Çisem Başak Budak, Turkey

- TITCK (Turkish Medicines and Medical Devices Agency), Medicinal Product Registration Department, Ministry of Health of the Republic of Turkey

GaBI Educational Workshops

First Turkish Interactive Workshop on Regulation and Approval of
SIMILAR BIOTHERAPEUTIC PRODUCTS/BIOSIMILARS

2–3 March 2016, Hacettepe University, Ankara, Turkey

Current regulatory approval standard and practice on biosimilars – Turkey

Çisem Başak Budak

3 March 2016

GaBI
GENERICS AND BIOSIMILARS INITIATIVE
Building trust in cost-effective treatments

HACETTEPE UNIVERSITY
PPCI
Pro Pharma Communications International

CURRENT REGULATORY APPROVAL STANDARDS AND PRACTICES ON BIOSIMILARS IN TURKEY

Çisem Başak BUDAK, Pharm, MSc.
Turkish Medicines and Medical Devices Agency
Medicinal Product Registration Department
2016

T.C. Sağlık Bakanlığı

Presentation Plan

1. Legal Basis
2. Organisation
3. Biosimilars
4. Registration Process
5. Numbers
6. Superior Policy Documents & Perspectives

Legal Basis

Pharmaceutical And Medical Preparations Law

(Law No : 1262 (Publication Date 26th May, 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»

Decree No. 663 of 2011

«Ministry of Health uses this authority with Turkish Medicines and Medical Devices Agency (TMMDA/TİTCK), which is affiliated to Ministry of Health.»

Regulation on the Registration of Medicinal Products for Human Use

(January 19, 2005 / Issue No.25705)

These regulations are in parallel to the directive of European Comission with issue number 2001/83.

Guidance Document on Biosimilar Products

(07.08.2008/5285)

TİTCK

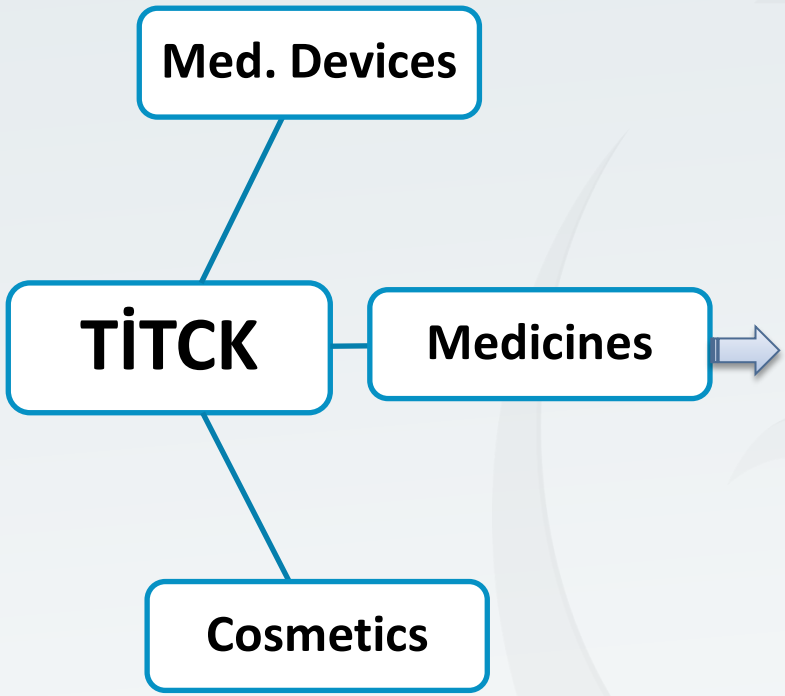
Mission:

To serve human health by developing and implementing regulatory, supervisory, and guidance policies in regard to pharmaceuticals, medical devices and cosmetic products.

