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REGULATORY STRATEGIES FOR FILING OF NDA IN ICH COUNTRIES (US, EUROPE and JAPAN)

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ABSTRACT

Developing new drugs requires great amount of research work in Chemistry, Manufacturing, Controls, preclinical science and clinical trials. Drug reviewers in regulatory agencies around the world bear the responsibility of evaluating whether the research data support the safety, efficacy and quality control of a new drug product to serve the public health. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs. This article focuses on drug approval process in different countries like USA, Europe and Japan.

Keywords: MAA, USFDA, Drug approval process, Clinical Trial.

INTRODUCTION

In the present scenario, countries have different regulatory requirements for approval of a new drug. The single regulatory approach for marketing authorization application and New Drug Application (MAA & NDA) of a new drug product applicable to ICH countries (on the basis of single dossier) is almost difficult. Therefore, the knowledge of exact and detailed regulatory requirements for MAA & NDA of each country should be known to establish a suitable regulatory strategy [1].

The new drug approval is of two phase process - the first phase for clinical trials and second phase for marketing authorization of drug. First, non-clinical studies of a drug are completed to ensure efficacy and safety, and then application for conduct of clinical trials is submitted to the competent authority of the concerned country. Thereafter, the clinical trials can be conducted (phase I to phase IV). These studies are performed to ensure the efficacy, safety and optimizing the dose of drug in human beings. After the completion of clinical studies of the drug, then an application to the competent authority of the concerned country for the approval of drug for marketing is submitted. The competent authority review the application and approve the drug for marketing only if the drug is found to be safe and effective in human being or the drug have more desirable effect as compare to the adverse effect [2]. Even after the approval of new drug, government should monitor its safety due to appearance of some side effects, when it is used in larger population. The interactions with other drugs, which were not assessed in a pre-marketing research trial and its adverse effects (in particular populations), should also be monitored

Main Objectives of the Study

- To understand the regulatory landscape of these Regions.
- List about the various marketing authorization procedures by which a manufacturer or applicant's generic drug can enters into market.
- Understand the regulatory requirements and forms which are required to file the application for marketing approval.
- To adopt the guidelines and regulations for ICH countries
- List about the various forms used to complete the application for marketing country approval

Methodology

Literature review was done mainly on collection of European Medicines Agency (EMA) legislations, Food and Drug Administrations (FDA) and Pharmaceuticals and Medical Devices Agency (PMDA) member state concentrating on their generic drug registration procedures. The research carried out with the collected data by analyzing the terms of the below parameters [3,4].

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Types of study

The study was conducted with an objective to chalk out the regulatory framework for generic drug registration legislations and guidelines. The major emphasis has been provided to the drug marketing approval in US, EU and Japan.

Source of data

Major part of secondary data collection was done by means of following sources

Literature review

Typically covered the books and regulatory guidelines published officially by government authorities, including the academic journals, online journals, market research reports and other resources.

Internet using the web page content

The literature was collected using numerous search engines e.g. Pharmabiz, RAPS, RAJ pharma, Google Scholar and many more. Online books also served as a good source of information. Key words in the search involved drug registration requirements along with the name of various parameters associated to pharmaceutical field, name of regulatory bodies and other variations were used.

International Conference on Harmonisation (ICH)

ICH stands for "International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use".

ICH's logo has been designed with a view to representing the letters "I", "C", "H" in a manner which embodies the letters in an abstract human form. The principle colour of the logo is blue, a colour often synonymous with healthcare, and which adds an air of vitality and wellbeing to the depicted abstract figure. Purple was chosen as being complementary to blue.

1. ICH mission

ICH's mission is to make recommendations towards achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration.

2. History

Since ICH's inception in 1990, the ICH process has gradually evolved. ICH's first decade saw significant progress in the development of Tripartite ICH Guidelines on Safety, Quality and Efficacy topics. Work was also undertaken on a number of important multidisciplinary topics, which included MedDRA (Medical Dictionary for Regulatory Activities) and the CTD (Common Technical Document). As the second decade the development of ICH Guidelines continued, but with more attention given to the following need to:

- Maintain already existing Guidelines as science and technology continued to evolve;
- Expand communication and dissemination of information on ICH Guidelines with non-ICH regions became a key focus;
- Facilitate the implementation of ICH Guidelines in ICH's own regions;
- Leverage with other organisations was also acknowledged, particularly for the development of electronic standards.

Entering into its third decade of activity, ICH's attention is directed towards extending the benefits of harmonisation beyond the ICH regions. Training, as well as active participation of non-ICH regions in Guideline development are seen as key in this effort.

Table 1. ICH countries regulatory bodies

Region	Regulatory Body	Research Based Industry
USA	FDA - Food and Drug Administration	PhRMA - Pharmaceutical Research and Manufacturers of America
Europe	EU - European Union	EFPIA - European Federation of Pharmaceutical Industries and Associations
Japan	MHLW - Ministry of Health, Labour and Welfare	JPMA - Japan Pharmaceutical Manufacturers Association

Table 2. ICH Countries Profile

Country	Currency	Official language	Ruling party	Regulatory authority
United states	Dollars	English	Federal presidential constitutional republic	US FDA (Food and Drug Administration)
Europe	Euros	German, Irish, Italian	European Peoples Party(EPP)	EMEA (European Medicines Agency)
Japan	Yen	Japanese	Liberal Democratic Party(LDP)	PMDA (Pharmaceuticals and Medical Devices Agency)

Table 3. List of top pharmaceutical companies in United States

S.No	Company	Total Revenues (USD billions)	Fortune 500 Ranking	Accurate as of (Date)
1	Johnson & Johnson	71.3	121	2014 (2013 Annual Report)
2	Pfizer	51.6	191	2014 (2013 Annual Report)
3	Abbott Laboratories	21.8	136	2014 (2013 Annual Report)
4	Merck & Co.	44.0	241	2014 (2013 Annual Report)
5	Eli Lilly	23.1	129	2014 (2013 Annual Report)
6	Bristol-Myers Squibb	16.4	176	2014 (2013 Annual Report)

