Hacer Coşkun Çetintaş, MSc, Turkey

- Head of the Medicines Marketing Authorization Department, Turkish Medicines and Medical Devices Agency (TİTCK), Turkey

GaBI Educational Workshops

24 September 2019, Ankara HiltonSA, Turkey

2nd Turkish Interactive Workshop on
REGULATORY ASSESSMENT OF BIOSIMILARS

Regulatory approval of biosimilars in Turkey: labelling and transparency

Hacer Coşkun Çetintaş, MSc

24 September 2019

GaBi
GENERICS AND BIOSIMILARS INITIATIVE
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REPUBLIC OF TURKEY
MINISTRY OF HEALTH
TURKISH MEDICINES AND
MEDICAL DEVICES AGENCY

MARKETING AUTHORIZATION PROCEDURE of BIOSIMILARS in TURKEY

Hacer COŞKUN ÇETİNTAŞ, Pharm (M.Sc.)

MARKETING AUTHORIZATION PROCEDURE

1. Department of Medicines Marketing Authorization
2. Marketing Authorization Process
3. Marketing Authorization - Numbers

LEGAL BASIS

Pharmaceutics and Medicinal Product Law

Law No: 1262 (Publication Date in the Official Gazette: May 26, 1928 / Issue No: 898)

«the competent authority for registering human medicinal products in Turkey, is Ministry of Health»

«any medicinal product can not be placed on the market, unless a marketing authorization has been issued by Ministry of Health of Turkey»

Presidential Decree No.4

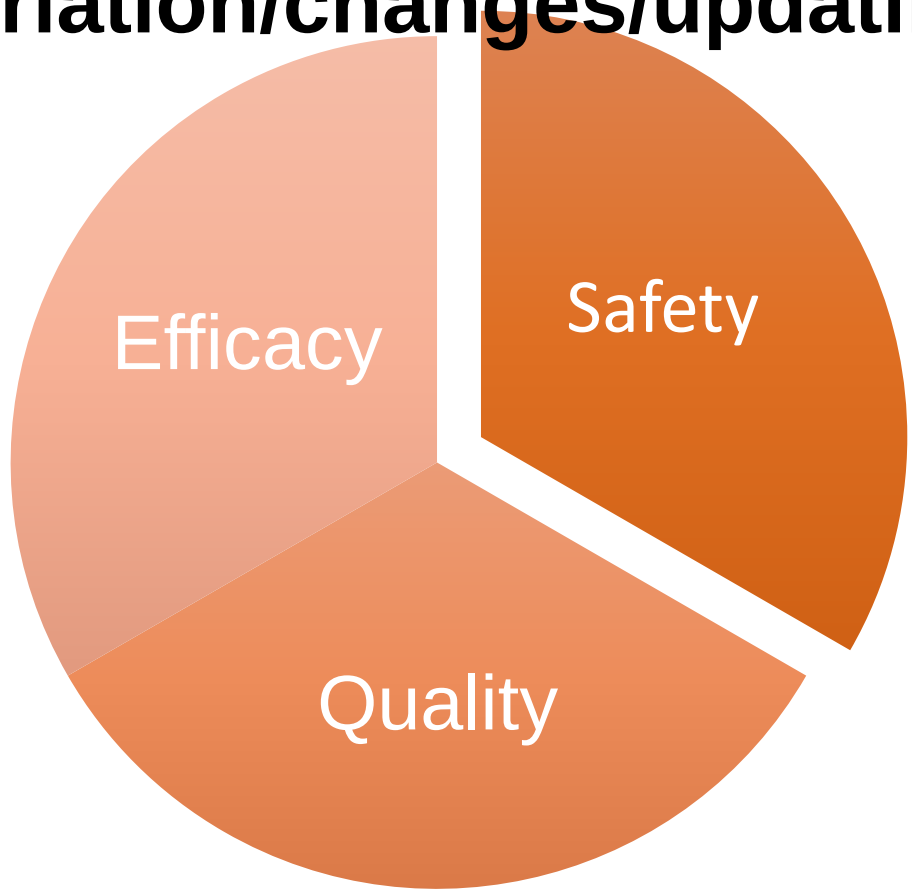
Publication Date in the Official Gazette: July 7, 2018 / Issue No: 30479

TITCK is an affiliated Agency with Ministry of Health.

