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Review Article

A comprehensive review on Drug Product registration and approval process in Brunei Darussalam and Ukraine

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Abstract

The drug and drug product registration and approval processes vary in each country which is regularized by the statutory drug regulatory agencies. This review gives detailed information on the regulatory requirements for drug product registration in Brunei Darussalam and Ukraine. Departments working under the administration of Ministry of Health are working for the drug product registration and approval in both the countries, respectively. Dossier submission is a preliminary requirement for any pharmaceutical product to be marketed. The specifications for Dossier in both the countries are likely to be similar but they adhere to different guidelines for Dossier requirements. The timelines for drug product registration depends upon the type of product and the adequacy of the data submitted to the authority. A comprehensive study of submission requirements, registration process and role of drug regulating departments of Brunei Darussalam and Ukraine will help to understand the regulatory procedures of both the countries in a precise manner.

Keywords: Brunei Darussalam Medical Control Authority (BDMCA), ASEAN Common Technical Dossier (ACTD), Dossier, drug registration Unit (DRU), State Expert Center (SEC).

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1. Introduction

The drug and drug product registration and approval process of a country is highly strict and regularized by the statutory bodies or regulatory agency of that country. This regularization in the process for a region or state of a country ensures safe and validated entry of drugs and drug products into the market. It directly fulfills the increasing demand for safe and efficacious medications thereby protecting public health and promoting national health of the citizens. (1) Each and every country has a statutory body which regularizes the manufacturing, processing, packaging, distribution and sales of various drugs and drug products. The drug registration and approval process in Brunei Darussalam and Ukraine is headed by the Ministry of Health of Brunei Darussalam and Ministry of Health of Ukraine respectively. (2,3) Both of these ministries have medicinal departments which exclusively work in the direction of drug regulation.

2. Drug registration and approval procedure in Brunei Darussalam (4)

The Department of Pharmaceutical Services (DPS) under the Ministry of Health works for the administration and regulation of drug and drug products in to the pharmaceutical market of Brunei Darussalam. The import, manufacturing, distribution and sales of pharmaceutical products are regulated under Drugs Order, 2007 and Drugs Regulations, 2010. The drug product registration and approval Procedure is regulated and headed by the Brunei Darussalam Drugs Control Authority (BDMCA).

A new product registration application is categorized as:

1. Innovator product (NCE/Biotech)
2. Generic product
3. Application for registration of medicinal products via the Abridged Route

For pharmaceutical product registration, the permissible application format is the ACTD (ASEAN Common Technical Dossier) Format. All applications for medicinal product registration are submitted with the required documents which are in line with the ASEAN Common Technical Dossier (ACTD) for the registration

of pharmaceuticals for human use and ASEAN Common Technical Requirements (ACTR). Applications for provisional product registration is done by submission of the letter of intent and by using the prescribed forms issued by the DPS (Department of Pharmaceutical Sciences).

In ASEAN CTD format, the modules are referred to as Parts which contain all the details similar to that of a regular Dossier but varies only in certain technical requirements. For submission, hard copies for Part – I and Part – II need to be submitted. Submission of Part – III and Part – IV can be done electronically in a CD/DVD. Applications must be duly supported with required documents as per the application type. To ensure thorough submission of dossier, application checklists are provided for all the Modules. These completed checklists should be attached at the front of each part while making a submission to the drug registration Unit (DRU). Submission of the applications must be made by appointment with the concerned officer at the DPS (Department of Pharmaceutical Sciences). Applications are submitted to the drug registration Unit of Department of Pharmaceutical Sciences, Brunei Darussalam. Upon acceptance of an application, an acknowledgement receipt is issued to the applicant and a reference number is generated which is used for future correspondence related to the drug product. (4)

Dossier Format

Table 1. Organization of ACTD (5, 6)