Table 4. Top pharmaceutical companies in Europe

S.No	Company	Country	Total Revenues (USD billions)	Fortune 500 Ranking	Accurate as of (Date)
1	Roche	Switzerland	52.1	196	2014 (2013 Annual Report)
2	Glaxo Smith Kline	United Kingdom	45.4	170	2014 (2013 Annual Report)
3	Novartis	Switzerland	57.9	157	2014 (2013 Annual Report)
4	Sanofi-Aventis	France	44.6	238	2014 (2013 Annual Report)
5	Astrazeneca	UK/Sweden	25.7	468	2014 (2013 Annual Report)
6	Bayer's Health Care	Germany	54.2	154	2014 (2013 Annual Report)

Table 5. Number of consultations on clinical trials [21,22]

Year	Total	Before the Clinical Trial Notification	At the Completion of Phase II	Before Application	Individual Consultation
Apr-Dec. 1998	101	33	21	5	42
Jan.-Dec. 1998	231	55	55	41	80

Table 6. Drug submission types: US, EU and Japan

United States of America	*New Drug Submission* (NDS)—for both drugs and biologics
European Union	*Biologic License Application* (BLA)—for biologics EU *Marketing Authorization Application* (MAA)—via the centralized procedure for eligible products . For other products, routes such as the decentralized procedure, the mutual reorganization procedure or national authorization apply
Japan	*New Drug Submission* (NDS)—for both drugs and biologics

Table 7. EU: Products eligible for the centralized procedure

Mandatory	Optional
Human medicines for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune and other immune dysfunctions, and viral diseases Medicines derived from biotechnology processes, such as genetic engineering Advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines Officially-designated "orphan medicines"(medicines used for rare human diseases)	Other new active substances not authorized in the European Community before May 20, 2004 Medicinal products that contribute significant therapeutic, scientific or technical innovation or are in the interests of patient health A generic copy of a centrally authorized product

Fig. 1. Organisation of ICH

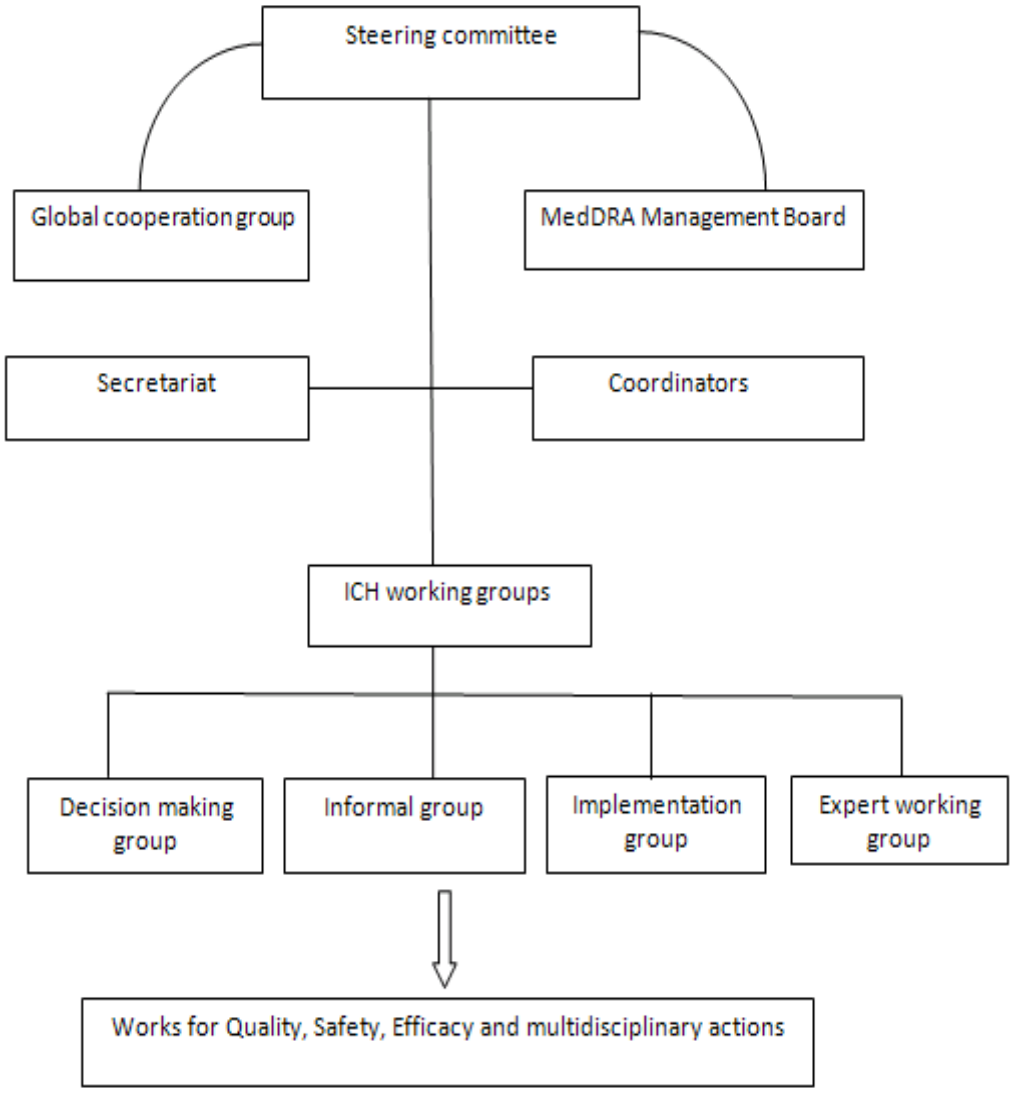


Fig. 2. Process of harmonization [6,7,8]