Regulation on the Marketing Authorization of Medicinal Products for Human Use (Publication Date in the Official Gazette: January 19, 2005 / Issue No: 25705)

The registration transactions conducted by our Agency are performed in line with the provisions of the “Regulation on the Marketing Authorization of Medicinal Products for Human Use” which was regulated according to Directive 2001/83/EC, is the basic Regulation for Marketing Authorization.

Marketing authorization
Post-authorization variation/changes/updating



UNITS

CTD Pre-assesment

Clinical Assesment

Pre-authorization Quality Assesment

BA/BE Assesment

Pharmacological Assesment

Biologics/Biotechnological Products

Advanced Theraphy Products

Authorization

Authorization Control

Prioritization

Authorised Products Quality Assesment

Authorised Products

Coordination

Official Support

DEPARTMENT WORKFORCE

105
Pharmacist

8
Biologist

14
Others

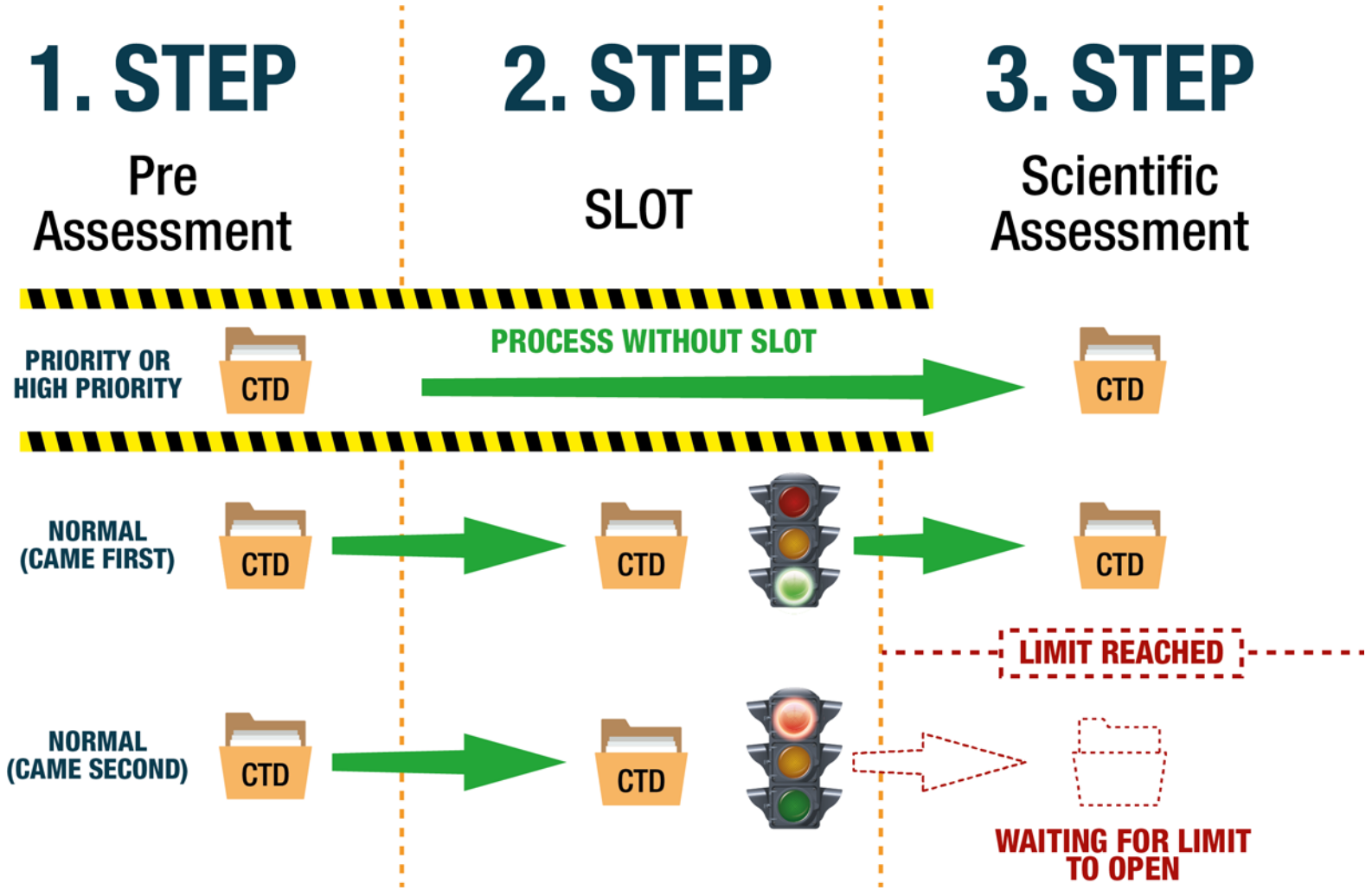
Total **127** Staff

68
Master Degree

15
PhD Degree

MARKETING AUTHORIZATION: AN OVERVIEW

SLOT IMPLEMENTATION



MARKETING AUTHORIZATION PROCESS / GMP Inspections

GMP PRIORITISATION APPLICATION → GMP INSPECTION → GMP CERTIFICATION

Conventional Products

GMP for finished product must be issued by TMMDA.

GMP for active substance it is acceptable approval of other authorities.

GMP 1 is only for finished product: Application is acceptable without GMP certification.

Biological and Biotechnological Products

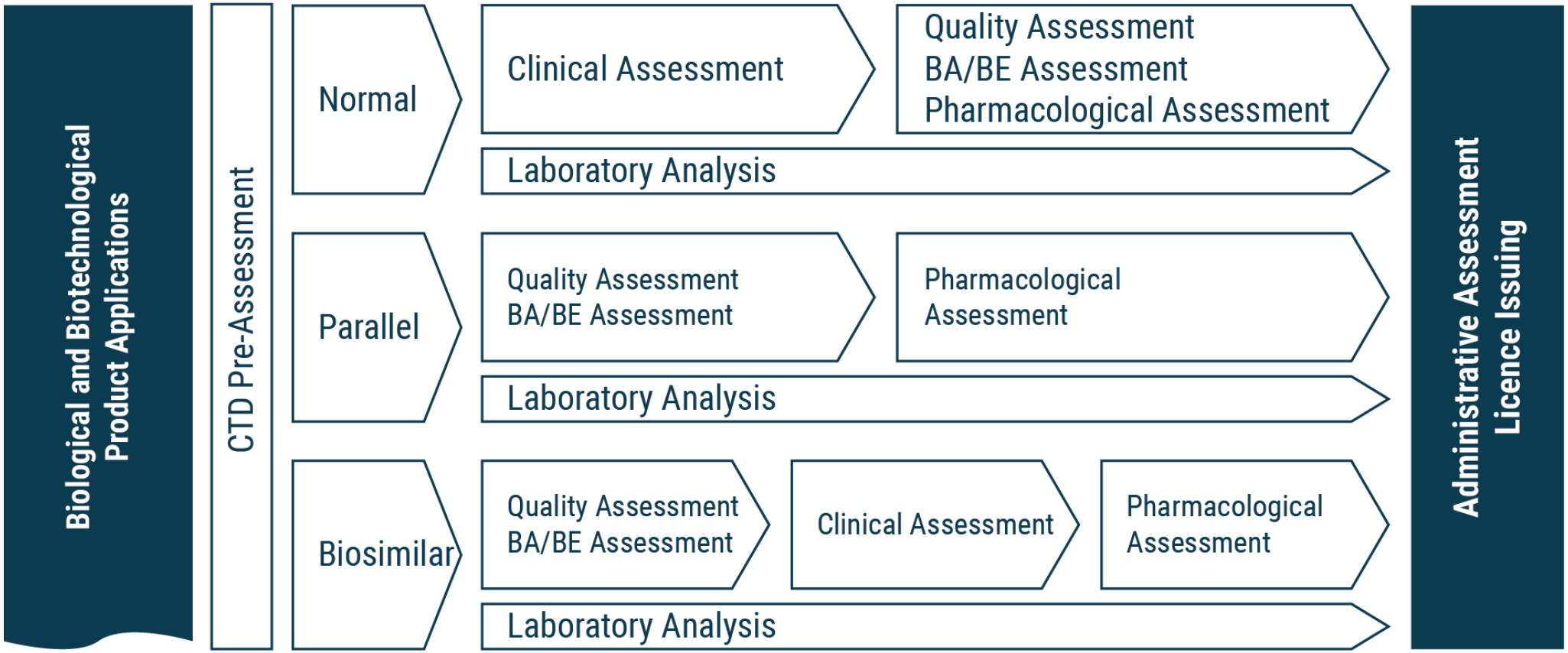
GMP for finished product and active substance must be issued by us.

