the QOS.

3.3.2 Module 2 (QOS)

The QOS of Module 2 is the main review document for the PDMA whereas the summary document is used as introduction for Module 3 in the EU. It is not used as basis for approval in the EU where Module 3 is reviewed and serves as basis for the assessment report. In Japan it is expected that the applicant summarizes all critical data from Module 3 together with a sufficient discussion on every critical point for ensuring the quality of the medicinal product. The QOS should be written in a way that it makes it possible for the reviewer to understand the characteristics of the drug within a short time and to review the J-NDA application efficiently. The QOS should include many figures and tables which summarize the critical data. It contains more detailed information

The Pharmaceutical Manufacturers Association of Tokyo, Osaka Pharmaceutical Manufacturers Association and Japan Health Sciences Foundation issued in July 2002 a Mock-up of the Japanese QOS (27, 28). This document can be used for the dossier preparation. Since companies also intend to prepare global dossiers which are applicable for ICH as well as Non-ICH countries the mock-up document can provide specific Japanese requirements which need to be incorporated. Since the QOS in Japan contains more detailed information compared to the QOS for the EU and US a separate QOS has to be prepared which generally contains much more than 100 pages. Writing the QOS in Japanese style facilitates the review process.

Items listed in the manufacturing process description require appropriate change control and are either subject to partial change application or minor change notification. Partial change application requires review and approval of the PMDA which could take 12-18 months. Minor change notification follow the principle of do and tell (within 30 days). Therefore it has to be carefully considered which items should be highlighted as partial change application (<< >>) and which as minor change notification ({ }).

The following outline of Module 2 is focusing especially on requirements for biotechnology products (30-36) and special Japanese requirements experienced during preparation and review of a J-NDA.

Table 4 Module 2 (QOS) content J-NDA vs EU-MAA

<table>
<tr><th>CTD Format - Module 2</th><th>J-NDA</th><th>Comparison to EU-MAA</th></tr>
<tr><td>2.3. Drug Substance</td><td></td><td></td></tr>
<tr><td>2.3.S.1
General Information</td><td></td><td></td></tr>
<tr><td>2.3.S.1.1
Nomenclature</td><td>Listing of the applicant’s (company) name and the Japanese accepted name for pharmaceuticals (JAN). The JAN has to be approved by the authority prior to J-NDA.</td><td>Special requirements for J-NDA</td></tr>
<tr><td>2.3.S.1.2
Structure</td><td>For biological products primary and secondary structure will be described, including e.g. disulfide bonds and glycosilation pattern. Three letter code for description of amino acid sequence is used. Reference is made to Section 2.3.S.3.1</td><td>Special requirements for J-NDA (format)</td></tr>
<tr><td>2.3.S.1.3
General properties</td><td>Detailed information on e.g. amino acid sequence, N-terminal amino acid sequence, C-terminal amino acid sequence, disulfide bond, carbohydrate composition and structure, molecular weight, electrophoretic pattern and size exclusion chromatography has to be provided in table format as shown below:
<table><tr><th>Item</th><th>Summary of results</th></tr><tr><td>Amino acid sequence</td><td>Reference can be made to Section 2.3.S.3.1</td></tr></table></td><td>Special requirements for J-NDA (format)</td></tr>
</table>

CTD Format - Module 2	J-NDA	Comparison to EU-MAA
2.3.S.2 Manufacture		
2.3.S.2.1 Manufacturer(s)		Equivalent to MAA
2.3.S.2.2 Description of Manufacturing Process and Process Controls	The manufacturing process and process parameters have to be shown as flow chart followed by description of the different steps (see Appendix 6). Description of manufacturing process includes items subject for change notification. Within the manufacturing description process parameters should be marked which are declared as notification or minor change items and which are subject to partial change application. In addition notes are attached at the end of the document which describes why these items are either subject to notification, minor change or partial change application. Critical component of the manufacturing steps are categorized as partial change application (e.g. viral removal and inactivation steps are considered to be of partial change application). In principle all manufacturing steps can be considered as partial change application whereas the process parameters and in-process controls are subject to minor change notification. Final formulation and concentration as well as storage conditions (temperature, shelf life, packaging components) are critical for the quality of the product and therefore also considered as partial change application. This description is included in the AAF and not mandatory for QOS. The definition for batch and scale size has to be provided.	Special requirements for J-NDA (process parameters need to be identified according to minor change or partial change application)

CTD Format - Module 2	J-NDA	Comparison to EU-MAA
2.3.S.2.3 Control of Materials	Raw materials used in the production need to be listed. It has to be shown if the starting material is tested according to pharmacopoeial standard or in-house standard. At this point in time the raw material does not need to be tested according to JP standard. For material of bovine origin, the use, source (tissue, body fluid), country of origin and any further useful information has to be listed. In case of recombinant DNA technology-related pharmaceuticals the preparation of the gene-construct has to be mentioned, the history of the gene preparation and the gene structure. The history of the preparation of the production cell bank, master cell bank (MCB) using the host and gene-construct as well as the preparation of the working cell bank (WCB) from the master cell bank has to be explained. For the MCB and WCB the test methods including identity tests and purity tests (several viral tests) as well as genetic stability analysis have to be described.	Equivalent to MAA
2.3.S.2.4 Controls of Critical Steps and Intermediates	Process controls and parameter ranges of relevant process steps employed during the manufacture have to be listed. Process parameters which belong to critical manufacturing steps such as viral removal steps are subject to partial change application**.** The other process parameters and in-process tests are subject to minor change notification.	Special requirements for J-NDA (process parameters need to be identified according to minor change or partial change application)
2.3.S.2.5 Process Validation and/or Evaluation	Detailed description of the different validation steps including short description of virus validation studies has to be provided. Reference is made to Section 2.3.S.A.2.	Equivalent to MAA