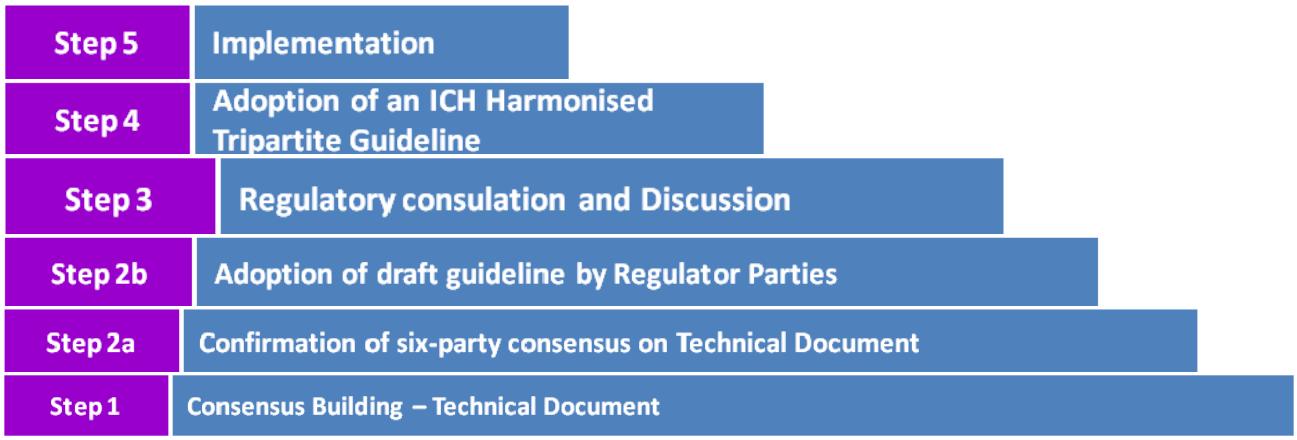


Fig. 3. New Drug Application Approval Process of FDA