GMP 1 is for finished product and active substance: Application is acceptable without GMP certification.

MARKETING AUTHORIZATION PROCESS / Pre-Assessment

- Pre-assessment contains, assessment of documents which are prepared accordingly Common Technical Documents (CTD) format, determined by International Conference of Harmonization (ICH) and an international standard.
- Registration applications are submitted in Common Technical Document (CTD) format since 2005 in Turkey.
- CTD applications have been accepted electronically since 2011.
- e-CTD transition studies are being carried out.

MARKETING AUTHORIZATION / Scientific Assesment



SCIENTIFIC ADVISORY COMMITEES

COMMISSIONS
(18 commissions,
64 of the 188 members are
from our Agency)

Clinical Assessment (1)
Technological Assessment (7)
Radiof./Radioopak Products Assessment (1)
Biological Products Assessment (2)
Biotechnological Products Assessment (2)
BA/BE Assessment (2)
Pharmacological Assessment (2)
Advanced Therapies Advisory (1)

INTERNAL COMMISSIONS
(3 commisions
12 members*)

Councils of Technological Assessment (2)
Council of Technological Assessment for Registered Products (1)

* Personnel of the Agency

COMMITEE MEMBERS - I

Agency	Total	Official Member	Alternate Member
Members	686	293	393
External Members	543	219	324
Internal Members	143	74	69

MA Department	Total	Official Member	Alternate Member
Members	371	182	189
External Members	274	118	156
Internal Members	97	64	33

COMMITEE MEMBERS - II

	Official Member	Expertise Area
Biotechnology-1	11	Analytical chemistry Pharmaceutical technology Molecular biologist Pharmacognosy
Biotechnology-2	9	Analytical chemistry Pharmaceutical technology Molecular biologist Pharmaceutical biotechnology

PRIORITISATION

According to the importance with regards to public health and public finance, innovation

R & D	Public Health
Biosimilar	Local Production
Innovator	For Export Purposes
Vaccine	Products Bringing from Abroad
First Generic	Import Permission
Strategic Importance	

PRIORITISATION - BIOSIMILARS

Evaluation criteria for biosimilar prioritization applications:

- ✓ Any clinical studies conducted in Turkey?
- ✓ Any localization plan in Turkey?
- ✓ Discount rate, any public financial advantage?