CTD Format - Module 2	J-NDA	Comparison to EU-MAA
2.3.S.2.6 Manufacturing Process Development	Manufacturing history including changes in manufacturing during development should be described Manufacturing of biotechnological products is a complex process. During development it is normal that manufacturing changes are introduced which can have an impact on the quality attributes and performance of the product. Changes in the expression system, cell culture conditions, or purification can influence the level of product-related substance and the degree of heterogeneity of the product. Intensive comparability studies including release specifications, characterization methods, impurity analysis and stability programs need to be performed to demonstrate comparability of the different development stages. The summary of manufacturing history should list all batches used for non-clinical and clinical studies that were compiled in the CTD.	Generally equivalent to MAA But detailed information on batches need to be provided (incl. main specification results)
2.3.S.3 Characterization		
2.3.S.3.1 Elucidation of Structure and Other Characteristics	Biotechnology products e.g. antibodies are characterized by highly specific secondary and tertiary structures. Due to translational modifications as glycosylation the final product can be very heterogeneous. Product variants showing a different glycosylation pattern are considered as product-related substances and not as impurities, provided those have the same biological activity as the desired product. Additional heterogeneity is introduced by product-related impurities caused by deamidation or by oxidation of amino acids. Therefore thorough characterization is required to assure identiy, purity, potency and safety of antibodies. Detailed characterization such as: structural characterization by C-	Equivalent to MAA

CTD Format - Module 2	J-NDA	Comparison to EU-MAA
	and N-terminal sequence analysis, peptide mapping, analysis of sulfhydryl groups, carbohydrate structure, oligosaccharide mapping as well as physicochemical properties like molecular weight, electrophoretic and chromatography pattern. In addition information on immunochemical properties and biological activity (potency) has to be provided.	
2.3.S.3.2 Impurities	Detailed description of impurity pattern including process related impurities e.g. HCP, DNA, media components, column components as Protein A and product related impurities e.g. aggregates, degradation products has to be provided	Equivalent to MAA
2.3.S.4 Control of Drug Substance		
2.3.S.4.1 Specification	Specifications for biotechnology products include assays to determine the biological activity (potency) and binding activity. If possible an assay to determine the glycosylation pattern e.g. oligomapping should be included.	Equivalent to MAA
2.3.S.4.2 Analytical Procedures	The description format, units and symbols used for specifications and test methods should be in accordance with those used in JP. The description of specifications and test methods in the QOS should be the same as in the AAF. Unless otherwise stated, the specifications and test methods have to be in accordance with the general notices and general tests in the JP. When using pharmacopeia methods it should be assured that not only Japanese but also European (EP) and United States (USP) methods are covered to avoid extra testing for different countries. In-house methods have to be described in more detail compared to EU MAA	Special requirements for J-NDA (detailed method description needs to be provided)

<table>
<tr><th>CTD Format - Module 2</th><th>J-NDA</th><th>Comparison to EU-MAA</th></tr>
<tr><td></td><td>(kind of “recipe” or “cooking book”)
Nevertheless the following statement “equivalent reagents and equipment may be used, procedures may be adopted if necessary” can be included to allow kind of flexibility in the test methods.</td><td></td></tr>
<tr><td>2.3.S.4.3
Validation of Analytical Procedures</td><td>Description of the validation has to be provided. Compendial methods do not have to be validated. Results should be described in table format.</td><td>Equivalent to MAA</td></tr>
<tr><td>2.3.S.4.4
Batch Analyses</td><td>The results of all batches need to be presented in one table as shown below, to be comparable:
<table>
<tr><th>Test method</th><th>Specification</th><th>Batch A</th><th>Batch B</th><th>Batch C</th></tr>
<tr><td>Appearance</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Purity assay</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Potency assay</td><td></td><td></td><td></td><td></td></tr>
</table></td><td>Special requirements for J-NDA (format)</td></tr>
<tr><td>2.3.S.4.5
Justification of Specification</td><td>Description of the justification of specification needs to be provided.</td><td>Equivalent to MAA</td></tr>
<tr><td>2.3.S.5
Reference Standards or Materials</td><td>Description of the reference standard including qualification, characterization and stability should be provided in table format. The origin of the reference standard has to be provided.</td><td>Equivalent to MAA</td></tr>
<tr><td>2.3.S.6
Container Closure System</td><td>Description of container closure system has to be provided.</td><td>Equivalent to MAA</td></tr>
</table>

CTD Format - Module 2	J-NDA	Comparison to EU-MAA
2.3.S.7 Stability		
2.3.S.7.1 Stability Summary and Conclusions	Summary of stability studies including storage conditions, storage time, container, batch description and results needs to be provided. Shelf life is normally based on real time data. Supportive data of pilot batches based on the same manufacturing concept may be used to extend shelf life.	Equivalent to MAA (shelf life can be based on extrapolation and supportive data)
2.3.S.7.2 Post-Approval Stability Protocol and Stability Commitments	Commitment to provide further stability data has to be given, if applicable.	Equivalent to MAA
2.3.S.7.3 Stability Data	The results of all batches need to be presented in one table to be comparable (see Section 2.3.S.4.4).	Special requirements for J-NDA (format)