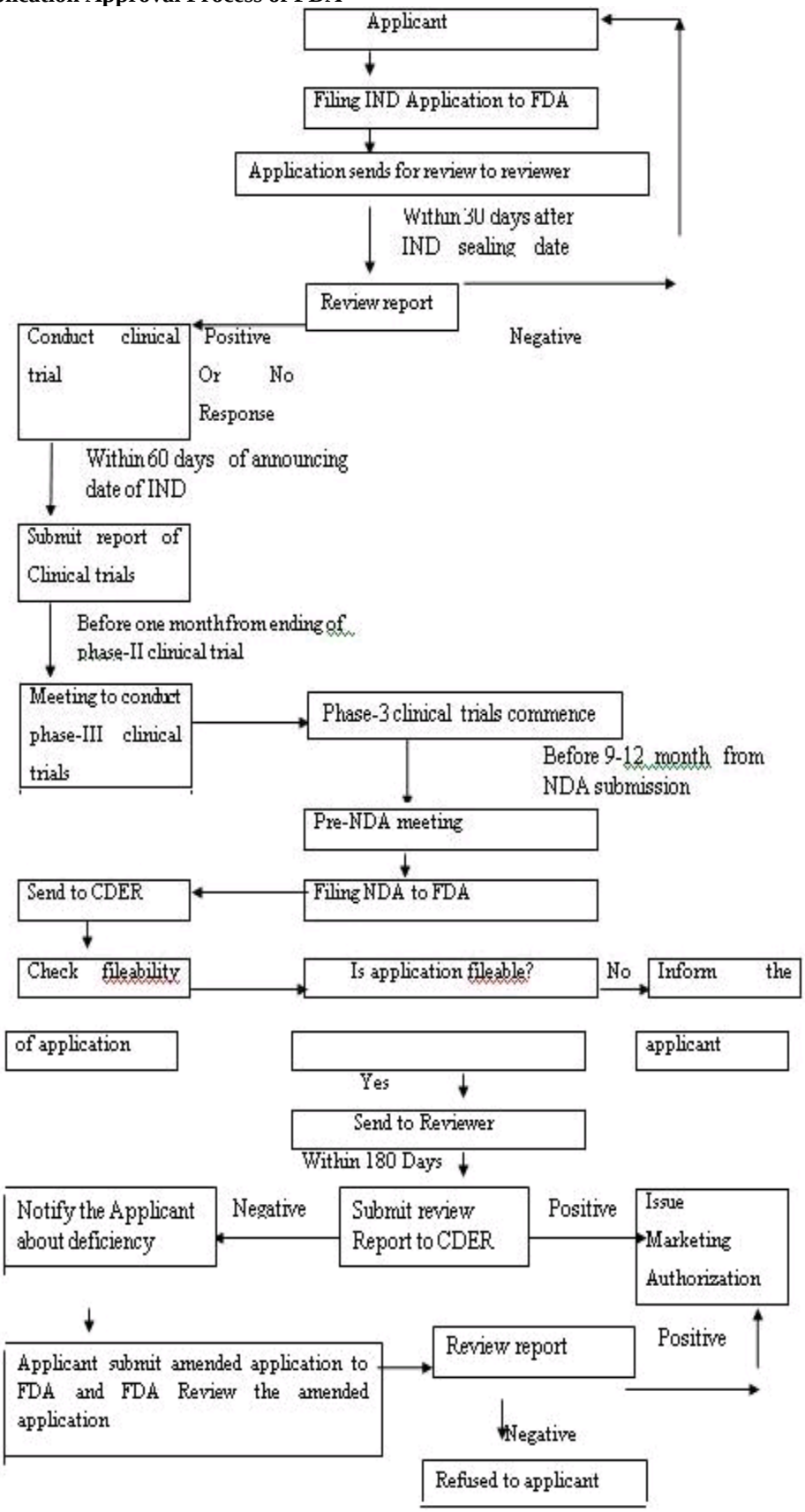
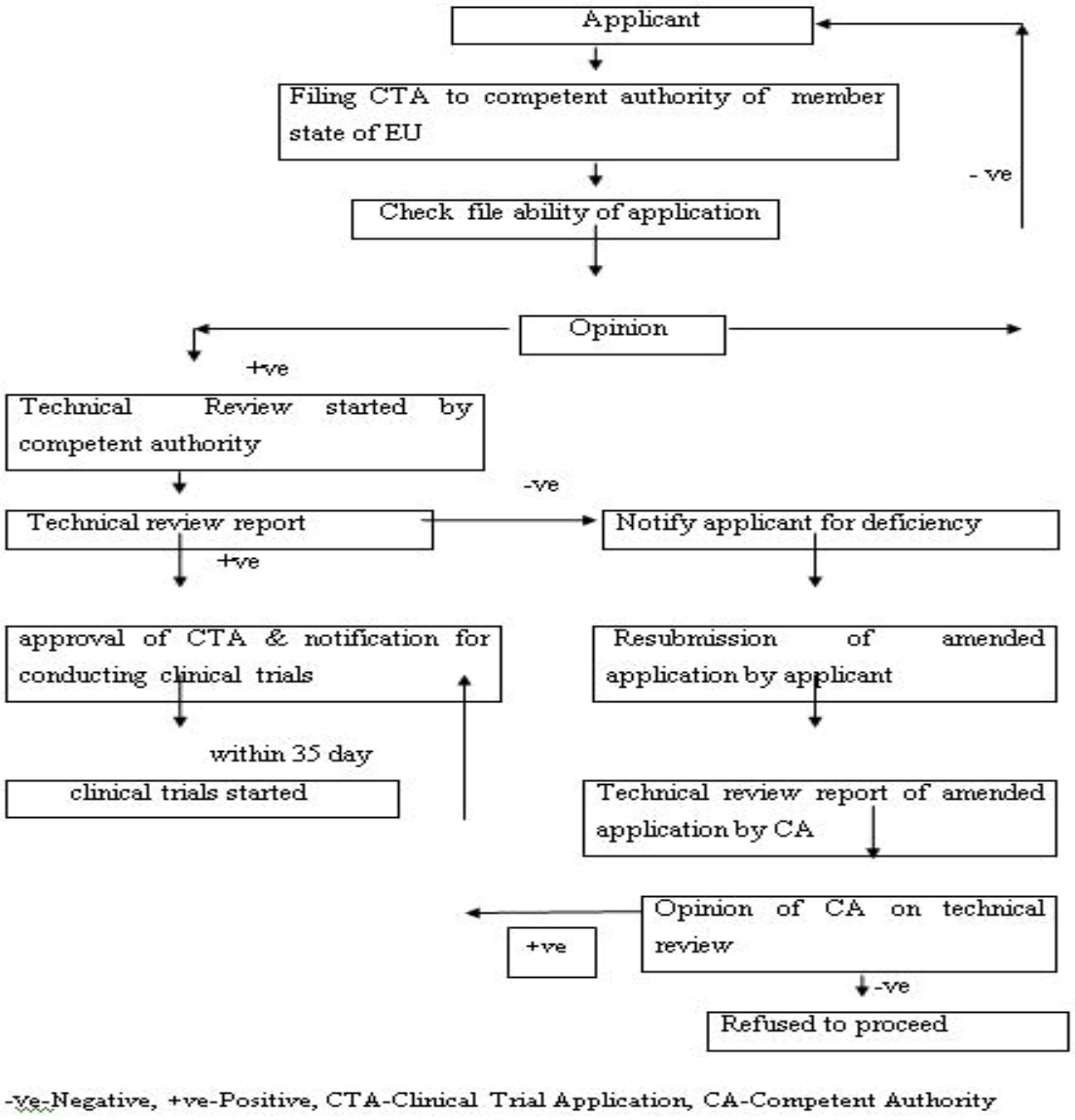