Sr. No.	Part of Dossier	Information
1.	**Part I: Administrative Data and Product Information**	
	Section 1	Application no. DPS/DRS/01
	Section 2	Letter of Authorization
	Section 3	Certifications
	Section 4	Product Labeling
	Section 5	Product Information
2.	**Part II: Quality Section**	
	Section 1	Drug Substance (Form no. BDMCA/DPS/02/A)
	Section 2	Drug Product (Form No. BDMCA/DPS/02/B)
3.	**Part III: Non-Clinical**	
	Section 1	Table of Contents
	Section 2	Non-clinical Overview
	Section 3	Non-clinical Summary (Written and Tabulated)
	Section 4	Non-clinical Study Reports
	Section 5	Literature References
4.	**Part IV: Clinical Documents**	
	Section 1	Table of Contents
	Section 2	Clinical Overview
	Section 3	Clinical Summary
	Section 4	Tabular Listing of all Clinical Studies
	Section 5	Clinical Study Reports
	Section 6	Literature References

Nonclinical documents (Part III) are not required for Generic products, Minor Variation products and some Major Variation products. Clinical Summary is not required for Generic products, Minor Variation products and some Major Variation products. (6)

Application Screening (4)

The submitted application is scrutinized and validated after which, the applicant is communicated within 10 working days and DRU may request for further information and additional supporting documents from the applicant through the query letter. Applicant must provide such information or documentation required for each correspondence within 60 calendar days from the date of the screening query letter. Once the feedback has been received, the requested information and documents will be screened for completeness. If no feedback is provided within 60 days of DRU request, the application will not proceed for further evaluation and thus DRU will issue a non-acceptance letter and the documents will be returned. (4)

Application Fees (4)

All the fees related to application of product registration are to be made in Cash/Cheque form. Cheques are to made payable to 'Kerajaan Brunei' or Government of Brunei. Payments can be done on working days, i.e. from Monday to Thursday only. An official receipt of fees payment is issued to the applicant.

Processing fee

The processing fee of B$ 200 is to be paid while submitting the application for product registration and it is non-refundable.

Product License fee

For issuing the product License Certificate, there is no charge for the first year but a charge of B$ 50 is charged for the subsequent years. The validity of the product License Certificate is 5 years.

Amendment fee

In case of any amendments applicable by BDMCA, a fee of B$ 150 for major amendments and B$ 50 for minor amendments is to be paid. (4)

BDMCA's Decision (7)

The applicant is informed regarding the final decision of BDMCA in writing. The final decision is in terms of either acceptance i.e. approval or rejection in cases where sufficient data has not been provided by the applicant. Upon approval, a registration number is issued which is specific for the product registered as specified in the registration documents. A product License certificate is issued for the registered drug product.

The BDMCA has the authority to cancel, reject or suspend the registration of any drug product if there are potential deficiencies in safety, quality or efficacy of the product or if the drug product fails to comply with the registration requirements. Such products are not permissible to be imported and marketed in the region. In such cases, the product License Certificate should be immediately surrendered to the BDMCA upon cancellation or suspension of registration of the product. (7)

Appeal against the BDMCA's Decision (7)

Whenever a product is rejected for registration by the drug registration Committee, the applicant can make a written appeal to the Chairperson of the Committee by filing an appeal form, i.e. Form no. DPS/DRU/Appeal/01 issued by the Department of Pharmaceutical Services within 30 calendar days from the date of the committee's notification (7)

An Overview of Drug Product Registration and Approval Process in Brunei Darussalam (5, 7)