CTD Format - Module 2	J-NDA	Comparison to EU-MAA
2.3.P Drug Product		
2.3.P.1 Description and Composition of the Drug Product	Description of components of drug product has to be provided. Components have to meet JP standard	Special requirements for J-NDA (JP standard)
2.3.P.2 Pharmaceutical Development	Description of pharmaceutical development including description of the components (excipients), formulation development, physicochemical and biological properties, photostability, formulation history, manufacturing process development, container closure system, microbiological attributes, compatibility has to be provided. List of drug product batches produced incl. detailed description of use needs to be stated. For J-NDA specifications of the batches used should be given. It's sufficient to only list main specifications (purity, concentration, potency) for non-clinical and clinical studies that were compiled in the CTD.	Equivalent to MAA
2.3.P.3 Manufacture		
2.3.P.3.1 Manufacturer(s)	See respective drug substance section	Equivalent to MAA
2.3.P.3.2 Batch Formula	Description of batch formula needs to be provided.	Equivalent to MAA

CTD Format - Module 2	J-NDA	Comparison to EU-MAA
2.3.P.3.3 Description of Manufacturing Process and Process Controls	See respective drug substance section including manufacturing step in Japan (final packaging and release).	Special requirements for J-NDA (process parameters need to be identified according to minor change or partial change application)
2.3.P.3.4 Controls of Critical Steps and Intermediates	See respective drug substance section including manufacturing step in Japan (final packaging and release). For sterile liquids 100 % visual inspection has to be performed. This inspection has to be performed by Japanese personnel since the controls performed by Japanese personnel is stricter compared to Western personnel e.g. scratches on the outside of the vial are considered to be critical and lead to rejection of the vial in Japan but not in Europe.	Special requirements for J-NDA (process parameters need to be identified according to minor change or partial change application)
2.3.P.3.5 Process Validation and/or Evaluation	See respective drug substance section.	Equivalent to MAA
2.3.P.4 Control of Excipients		
2.3.P.4.1 Specifications	Specifications of excipient should follow JP standard.	Special requirements for J-NDA (JP standard)
2.3.P.4.2 Analytical Procedures	Excipients have to betested according to JP quality standard	Special requirements for J-NDA (JP standard)

CTD Format - Module 2	J-NDA	Comparison to EU-MAA
2.3.P.4.3 Validation of Analytical Procedures	Compendial methods do not have to be validated.	Equivalent to MAA
2.3.P.4.4 Justification of Specifications	Justification is based on quality standard of current JP	Special requirements for J-NDA (JP standard)
2.3.P.4.5 Excipients of Human or Animal Origin	For excipients from human or animal origin explanation should be given as provided in Section 3.2.A.2	Equivalent to MAA
2.3.P.4.6 Novel Excipients	Not applicable	Not applicable
2.3.P.5 Control of Drug Product		
2.3.P.5.1 Specifications	See respective drug substance section. Specifications have to ensure drug product quality and safety.	Equivalent to MAA
2.3.P.5.2 Analytical Procedures	See respective drug substance section.	Special requirements for J-NDA (detailed method description needs to be provided)
2.3.P.5.3 Validation of Analytical Procedures	See respective drug substance section.	Equivalent to MAA

CTD Format - Module 2	J-NDA	Comparison to EU-MAA
2.3.P.5.4 Batch Analyses	See respective drug substance section.	Special requirements for J-NDA (format)
2.3.P.5.5 Characterisation of Impurities	Process related impurities are described in the respective drug substance section. For sterile products no additional product-related impurities appear (evtl. during stability).	Equivalent to MAA
3.2.P.5.6 Justification of Specification(s)	See respective drug substance section.	Equivalent to MAA
2.3.P.6 Reference Standards or Materials	See respective drug substance section.	Equivalent to MAA
2.3.P.7 Container Closure System	See respective drug substance section.	Equivalent to MAA
2.3.P.8 Stability		
2.3.P.8.1 Stability Summary and Conclusion	Shelf life is based on real time data. Normally PMDA wants to see 36 months data. If these data are not available shelf life will be based on actual data e.g. 18 months or 24 months even supportive data from pilot scale batches for 36 months would be available. Only if data from pilot batches which are produced by the same manufacturing process are available these data can be used as supportive.	Equivalent to MAA (shelf life can be based on extrapolation and supportive data)

CTD Format - Module 2	J-NDA	Comparison to EU-MAA
2.3.P.8.2 Post-Approval Stability Protocol and Stability Commitment	Commitment to provide further stability data needs to be provided, if applicable-	Equivalent to MAA
2.3.P.8.3 Stability Data	The results of all batches need to be presented in one table (see Section 2.3.S.4.4).	Special requirements for J-NDA (format)