Fig. 4. Drug Approval Process in Europe; Authorization Process in EU



-ve-Negative, +ve-Positive, CTA-Clinical Trial Application, CA-Competent Authority

Fig. 5. Centralized Procedure for Marketing Authorization

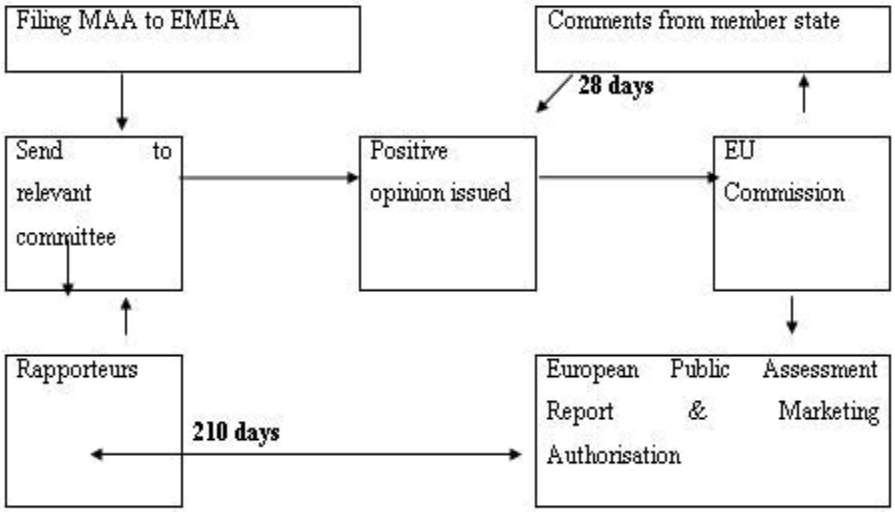


Fig. 6. Decentralised Procedure for Marketing Authorization in EU

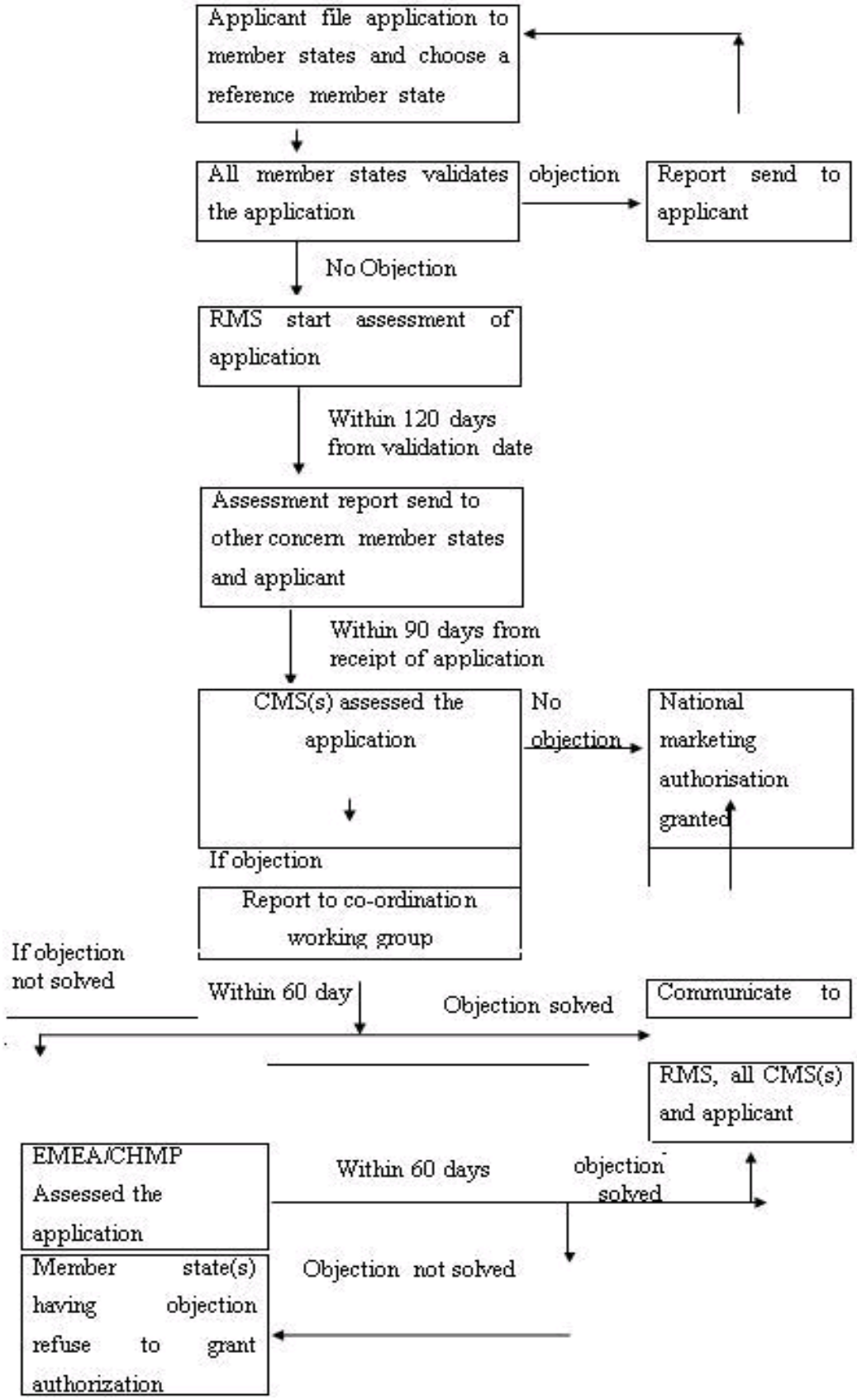
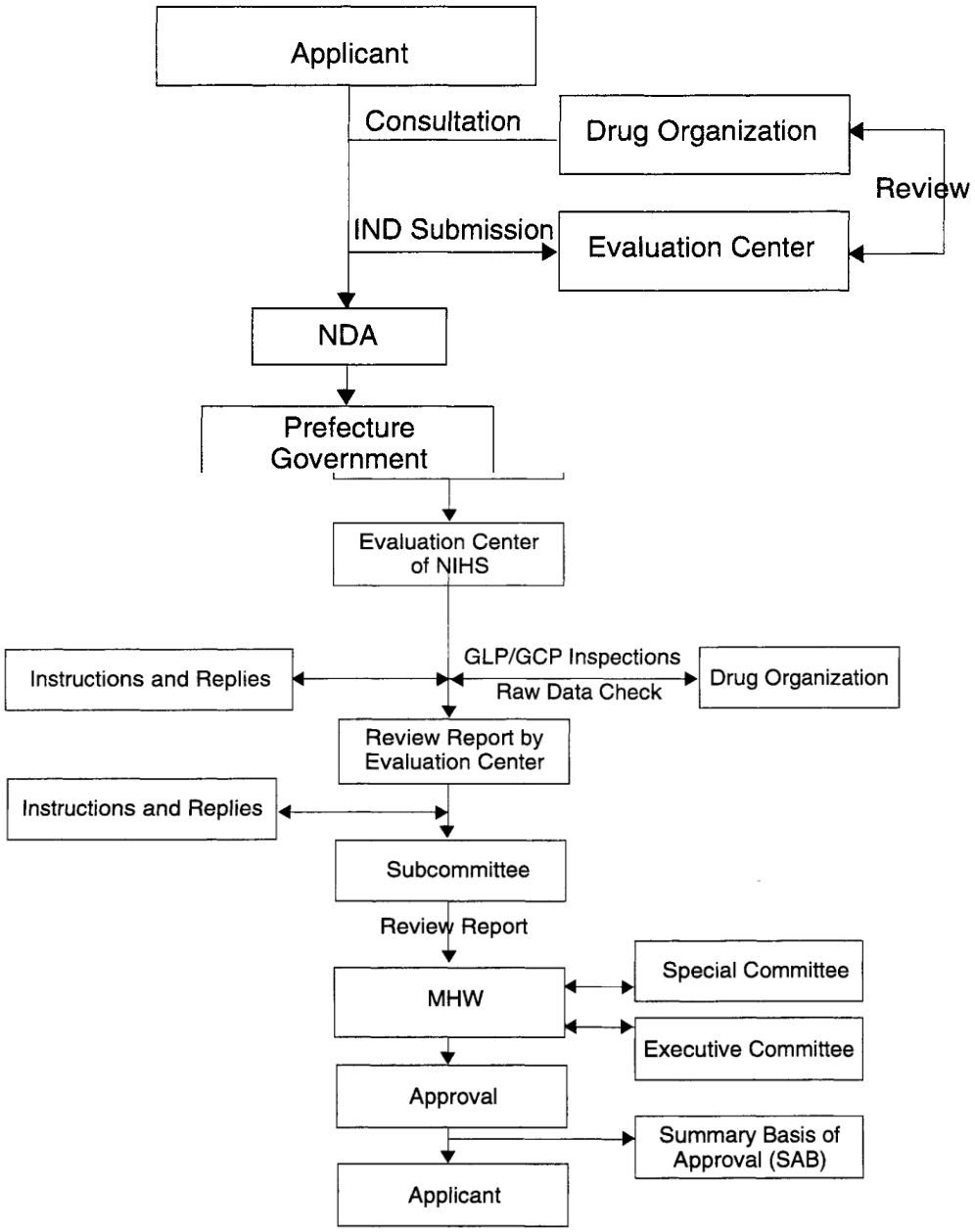