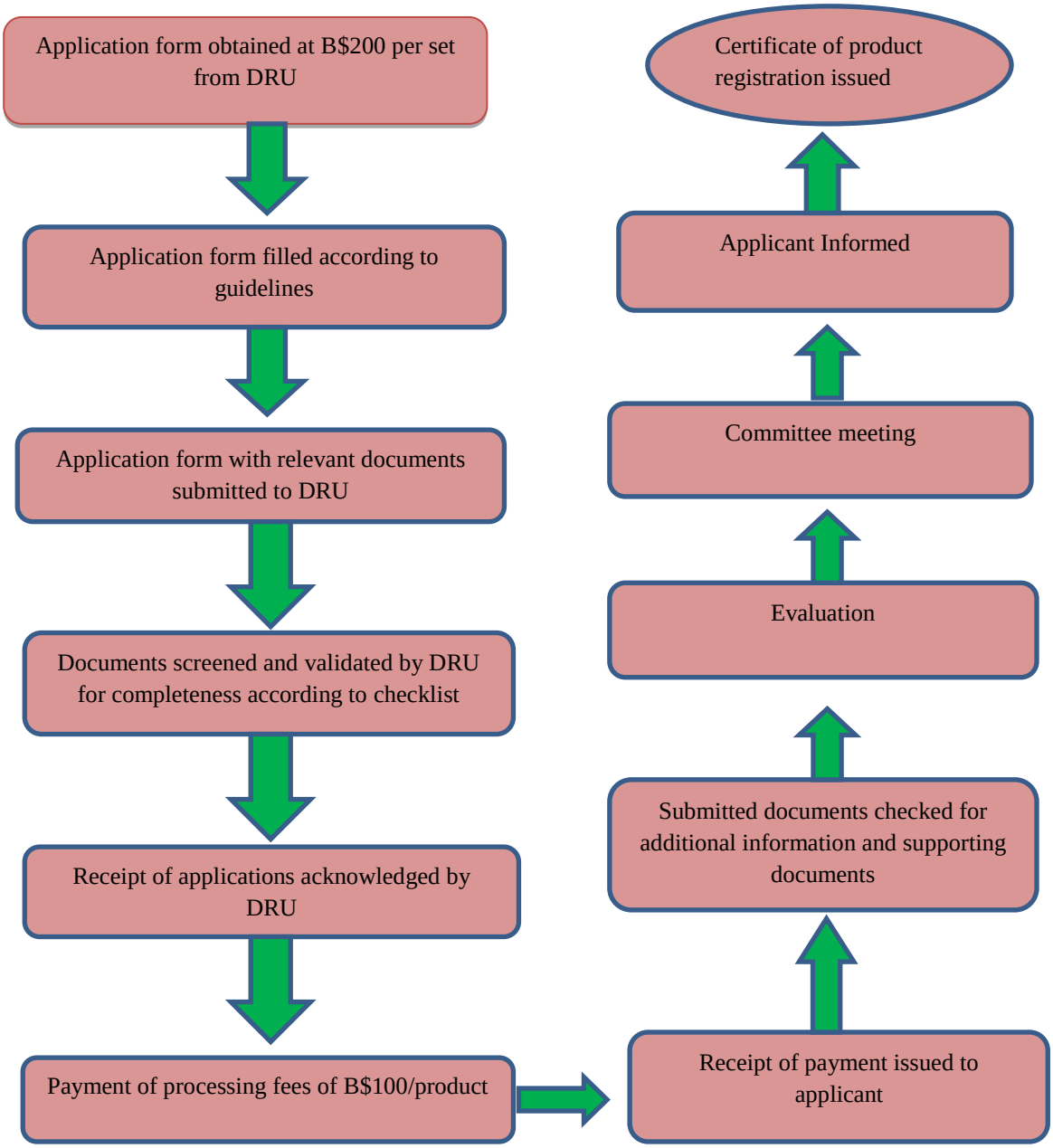

Figure 1. Drug Product Registration and Approval Process in Brunei Darussalam (5,7)