CTD Format - Module 2	J-NDA	Comparison to EU-MAA
2.3.A Appendices		
2.3.A.1 Facilities and Equipment	Description facilities and equipment including testing and release facility in Japan need to be provided.	Equivalent to MAA
2.3.A.2 Adventitious Agents Safety Evaluation	Description of the control of sourcing material especially considering raw material from animal origin has to be provided. If raw material from animal origin is used the source and production of such raw materials have to be provided in detail. Any measurements performed by the vendor e.g. viral inactivation steps and viral testing methods need to be described. A transmissible spongiform encephalopathy risk assessment for animal (bovine) derived raw materials needs to be presented. If bovine derived raw materials are still sourced from the U.S. it has to be explained in detail why no different source is available and if there is any possibility to switch to a different source (incl. timelines). (see Appendix 7) Viral testing of MCB and WCB has to be explained. Assuring viral safety of biotechnological products is a complex process and in-depth assessment has to be performed. The ability of specific manufacturing steps to remove or inactivate viruses has to be described. A viral risk assessment has to be provided.	Special requirements for J-NDA (format)
2.3.A.3 Novel Excipients	Not applicable	Not applicable

CTD Format - Module 2	J-NDA	Comparison to EU-MAA
2.3.R Regional information		
2.3.R.1 Batch Records	Not applicable	Not applicable
2.3.R.2 Process Validation Scheme	Not applicable	Not applicable
2.3.R.3 Medical Device	Not applicable	Not applicable
2.3.R.4 Materials of Animal Origin	Not applicable	Only required for EU MAA

3 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.

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
	FUMs and Committments	-

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.

Module 2 of the J-NDA contains more detailed information compared to the Module 2 of an EU MAA where detailed information can be found in Module 3. There are specific guidelines and rules how to prepare such a dossier, e.g. table format, description of analytical methods (“recipe”, “cooking book”). In addition items in the manufacturing process which are subject to change control have to be highlighted according to partial change application or minor change notification. A summary of the information provided in the QOS of the J-NDA will be listed in the AAF. Manufacturing description and in-process controls are provided in special formats whereas specifications and test methods should be a copy of the information depicted in the QOS. The AAF is attached to the license and the items described are therefore binding.

Special requirements have to be fulfilled for biotechnological products e.g. description of cell culture system and viral safety studies. These requirements are comparable for an EU MAA and a J-NDA, respectively since they are based on the same ICH guidelines. Nevertheless additional guidelines and requirements apply for Japan. Biological products have to undergo a product designation review to define the classification of the product according to special precautions which have to be taken in terms of public health and safety. In addition stricter guidelines and rules for biological ingredients from animal sources apply when raw material is sourced from countries where BSE cases occured. Under such circumstances further evidence has to be provided that the medicinal product is safe and does not posses any risk to the health of the public when applied.

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.

It is possible to use Module 3 submitted in the EU as basis for preparation of Module 2 to be submitted in Japan since more information has to be provided in Japan. Due to specific requirements on the format Module 2 for a J-NDA has to be prepared separately. The J-NDA contains the AAF which is a binding document. Items described in the AAF are subject to change control procedures.

4 Conclusion

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

a) 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.

b) 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 can not 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 / translators which also know the pharmaceutical business and technical terms.

c) 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

d) 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.

e) 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.

5 References

1) Notice to Applicants: Vol. 2A Procedures for Marketing Authorisation Chapter 4 Centralised Procedure

2) EMEA/CHMP/121944/2007: Scientific Aspects and Working Definitions for the Mandatory Scope of the Centralised Procedure

3) Guideline on Article 3(2) of Regulation (EC) No. 726/2004 - Optional scope of the centralised procedure

4) EMEA Pre-Submission Guidance for Users of the Centralised Procedure (2008)

5) EMEA/382712/2006: Guidance on Pre-Submission Meetings for initial Marketing Authorisation Applications for Human Medicinal Products in the Centralised Procedure

6) CHMP/328/98 rev. 4: Guideline on the acceptaibility of invented names for human medicinal products through the centralized procedure

7) EMEA/124066/005: Rapporteur/Co-Rapporteur appointment: Principles, objective criteria and methodology

8) CPMP/2270/02: Guidance on the rapporteurs' meeting with applicants on the CHMP list of questions

9) EMEA/563366/2007: EMEA implementation of electronic-only submissions and eCTD submissions in the centralised procedure: statement of intent

10) Notice to Applicants: Vol. 6 Decision making procedure for the adoption of Commission Decisions

11) EMEA/SOP/H/3007: Management of follow-up measures of marketing authorisation holder for centrally authorised medicinal products for humans

12) Japan Pharmaceutical Manufacturers Association: Pharmaceutical Administration and Regulation in Japan (March 2008)

13) PFSB Notification No. 0520001: Guideline for descriptions on application forms for marketing approval of pharmaceuticals, etc. under the revised Pharmaceutical affairs law, 2005

14) PFSB Notification No.0303003: Improvement of clinical trial consultations for new medicinal products, 2008

15) PFSB Notification No. 0619002: Forms to be attached to applications for authorization of manufacture of pharmaceuticals, etc and accreditation of foreign manufacturers, 2007

16) PFSB Notification No. 0619004: Handling of application for accreditation of foreign manufacturers, 2007

17) PFSB Notification No. 0527004: eCTD specification, 2005

18) PFSB Notification No. 0433004: Handling of disclosure of information concerning approval evaluation of new medicinal products, 2005

19) PFSB Notification No. 0705001: Partial revision of the standard for biological materials, 2004

20) PFSB Notification No 0928001: Handling of pharmaceutical products using bovine-derived materials to comply with partial revision of the standards for biological materials, 2007