Fig. 7. NDA approval Process of Japan



CMS(s)-Concerned Member State(s), RMS-Reference Member State, CHMP-Committee for Human Medicinal Products

III - JAPAN

Pharmaceutical sector in Japan

Japan's ageing and affluent population represents strong opportunities for foreign drugmakers. However, given its weak macroeconomic, there is a risk that the country will not be able to sustain its generous welfare for the people and will seek to save costs through the use of more generic drugs and price cuts. Nevertheless, the current profile broods well for generic drugmakers as well as companies focusing on eldercare and chronic disease management.

Japan based Pharmaceutical companies

Top four pharmaceutical companies:

- Astellas Pharma
- Takeda
- Dailchi sankyo
- Eisei

Others:

- Meiji Seika
- Lion Corporation

- Green Cross

Expenditure Projections

- Pharmaceuticals: JPY10,157bn (US$127.4bn) in 2011 to JPY10,206bn (US$130.9bn) in 2012; +0.5% in local currency terms and +2.7% in US dollar terms. Ourforecast is unchangedsinceQ312.
- Healthcare: JPY47,810bn (US$599.60bn) in 2011 to JPY49,305bn (US$632bn) in 2012; +3.0% in local currency terms and +5.4% in US dollar terms. Ourforecasthasbeenrevisedupwardsslightly from Q412 following reassessment of historic data.
- Medical Devices: JPY2,220bn (US$27.8bn) in 2011 to JPY2,212bn (US$28.4n) in 2012; -0.5% in local currency terms and +1.9% in US dollar terms. Forecast slightly downgradedfrom Q412due to reassessment of historic values [5].

New Drug Development and Review Process

Approval and Licensing Procedures

The MHW grants approvals to manufacture or import drugs (excluding drugs with specified standards designated by the MHW as not requiring approval). The application approval of the drugs submitted was reviewed on the basis of the submitted documents and data by MHW officers and the Central Pharmaceutical Affairs Council (CPAC). Regarding the drugs which are equivalent to an approved drug, the Organization for Adverse Drug Reaction Relief, Research and Development Promotion and Product Review (Drug Organization) reviews the equivalency and then the MHW reviews the results reported by the Drug Organization [9,10].

In accordance with the revision of the PAL in 1996, the decision was made to reorganize the MHW Drug Organization and National Institute of Health Sciences (NIHS) for intensifying the review and approval system of drugs and medical devices. After the reorganization, the MHW Drug Organization and NIHS now have respective roles for consultation, GCP/GLP/GPMSP inspections and raw data check, and reviews and approval with the CPAC. Prior to the reorganization of the MHW and NIHS, the Drug Organization was reorganized first to include the Clinical Trials Department established in April 1997. Pharmaceutical companies have started to consult this department on their development plans, clinical trial protocols, necessary studies, etc., with fees (See Table 1). The Evaluation Center of the NIHS is responsible for reviews after the submission of NDA to the reviews by the subcommittee of the CPAC. Then the Evaluation and Licensing Division is responsible from the deliberation to the Special Committee and Executive Committee to the approval on the drugs passed at the subcommittee. The Drug Organization is also responsible for reviews of raw data check of data submitted for application, GLP/GCP/GPMSP inspections and reviews on equivalency of generic products for application. In the case of the changes of the approved drugs, there are two application procedures. For the change of brand name, active ingredient or its quantity and dosage form the new approval application must be submitted. For the changes of excipients or their quantity, dose, indications or standards and test methods, only the approval application as partial change is required. If an approval for a drug has not been obtained, no manufacturing or import license is granted (Article 13, 18 and 23 of the PAL). Unless the application for the approval of a substance has been made, it is not permitted to apply for the manufacture or import and marketing business licenses since approvals and license applications are a prerequisite for obtaining manufacturing or importing licenses. Therefore, approval and license applications are generally made simultaneously in Japan. Drugs requiring no approval such as ones with specified standards designated by the MHW (e.g., bulk drugs used for exclusively in the manufacture of drugs) do not follow this procedure (Article 14 and 23 of the PAL. Notification No. 104 of the MHW dated 28 March 1994) [11].

Direct Approval Application by Drug Manufacturers in Foreign Countries

Foreign manufacturers can directly obtain approvals of drugs after reviews by the health authority (Article 19-2 of the PAL). Foreign manufacturers can submit manufacturing approval applications to the MHW in their names with the required data and documents. Foreign manufacturers can also submit manufacturing approval applications via their local representative (called "in-country caretaker").

Orphan Drugs and Prioiity Review

Promotion of R & D for orphan drugs and procedure of priority review for them are described in the PAL (Article 1 of the PAL. Notification No. 725 of the PAB in 1993). Essential conditions for orphan drugs include the following:

• The number of patients should be less than 50,000.
• No alternative drug or treatment is available.
• There is an expectation of excellent efficacy and safety compared to the existing drugs.

The number of orphan drugs approved in 1997 were 9 ingredients or 9 products.

Standard Period for Approval Review

The standard periods for the review of a new application from the day of the receipt by the local government until the approval by the MHW are specified as follows (Notification No. 960 in 1985, No. 240 in 1986 and No. 26 in 1990 of the PAB). This period excludes the time required for preparing replies to the questions given by the health authority. However, it is anticipated to shorten the review time of new drugs to 12 months from April 2000 by revision of the review system such as elimination of the subcommittees for new drugs.

Ethical drugs: 18 months (12 months for partial change)
Proprietary drugs: 10 months
In vitro diagnostics: 6 months (3 months for partial changes of storage method and expiration) [12,13]

Promotion of regulatory science

PMDA's scientific activities must consist of accurate estimation, evaluation, and judgment based on clear evidence, while incorporating the latest scientific findings. To improve such activities, it is important to advance regulatory science,* which forms the basis of regulatory activities.