3. Drug registration and approval process in Ukraine (3, 8-11)

The regulations on registration and marketing of the pharmaceutical products in Ukraine is in harmonization with the EU legislation since 2005. (3) The general submission requirements and application evaluation process are likely to be parallel with the European directives, although there are Ukraine-specific conditions which make the drug regulatory system of Ukraine quite unique. (8) For import and marketing of drug products in Ukraine, it is necessary for the products to meet the legal requirements as well as quality fulfillments and state registration of the drug products is compulsory. (9,10) The Ministry of Health of Ukraine accepts the applications for the drug product registration and approves decisions on registration by issuing orders. The State Expert Center (SEC) of the Ministry of Health of examines the registration materials (dossiers) for the drug product and supervises the product safety. The State Service of Ukraine on Drugs and Drugs Control (SMDC) implements the state policy on quality control of the drug products and medical devices, carries out activities on recognition (certification) of manufacturing compliance with the GMP (Good Manufacturing Practice) requirements. (11)

Drug Product Registration Requirements (12-15)

- An Application for registration which is to be filled as per the National Application Form.
- Registration form containing legal and administrative information
- Dossier prepared as per ICH guidelines
- Translation of the contents of CTD into Ukrainian or Russian (12)
- Power of Attorney
- Certified copies of GMP Certificate or Conclusion of Compliance to the GMP requirements
- Copy of Registration Certificate issued by the competent authority
- Justification of absence of Registration Certificate (if applicable)
- A brief listing of countries where the drug product is registered
- Suitability Certificate for Monographs as per EU
- Written obligation of the applicant to ensure operation of adequate system to supervise safety of the medicinal product during its medical use including the territory of Ukraine (13)
- Bio-data of contact person
- Bio-data of qualified person responsible for pharmacovigilance with location in Ukraine
- Letter of the applicant with confirmation that rights of third party are not violated due to registration of the medicinal product
- Copies of patents for the invention, utility model or industrial design
- Copy of trademark certificate (if available) (14,15)

Dossier Format

Table 2. Organization of CTD (Dossier) (16,17)

Module No.	Sr. No.	Contents
1.	1.0	Administrative Documentation
	1.1	Table of contents
	1.2	Application with micro dossier.
	1.3	Summary of product characteristics (SmPC), labelling and instructions for medical use
	1.4	Information about the independent experts
	1.5	Specific requirements for different types of applications
	1.6	Environmental risk assessment
2.	2.0	**CTD Summary**
	2.1	CTD Table of Contents (Module 2 – 5)
	2.2	CTD Introduction
	2.3	Quality Overall Summary
	2.4	Nonclinical Overview
	2.5	Clinical Overview
	2.6	Nonclinical Written and Tabulated Summary
	2.7	Clinical Summary
3.	3.0	**Quality**
	3.1	Table of Contents
	3.2	INTRODUCTION
	3.3.S	**DRUG SUBSTANCE (NAME, MANUFACTURER)**
	3.3.S.1	General Information (name, manufacturer)
	3.3.S.2	Manufacture (name, manufacturer)
	3.3.S.3	Characterisation (name, manufacturer).
	3.3.S.4	Control of drug Substance (name, manufacturer)

	3.3.S.5	Reference Standards or Materials (name, manufacturer)
	3.3.S.6	Container Closure System (name, manufacturer)
	3.3.S.7	Stability (name, manufacturer)
	3.3.P	**DRUG PRODUCT (NAME, DOSAGE FORM)**
	3.3.P.1	Description and Composition of the drug product (name, dosage form)
	3.3.P.2	Pharmaceutical Development
	3.3.P.3	Manufacture
	3.3.P.4	Control of Excipients
	3.3.P.5	Control of drug product
	3.3.P.6	Reference Standards or Materials
	3.3.P.7	Container Closure System
	3.3.P.8	Stability
	3.3.A	APPENDICES
	3.3.R	REGIONAL INFORMATION
4.	4.0	**Preclinical Study Reports**
	4.1	Table of Contents of Module 4
	4.2	STUDY REPORTS
	4.2.1	Pharmacology
	4.2.2	Pharmacokinetics
	4.2.3	Toxicology
	4.3	LITERATURE REFERENCES
5.	5.0	**Clinical Study Reports**
	5.1	Table of Contents of Module 5
	5.2	Tabular Listing of All Clinical Studies
	5.3	Clinical Study Reports
	5.3.1	Reports of Biopharmaceutical Studies
	5.3.2	Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials
	5.3.3	Reports of Human Pharmacokinetic (PK) Studies
	5.3.4	Reports of Human Pharmacodynamic (PD) Studies
	5.3.5	Reports of Efficacy and Safety Studies
	5.3.6	Reports of Post-Marketing Experience
	5.3.7	Case Report Forms and Individual Patient Listings
	5.4	Literature References