21) PFSB Notification No. 0705001: Handling of approval applications concerning quality and ensuring safety of drugs and medical devices manufactured using bovine and other ruminant-derived products and bovine and other ruminant-

derived spinal products from the United States associated with partial revision of the standard for biological materials, 2004

22) PFSB Notification No. 210: Standards for biological ingredients, 2003

23) PFSB Notification No. 0325003: Handling of TSE data associated with enforcement of the partially revised PAL, 2005

24) PFSB Notification No 0801001: Risk assessment during partial amendment approval applications for medicines and medical devices using bovine ingredients, 2003

25) ICH M2 Common Technical Document

26) ICH eCTD Specification V 3.2

27) CTD - QOS: Mock-up for drug substance / drug product (description examples), 2002

28) PFSB Notification No. 0210001: Guidelines on mentions in manufacturing/marketing approval application dossiers for pharmaceuticals and others based on revised pharmaceutical, 2005

29) European Commission Directive 2001/83/EC, as amended

30) ICH Q5A: Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin, 1997

31) ICH Q5B: Quality of biotechnological products: Analysis of the expression construct in cells used for the production R-DNA derived protein products, 1995

32) ICH Q5D: Derivation and characterisation of cell substrates used for the production of biotechnological/biological products, 1997

33) ICH Q5E: Comparability of biotechnological/biological products subject to changes in their manufacturing process, 2004

34) ICH Q6B Specifications: Test procedures and acceptance criteria for biological/biotechnological products, 1999

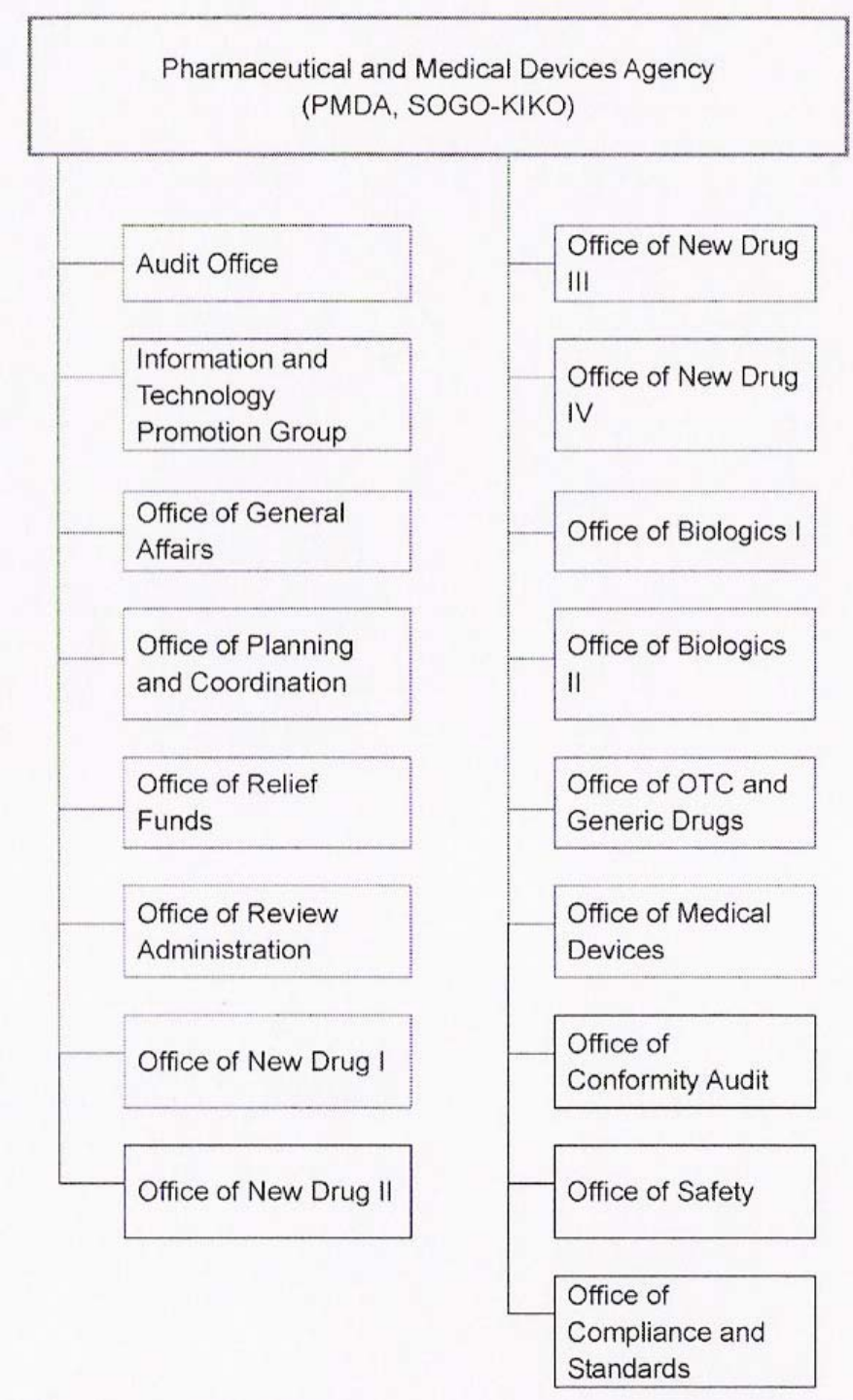
35) EMEA/410/01 Rev.2: Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (2004/C24/03)