PMDA is committed to promoting regulatory science and fostering regulatory scientists through expansion of training programs for employees, implementation of research on PMDA's three services (product reviews, safety measures, and relief services for adverse health effects), and education by way of the Joint Graduate School Program. Under the Initiative to facilitate development of innovative drugs, medical devices, and cellular and tissuebased product, personnel exchanges between PMDA and universities/research institutions has been enhanced since fiscal 2012. Through this approach, PMDA endeavors to establish methods of evaluating the safety and efficacy of innovative drugs, medical devices, and cellular and tissue-based products and thus to develop guidelines, while nurturing human resources who are wellversed in innovative technology and regulatory science. * Regulatory science is the science serving precise estimation, evaluation, and judgment to regulate the fruits of technology so that they assume the most desirable form in harmony with humankind and society to benefit the public and society [14,15].

The University of Tsukuba Graduate School of Comprehensive Human Sciences; the Yokohama City University Graduate School of Medicine; the Yamagata University Graduate School of Medical Science; the Gifu Pharmaceutical University Graduate School of Pharmaceutical Science; Kobe University Graduate School of Medicine; the Chiba University Graduate School of Medical and Pharmaceutical Sciences/Graduate School of Medicine; the Musashino University Graduate School of Pharmaceutical Sciences; the United Graduate School of Drug Discovery and Medical Information Sciences, Gifu University; the Teikyo University Graduate School of Medicine/Graduate School of Pharmaceutical Sciences ; the Graduate School of Integrated Pharmaceutical and Nutritional Sciences, University of Shizuoka; the Osaka University Graduate School of Medicine; the Kyoto Pharmaceutical University Graduate School of Pharmaceutical Sciences; the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences; the Nagoya University Graduate School of Medicine; the Nagoya City University Graduate School of Pharmaceutical Sciences; and the Hokkaido University Graduate School of Medicine [16].

Overall Drug submissions Procedures to reach regulatory approval

Before a new drug or biologic can go to market, a drug submission must be compiled and filed with all relevant regulatory agencies to seek a review and, ultimately, regulatory approval. US, EU and Japan each require different types of drug submissions.

Review and approval procedures for drug submissions

Each jurisdiction has its own procedures to review drug submissions filed to their regulatory agency. These procedures can vary substantially with respect to how the drug submission will be handled, the composition of the review team, review timelines and so on. Despite the differences, the procedures to reach regulatory approval generally follow these stages:

Pre-submission meeting

Although optional, a pre-submission meeting is often useful so that any scientific or submission issues can be discussed and resolved prior to the actual submission. This meeting also provides the agency insight into your drug or biologic submission and allows them to organize their internal resources accordingly. *Tip:* Ensure the issues discussed are addressed in the submission dossier, with additional data or a sound scientific justification provided.

Pre-submission activities

Review what communication is required prior to submitting your marketing application. In Japan, sponsors (that is, applicants) are requested to send advance requests for Priority Review status and for Requests for Advance Consideration under the NOC/c.[6] In the EU, an applicant should notify the European Medicines Agency (EMA) of its intention to submit via the centralized procedure at least seven months before the drug submission. Any orphan drug designation should also be requested and approved before your drug submission will be reviewed as an orphan product [17].

Administrative review

Once a drug submission is filed, it goes through an administrative review to ensure its acceptability (for example, completeness). A submission number (such as NDS Control Number or NDA number) is assigned and this number must be used in all subsequent communication with the regulatory agency. If the drug submission is found to be acceptable at this stage, it will be accepted for review. If minor deficiencies are identified (for example, missing forms), the agency will normally allow the sponsor time to respond. If the response is satisfactory, then the submission will proceed to review. If the sponsor fails to provide the requested information within the set timeframe, or if that the response is unsatisfactory, the agency can reject (refuse to file) the submission [18]. *Tip:* Adhere to the response timeline indicated. Should you need more time, contact the agency and request an extension, providing a justification. The agency will determine if an extension can be granted.

Agency review and sponsor response

Once a drug submission is accepted, it is evaluated by reviewers with the necessary expertise. In the US, for

example, a review team may include clinicians, pharmacokinetics, pharmacologists, toxicologists, statisticians, microbiologists and chemists, as well as a regulatory project manager (RPM). The objective of the review is to confirm and validate the sponsor's conclusion that the drug is safe and effective for its proposed use. Once the technical review is complete, an evaluation report will be generated. If the submission is deemed acceptable, then the technical review of the submission is complete. If deficiencies are identified, then the agency will issue a list of questions for the sponsor to address within a set timeline. This review also evaluates the text in the proposed labeling, which needs to be justified by the data submitted in the submission. If the reviewers question the proposed labeling, they will discuss revised wording with the sponsor. *Tip:* Assemble a response team that can address agency questions and requests for additional information. A quick response by the sponsor facilitates the review process. Activities prior to the agency's decision These may include any necessary-approval inspections (for example, of drug manufacturing sites or clinical trial sites). In the US, for example, the Food and Drug Administration (FDA) may decide to convene an advisory committee (AC) meeting and seek input. Based on the discussions at the AC meeting and its recommendations, the FDA may ask for additional data or analyses to review 19,20].

Decision

The decision made at the end of the review process normally results in regulatory approval, an approval with conditions, or a rejection. *NOC/c = Notice of Compliance with conditions

Disclaimer

The information presented in these articles is intended to outline the general processes, principles and concepts of the healthcare product development lifecycle. Since regulatory requirements are ever-changing, it is ***current only as of the date of publication*** and not intended to provide detailed instructions for product development.