Application Examination (12)

The State drug Inspectorate examines documents submitted by the applicant within 90 days. The State drug Inspectorate engages expert institutions for conducting expert testing and review. The obtained results of the expert examination are quoted in a report which is communicated to the State drug Inspectorate or handed over directly to the applicant. Based on conclusion of expert institutions the State drug Inspectorate accepts testing of the medicinal product. Based on consideration of expert examination (testing) report and recommendation of the advisory body, the State drug Inspectorate makes a decision on registration approval or rejection in registration in circumstances where conclusion on safety, quality and efficacy of the product is not confirmed. The applicant is informed in writing by the State drug Inspectorate. Based on the decision, drug product is included to the State Register of Medical Equipment and Medicinal products kept by the State drug Inspectorate, and the applicant will receive a certificate of registration. This Certificate of registration is valid for a period up to 5 years (12)

Timelines for Examination

Table 3. Timelines for Expert Evaluation (14)

Sr. no.	Type of Application	Duration of Expert Evaluation
1.	Drug product, Medicinal Immunobiological Products and Biosimilars	210 working days
2.	Generics, drug products of well-known medical use and a number of other types	90 working days
3.	Orphan products and drug products for treatment of socially Dangerous diseases (HIV, Viral Hepatitis, Tuberculosis, Oncological Diseases)	45 working days
4.	Drug products registered by competent authorities of the USA, Switzerland, Japan, Australia, Canada and Medicinal products registered via the Centralized Procedure by the European Union competent authority	10 working days
5.	Drug products, which are supposed to be purchased by specialized International Organizations	5 working days

Fees (18)

Applicable charges for state registration of a drug product (except radioactive drug products or complex preparations from herbal raw materials) is:

- EUR100 per pharmaceutical form.
- EUR10 for each subsequent dose.
- EUR10 for every package of the drug product.

Apart from this, fees for expert evaluation for conducting examination is also chargeable to the applicant, which depends on the type of application (18)

An Overview of Drug Product Registration and Approval Process in Ukraine (18)