36) CPMP/BWP/268/95 Note for guidance on virus validation studies: The design, contribution and interpretation of studies validating the inactivation and removal of viruses, 1996

6 Annex

Annex 1

Pharmaceutical and Medical Devices Agency (PMDA, SOGO-KIKO)



Annex 2

PMDA consultation meeting: Comparison between notified and new procedure

		New notified procedure	Old notified procedure
- 4 M	1st working day of the month	➢ Find provisional slots from PMDA website ➢ Determine preferred slots and adjustable date / time	➢ Find provisional slots from PMDA website ➢ Determine preferred slots
	15th of the month*	➢ Send the provisional application	
- 3 M	1st working day of the month		➢ Request for the arrangement of the consultation slot ➢ Receive the notification of the result [If obtaining the slot, the following procedure is taken] ➢ Apply for the consultation
	15th of the month*	➢ Find provided slots from PMDA website	
- 2 M	1st working day of the month	➢ Request for the arrangement of the consultation slot ➢ Receive the notification of the result [If obtaining the slot, the following procedure is taken] ➢ Officially apply for the consultation ➢ Submit the draft dossier ➢ Pre-consultation meeting is held (A phone call only would be done if PMDA's comment is simple)	
- 5 W **		➢ Submit the dossier ➢ Q&A	➢ Submit the dossier ➢ Q&A
- 1 W		➢ Receive the official scientific advices (via fax) (at latest 4 days before the consultation)	
- 1 D		➢ Send PMDA the presentation materials and participants list	➢ Send PMDA the presentation materials and participants list
0		At the consultation 1. Short presentation (< 10 min.) 2. Confirmation of the acceptance to the advices 3. Qs from PMDA, Qs from the applicant 4. Further comments from PMDA	At the consultation 1. Presentation (approx. 15 min.) 2. Qs from PMDA 3. PMDA official scientific advices 4. Discussion
+ 1 W		➢ Receive the first draft of the minutes	
+ 1 M		➢ Send comments on the draft ➢ Fix the minutes	➢ Receive the first draft of the minute ➢ Send comments on the draft
(+ 2 M)			➢ Fix the minutes

* Change the day to the first subsequent working day instead of '15th of the month' if the day falls on a weekend or a public holiday