High priority		Priority		Normal	
2017	2018	2017	2018	2017	2018
6	2	9	2	20	1

* MA Priority

NUMBERS (2017 - 2018)

		Applications		Approvals	
		2017	2018	2017	2018
Biological / Biotechnological	Imported	36 (15*)	38 (17*)	30 (2*)	42 (5*)
	Local	1 (1*)	3 (3*)	0	5*
	Total	**37**	**41**	**30**	**47**

* Biosimilar Product

SmPC & PL

SmPC and PL texts of biosimilar products are same as the original product except product specific information and statements specific to biosimilars.

Statements specific to biosimilars to be included in SmPC and PL:

a. Inclusion of statement that the active ingredient is a biosimilar into qualitative and quantitave composition section and section 5.1

Active ingredient: *… (Insulin glargine), is a biosimilar produced by recombinant DNA technology in Escherichia coli.*

5.1 Pharmacodynamic properties

… is a biosimilar product.

b. Inclusion of information about potential immunogenicity (SmPC 4.4 special warnings and precautions for use section, PL special care section)

As with all other therapeutic proteins immunogenicity risk for X is present.

c. Inclusion of the necessary statement to monitor the medicine and follow the adverse reaction (SmPC 4.4 special warnings and precautions for use section, PL special care section)

In order to track biosimilar products trademark and lot number of the product administered must be registered to patient dossier.

INTERCHANGEABILITY & SUBSTITUTION

TITCK is responsible for marketing authorization and pricing human medicinal products. The Social Security Institution (SSI) is responsible for reimbursement.

TITICK has not any official position paper etc. On interchangeability, switching, and substitution

In practise/practicioner level/ pharmacy level

KAMAG PROJECTS

Project title	Active ingredient
Local development and manufacturing of biosimilar products	Ranibizumab
Project of development and manufacturing of biosimilar product with active ingredient setuximab	Cetuximab
Development and manufacturing of biosimilar product with monoclonal antibody for cancer and osteoporisis treatment	Denosumab
Development and manufacturing of biosimilar product with active ingredient bevacizumab	Bevacizumab

WORK IN PROGRESS

1. Regulation on the Registration of Medicinal Products for Human Use
2. **Guideline on Biosimilar Medicinal Products**
3. Regulation and Guideline on Variations in Registered Medicinal Products for Human Use
4. Guideline on the Examination of Bioavailability and Bioequivalence of Medicinal Products for Human Use
5. Guideline on Scientific Advice
6. Guideline on Allergen Products
7. Guideline on Advanced Therapy Medicinal Products

USEFUL LINKS

Authorised products list
(http://www.titck.gov.tr/RuhsatliUrunlerListesi)

Substance list
(http://www.titck.gov.tr/EtkinMaddeListesi)

Legislations
(http://www.titck.gov.tr/Mevzuat/Y%C3%B6netmelik)

Draft guidelines/legislations
(http://www.titck.gov.tr/Mevzuat)

FUTURE PLANS

ICH
harmonisation for better health

World Health Organization

CIRS CENTRE FOR INNOVATION IN REGULATORY SCIENCE

INTERNATIONAL PUBLICATIONS

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 25 January 2018
doi: 10.3389/fphar.2018.00009

The Turkish Medicines and Medical Devices Agency: Comparison of Its Registration Process with Australia, Canada, Saudi Arabia, and Singapore

*Emel Mashaki Ceyhan[1,2], Hakki Gürsöz[3], Ali Alkan[3], Hacer Coşkun[3], Oğuzhan Koyuncu[3] and Stuart Walker[1,2]**

[1] Centre for Innovation in Regulatory Science, London, United Kingdom, [2] School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Cardiff, United Kingdom, [3] Turkish Medicines and Medical Devices Agency, Ankara, Turkey

Introduction: Regulatory agency comparisons can be of more value and facilitate improvements if conducted among countries with common challenges and similar health agency characteristics. A study was conducted to compare the registration review model used by the Turkish Medicines and Medical Devices Agency (Türkiye Ilaç ve Tibbi Cihaz Kurumu; TITCK) with those of four similar-sized regulatory agencies to identify areas of strength and those requiring further improvement within the TITCK in relation to the review process as well as to assess the level of adherence to good review practices (GRevP) in order to facilitate the TITCK progress toward agency goals.