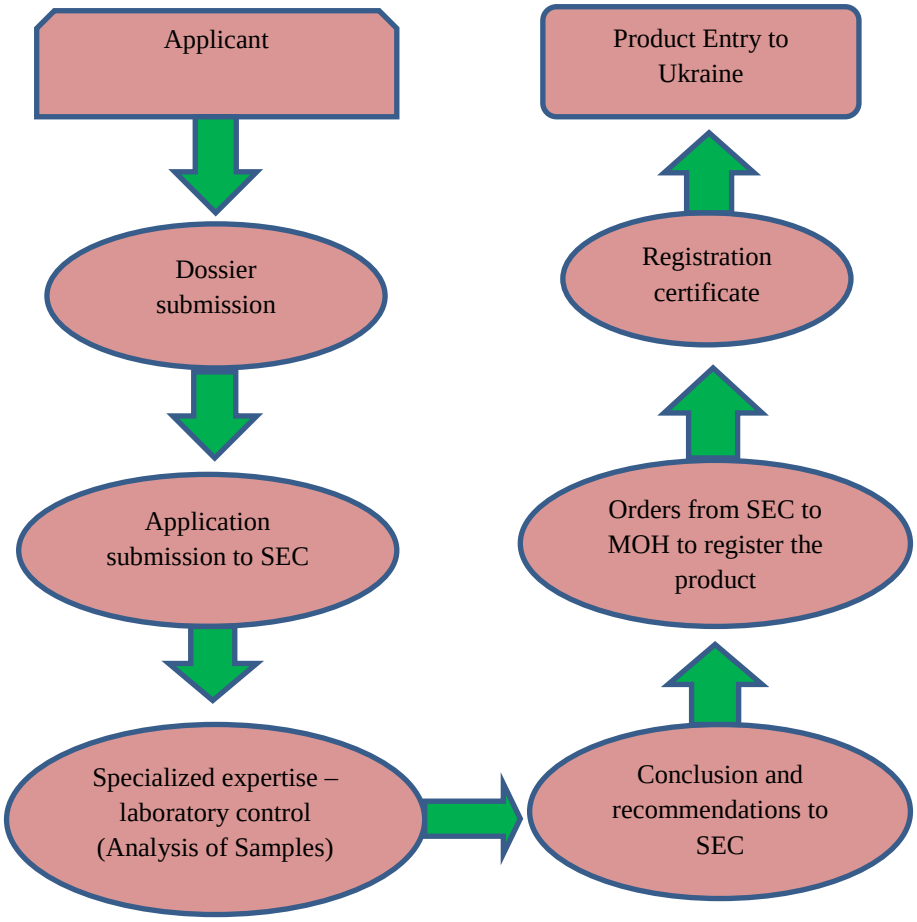

Figure 2. Drug product registration and approval process in Ukraine (18)

Table 4. Comparison of Drug Product Registration and Approval Requirements in Brunei Darussalam and Ukraine (4, 14, 19, 20)

Sr. No.	Parameters	Brunei Darussalam	Ukraine
1.	**Regulatory Authority**	Department of Pharmaceutical Services (DPS), Ministry of Health, Brunei Darussalam	State Expert Center (SEC), Ministry of Health, Ukraine
2.	**Working Department for Registration**	Brunei Darussalam Drugs Control Authority (BDMCA)	State Service of Ukraine on Drugs and Drugs Control
3.	**Dossier format**	ASEAN CTD (ACTD)	ICH – CTD
4.	**Data required in Dossier**	Part 1 – Administrative Data and Product Information Part 2 – Quality Section Part 3 – Non -Clinical Part 4 – Clinical Documents	Module 1 – Administrative Documentation Module 2 – CTD Summary Module 3 – Quality Module 4 – Pre-clinical Study Reports Module 5 – Clinical Study Reports
5.	**Dossier Examiner**	Drug Registration Unit (DRU)	State Drug Inspectorate & State Expert Center (SEC)

6.	**Timeline for Registration**	70 Days for examination 12 – 24 months for final registration	90 Days for examination 8 – 24 months for final registration
7.	**Fees**	B$ 200	EUR 100
8.	**Registration Certificate Charges**	B$ 50	No separate charges

4. Conclusion

This review study was conducted to provide a brief idea on the regulatory requirements for drug and drug product registration and approval in Brunei Darussalam, which is a part of ASEAN and in Ukraine which is a part of Commonwealth Independent States (CIS). There are stricter rules and regulations for drug and drug product registration in both Brunei Darussalam and Ukraine, which makes it difficult for applicants to understand the whole registration process. For drugs and drug products to enter the pharmaceutical market, the submission of a Dossier containing all the technical requirements is a must. In Brunei Darussalam, The Brunei Darussalam Drugs Control Authority (BDMCA) carries out all the regulatory processes and the prescribed format for Dossier submission is ACTD. (ASEAN Common Technical Dossier). In Ukraine, it is compulsory for a drug product to have a state registration in order to be registered in the National Register. The submitted dossier is evaluated by the State Expert Center of the Ministry of Health.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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