** Monday of the week 5 weeks prior to the scheduled consultation date

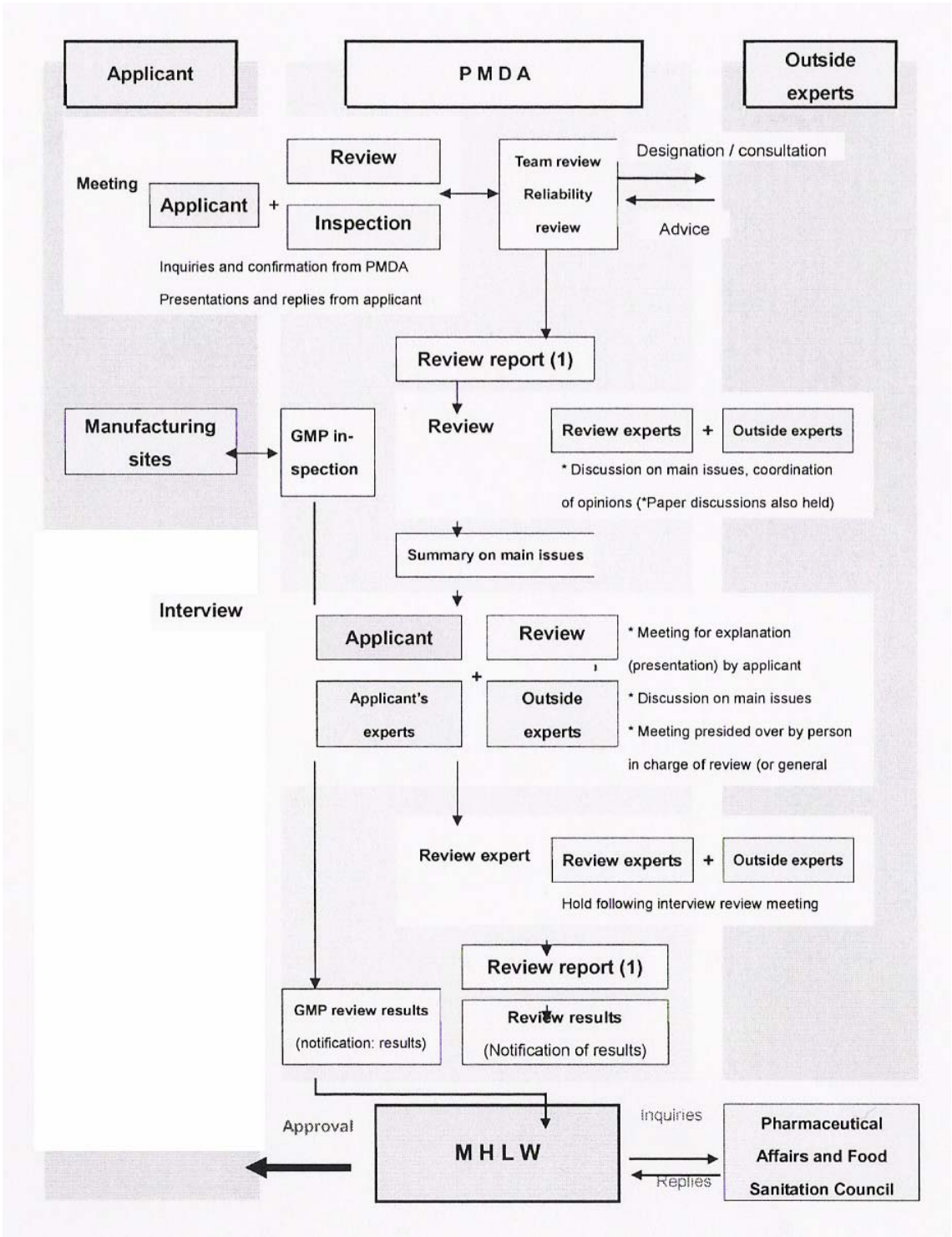
Annex 3

PMDA consultation meeting: Detailed steps of new procedure

- 4M	1st working day of the month	➢ Find provisional slots from PMDA website	PMDA provides 15 categories. Each category show provisional slots (1-6 slots: PMDA decide the number of the slots based on their assumption how many applicants request in one month).
		➢ Determine preferred slots and adjustable date / time	The applicant has to decide preferred slots among the slots PMDA proposes as well as dates (time) when you can adjust if other date / time can be provided by PMDA
	15th of the month	➢ Send the provisional application	The applicant has to determine preferred slots, adjustable dates (with time) and non-preferred dates (with time)
- 3M	15th of the month*	➢ Find provided slots from PMDA website	The applicant has to describe preferred slots, adjustable dates (with time) and non-preferred slots
-2M	1st working day of the month	➢ Request for the arrangement of the consultation slot	The applicant has to fax the request form 9:30-16:00
		➢ Receive the notification of the result	It takes a few days for the selection. PMDA arranges the meeting in accordance with published rule. The result is sent via fax.
		[If obtaining the slot, the following procedure is taken]	
		➢ Officially apply for the consultation	The application and the payment have to be done within 3 weeks after receiving the notification.
		➢ Submit the draft dossier	5 sets are usually submitted.
		➢ Hold the pre-consultation meeting (or discuss via phone)	PMDA usually requests to revise the contents of the dossier or submit additional data at the pre-consultation meeting. If the requests are not complicated, a phone-call may be enough.
		➢ Submit the revision	
		➢ (Q&A)	Further discussion might be needed.
		➢ Receive the acceptance from PMDA	The applicant needs to confirm that PMDA does not have further request
- 5W		➢ Submit the dossier	20 sets are usually submitted.
		➢ Q&A	Q&A is usually done via fax. The applicant has to answer asap so that PMDA prepares the official advices. Answers sometimes can not be done prior to the meeting due to limited time.
- 5 D		➢ Receive the official scientific advices (via fax)	The advices are made together with the argumentation of the applicant.
- 1 D		➢ Send PMDA the presentation materials and participants list	In principle, the applicant has to select 18 participants or less due to provided microphone. 20 sets of the documents are usually submitted.
0		At the consultation 1. Short presentation (< 10 min.) 2. Confirmation of the acceptance to the scientific advices 3. Qs from PMDA 4. Qs from the applicant 5. Further comments from PMDA	The meeting usually is done within 2 hours. PMDA records the meeting. The applicant gets the duplicate. At the meeting, the confirmation of the official advices from the applicant and additional Q & A are mainly discussed.
+ 1 W		➢ Receive the first draft of the minutes	
+ 1 M		➢ Send comments on the draft	The reason should be indicated for each point.
		➢ Fix the minutes	