Methods: A questionnaire was completed and validated by the TITCK to collect data related to agency organizational structure, regulatory review process and decision-making practices. Similar questionnaires were completed and validated by Australia's Therapeutic Goods Administration (TGA), Health Canada, Singapore's Health Science Authority (HSA), and the Saudi Arabia Food and Drug Administration (SFDA).

Results: The TITCK performs a full review for all new active substance (NAS) applications. Submission of a Certificate of Pharmaceutical product (CPP) with an application is not required; however, evidence of approval in another country is required for final authorization by the TITCK. Pricing data are not required by the TITCK at the time of submission; however, pricing must be completed to enable products to be commercially available. Mean approval times at the TITCK exceeded the agency's overall target time suggesting room for improved performance, consistency, and process predictability. Measures of GRevP are in place, but the implementation by the TITCK is not currently formalized.

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Edited by:
Claudio Bucolo, Università degli Studi di Catania, Italy

Reviewed by:
Lucia Gozzo, Policlinico Universitario di Catania, Italy
Lise Aagaard, Bech-Bruun, Denmark

***Correspondence:**
Stuart Walker
swalker@cirsci.org

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Mashaki Ceyhan E, Gürsöz H, Alkan A, Coşkun H, Koyuncu O and Walker S

Quality, Non-clinical and Clinical Considerations for Biosimilar Monoclonal Antibody Development: EU, WHO, USA, Canada, and BRICS-TM Regulatory Guidelines

Hasumati Rahalkar[1,2], Hacer Coskun Cetintas[3] and Sam Salek[1]*

[1] School of Life and Medical Sciences, University of Hertfordshire, Hatfield, United Kingdom, [2] Department of Regulatory Sciences, Metina PharmConsulting Pvt Ltd, Mumbai, India, [3] Department of Marketing Authorization of Medicines, Turkish Medicines and Medical Devices Agency, Ankara, Turkey

Objective: The aim was to critically evaluate well-established regulatory agencies mAb biosimilar guidelines for development and marketing authorization about quality, efficacy and safety and compare to BRICS-TM regulations to identify challenges.

Materials and Methods: The current valid guidelines of EMA, WHO, USFDA, BGTD/HC, ICH, and BRICS-TM were obtained from official websites and comparative qualitative review was performed.

Results: The review revealed that Health Canada uses mAb specific guidelines from EMA or USFDA when necessary. The BRICS agencies (except Russia) have incorporated some or most of the WHO SBP TRS and related annexes in similar national biotechnological/biological guidelines; however, gaps or insufficient information have been identified. The Russian Federation has issued general product registration guideline/s with very brief information about mAbs. The TMMDA (Turkey) has published an updated biosimilar guideline which parallels those of the EMA and the ones from WHO; however, no mAb specific guidelines are published. COFEPRIS (Mexico) has published a biotechnological/biological product registration guideline with no information about mAb. The SAHPRA biosimilar guideline has an annex on mAbs which focuses on non-clinical and clinical aspects.

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Edited by:
Jean-Paul Desiypere, Besins Healthcare, Thailand

Reviewed by:
Kuo-Wei Chan, Independent researcher, Belgium
Suyash Prasad, ntes Therapeutics, United States

***Correspondence:**
Hasumati Rahalkar
nati@metinapharmconsulting.com

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REPUBLIC OF TURKEY
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TURKISH MEDICINES AND
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www.titck.gov.tr | hacer.coskun@titck.gov.tr | Tel: +90 312 218 3000