RESULTS AND DISCUSSION

Table 8. Principle differences between US, EU & Japan

S. No	Requirements	USA	EUROPE	JAPAN
1	Agency	One Agency USFDA	Multiple Agencies 1. EMEA 2. CHMP 3. National Health Agencies	1.PMDA 2.MHLW
2	Registration Process	One Registration Process	Multiple Registration Process 1. Centralized (European Community) 2. Decentralized (At least 2 member states) 3. Mutual Recognition (At least 2 member states) 4. National (1 member state)	One Registration Process
3	TSE/BSE Study data	TSE/BSE Study data not required	TSE/BSE Study data required	TSE/BSE Study data required
4	Braille code	Braille code is not required on labelling	Braille code is required on labelling	Braille code is not required on labelling
5	Post-approval changes	Post-approval changes in the approved drug: 1. Minor changes. 2. Moderate changes. 3. Major changes.	Post-variation in the approved drug: 1. Type IA Variation 2. Type IB Variation 3. Type II Variation	Post-approval changes in the approved drug: 1. Minor changes. 2. Moderate changes. 3. Major changes

Table 9. Administrative Requirements (As of 2014)

Requirements	USA	EUROPE	JAPAN
Application	ANDA / NDA	MAA	ANDA / NDA
Debarment classification	Required	Not Required	Required
Number of copies	3	1	
Approval Timeline	~18 Months	~12 Months	~18 Months
Fees	Under $2 million-NDA Application $51,520 – ANDA Application	National fee (including hybrid applications): £103,059 Decentralised procedure where UK is CMS: £99,507	
Presentation	eCTD & Paper	eCTD	eCTD & Paper

Table 10. Bioequivalence Requirements (As of 2014)

Requirements	USA	EUROPE	JAPAN
CRO (Audits)	Audited by FDA	Audited by MHRA	Audited by MHW
Reserve Sample	5 times the sample required for analysis	No such requirement	5 times the sample required for analysis
Fasted / Fed	Must be as per OGD recommendation	No such requirement	Must be as per OGD recommendation
Retention of samples	5 years from date of filing the application	No such requirement	5 years from date of filing the application
BE study for generic drugs	Against US RLD in any country. To refer 'BE recommendations' in FDA site for guidance.	Against EU reference product (ERP) in any country	Against Japanese reference product (JRP) in any country

CONCLUSION

Generally, the drug approval process comprised mainly the two steps, application to conduct clinical trial and application to the regulatory authority for marketing authorization of drug. The new drug approval process of various countries is similar in some of the aspects whereas it differs in some aspects. In most of the counties, sponsor first files an application to conduct clinical trial, and only after the approval by the regulatory authority, the applicant conducts the clinical studies and further submits an application to the regulatory authority for marketing authorization of drug. In all countries, information submitted to regulatory authorities regarding the quality, safety and efficacy of drug is similar; however, the time, fee and review process of clinical trials and marketing authorization application differs. For the purpose of harmonisation, the International Conference on Harmonisation (ICH) has taken major steps for recommendations in the uniform interpretation and application of technical guidelines and requirements. This step will ultimately reduce the need to duplicate work carried out during the research and development of new drugs.

REFERENCES

1. Anonymous 1. www.ich.org Introduction and structure of ICH
2. Significant Dates in U.S. Food and Drug Law History, http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm (assessed on March 09th 2010)
3. Stringer S. What Has Been Happening With Over-the-Counter Drug Regulation. *Food and Drug Law Journal*, 5, 1998, 633-91.
4. Martinez LJ. FDA Overview: An Overview of the Drug Approval Process. *Research Initiative Treatment Action (RITA)*, 2002, 8.
5. CFR: Title 21, Food and Drugs: Chapter I--Food and Drug: PART 312--Investigational New Drug Application http://www.access.gpo.gov/nara/cfr/waisidx_03/21cfr312_03.html (assessed on March 09th 2010).

6. Investigational New Drug Application (IND) http://www1.pointcross.com/source/ddg/steps/ind/index.html (assessed on March 09th2010).
7. Horner A., Comparison of a global submission of new biological entity and a new chemical entity - strategic decisions and criteria for implementation (2005) http://www.dra.uni-bonn.de/hoerner. (assessed on March 09th 2010).
8. Ng R. Drugs: from Discovery to Approval (2004) http://www.pharmatext.org/2008/06/drugs-from-discovery-to-approval.html
9. Anonymous 2. www.worldatlas.com Europe map/ Map of Europe – Facts, Geography, history of Europe
10. Ghalamkarpour A. Marketing Authorization Procedures in the European Union - Making the Right Choice (2009). http://www.lsnewscr.sgs.com/lsnewscr/lsnewscr-december-issue/marketing-a... (assessed on May 11th 2010).
11. Anonymous 3. http://www.seoho.biz/GMP_Quick_Search/Data/2.%20European%20Documents/2.4.... (assessed on October 21st 2009).
12. European Commission: The Notice to Applicants; Volume 2A; Procedures for marketing authorisation-2005, http://ec.europa.eu/health/files/eudralex/vol-2/a/vol2a_chap1_2005-11_en... (assessed on May 21st 2010).
13. Marketing Authorization Procedures in the European Union - Making the Right Choicehttp://www.lsnewscr.sgs.com/lsnewscr/lsnewscr-december-issue/marketing-a... (assessed on May 27th 2010).
14. Davis H., An overview of the licensing process as it applies to medicinal products in the UK http://www.ukmi.nhs.uk/Med_info/licensing_process.pdf. (assessed on May 13th 2010).
15. European Commission: Notice to Applicants: Volume 2A; Procedures for Marketing Authorisation; Chapter 2; Mutual Recognition http://www.imb.ie/images/uploaded/documents/Chap2NTA.pdf. (assessed on May 08th 2010).
16. Anonymous 4. http://www.alzheimereurope.org/index.php/EN/OurResearch/Understanding-de.... (assessed on May 19th 2010).
17. Anonymous 5. www.pharmaceutical-technology.com – Japan pharma sector
18. Anonymous 6. http://www.lsnewscr.sgs.com/lsnewscr/lsnewscr-december-issue/marketingau.... (assessed on May 13th 2010).
19. Zhen LH. The drug registration application. *J Pharm Pharmaceut Sci*, 6(2), 2003, 211-214.
20. SFDA Order No. 28:Provisions for Drug Registrationhttp://eng.sfda.gov.cn/cmsweb/webportal/W45649039/A64028429.html (assessed on June 09th 2010).