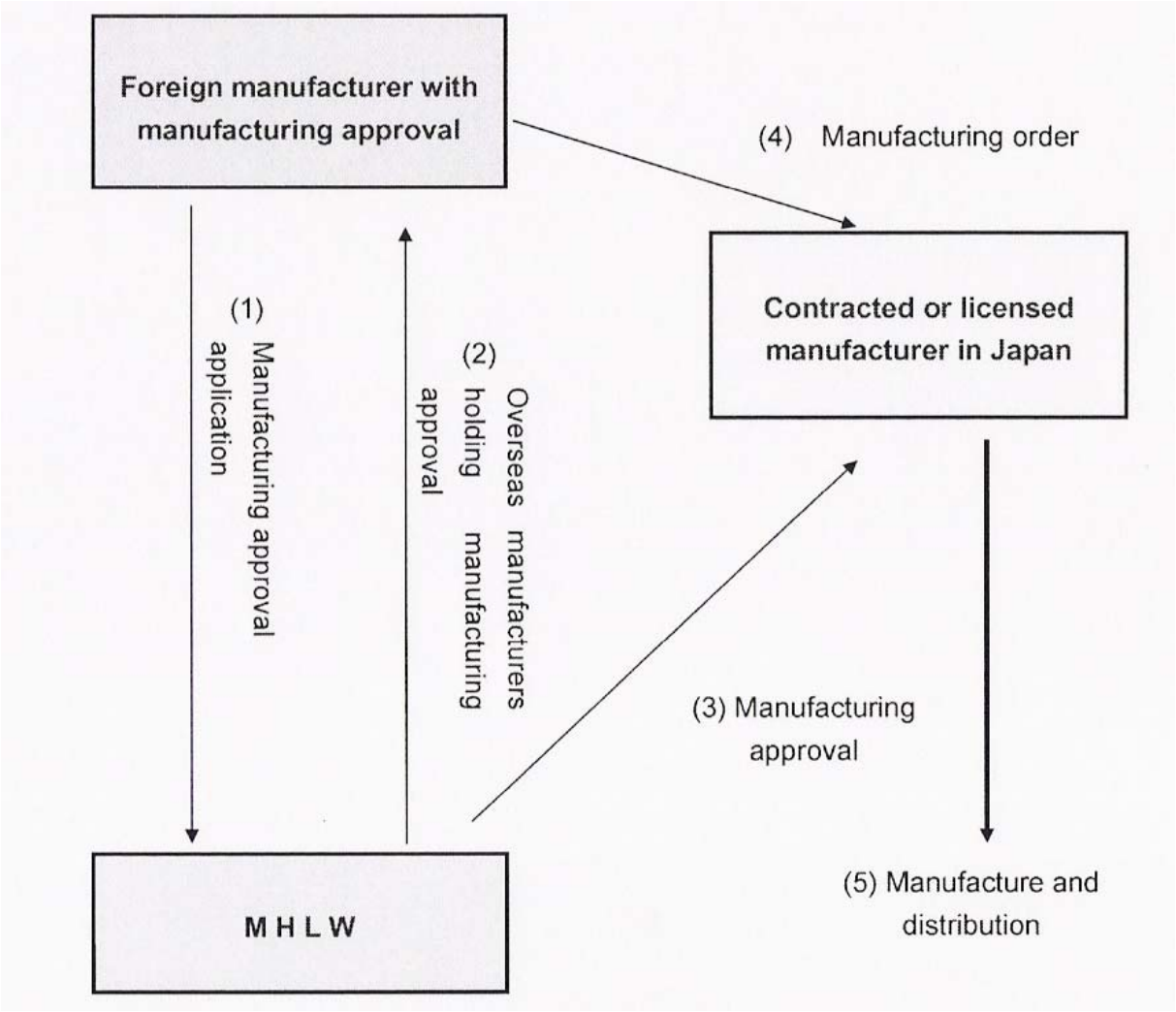
Annex 4

Flowchart of approval review



Annex 5

Procedure for manufacturing and distribution of drugs for overseas manufacturers in Japan



Annex 6

Manufacturing Flow Chart (example for antibody purification)

Working Cell Bank		
	WCB	
	Operation control item	OOF cell viability
Cell Culture Process		
Step 1 / 2 / 3		
	Purpose	Inoculum expansion
	Culture instrument (e.g.)	T-flask (25 to 75 cm^2) T-flask (75 to 175 cm^2) Spinner flask (12 L)
	Culture medium	Medium 1
	Operation control ite	Temperature pH Media osmolality Inoculum density Harvest density Cell viability Cultivation time
Step 4		
	Purpose	Inoculum expansion
	Culture instrument	Bioreactor
	Culture volume	400 L / 2000 L /10.000 L
	Culture medium	Medium 1
	Operation control item	Temperature pH Media osmolality Inoculum density Harvest density Cell viability Cultivation time
	Harvest	Time
Harvest Process		
Collection		
	Purpose	Separation and collection of culture supernatant
	Method	Filtration
	Operation control item	Cross flow rate Permeate flow rate Permeate volume
	Equilibration	Buffer
Clarification and Concentration		
	Purpose	Purification of supernatant
	Method	Filtration
	Operation control item	pH
	Equilibration	Buffer
	Final filtration	0.2 µm

Purification 1		
	Purpose	Separation of antibodies from process impurities
	Method	Chromatography
	Maximum load	
	Column diameter	
	Bed height	
	Operational control items	pH Linear velocity Conductivity
	Equilibration and Wash	Buffer
	Elution	Buffer
Virus inactivation process		
	Purpose	Virus inactivation
	Method (e.g.)	Low pH treatment
	Operational control items	pH Incubation time
	Neutralization	pH
Purification 2		
	Purpose	Removal of potential impurities
	Method	Chromatography
	Maximum load	
	Column diameter	
	Bed height	
	Operational control item	pH Linear velocity Conductivity
	Equilibration	Buffer
Virus removal process		
	Purpose	Virus removal
	Method (e.g.j)	Filtration
	Operational control items	Pre-filtration pH Conductivity Load concentration
	Equilibration	Buffer
Preparation of drug substance		
	Purpose	Manufacture of Drug Substance Optional holding step
	Method	Filtration and concentration
	Operational control limit	pH Conductivity Target concentration prior diafiltrationFinal target concentration Diafiltration volume
	Equilibration	Buffer
	Filtration	0.2 µm

Annex 7

Evaluation of medical products manufactured using bovine-derived components

Proprietary name	
Generic name	
Submitted by	
Indication	
Dosage and administration	
Used material / manufacturing process	
Risk to the quality	Including the evaluation of BSE risk value
Same type and indication of drug	
Usage status overseas	
Clinical benefit of the drug	
Schedule for implementation of change	e.g. Change of US source of raw material
Control of bovine-derived raw material	Donor screening / testing
Justification	Comparative consideration of BSE risk versus benefit
Comprehensive evaluation	
Measures for providing information	The following description is included in the package insert.

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Dr. Beatrix Metzner Roßdorf, July 2008