Vision:

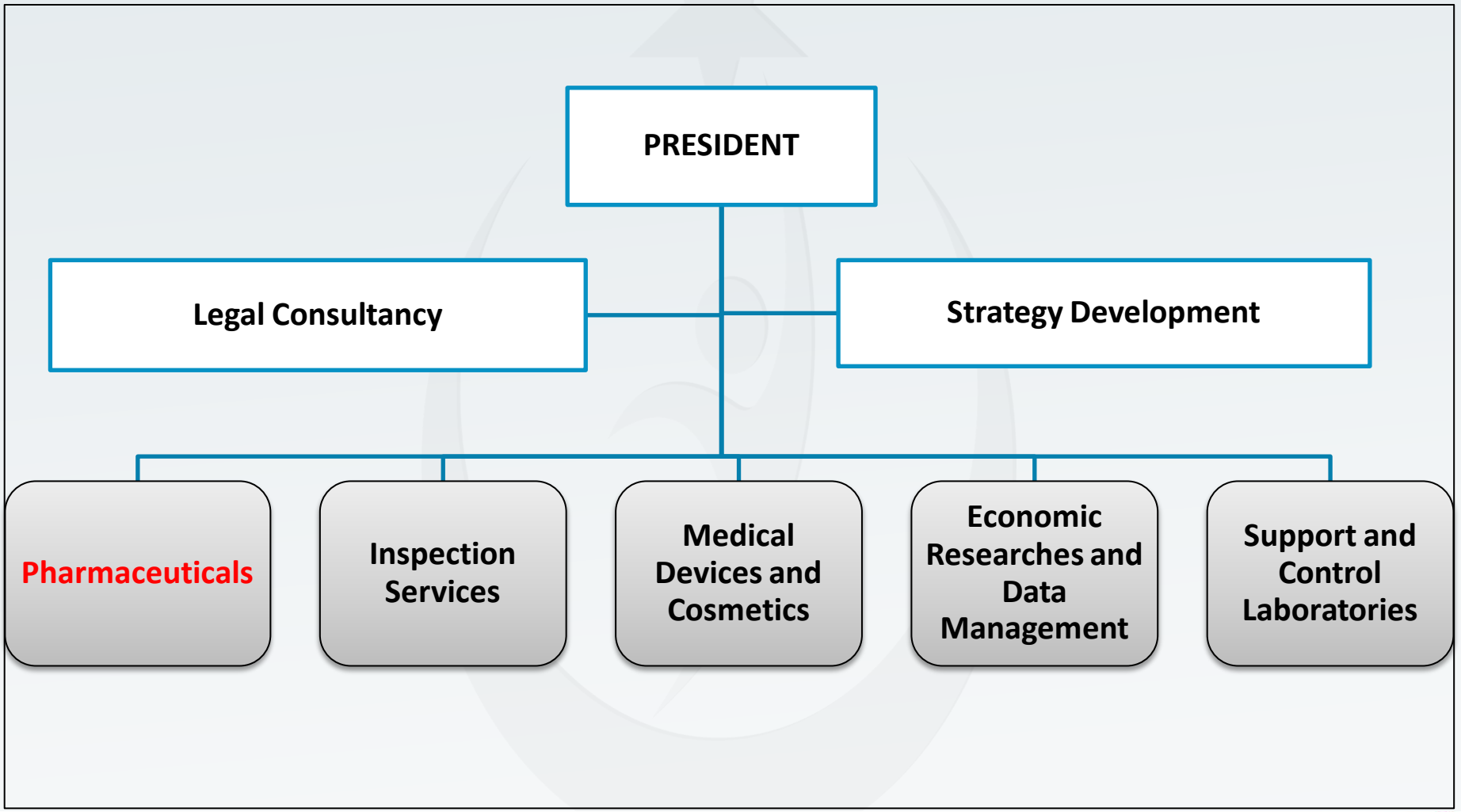
Being a pioneer and a reference institution in the international arena aiming for excellence, on the basis of health and science.

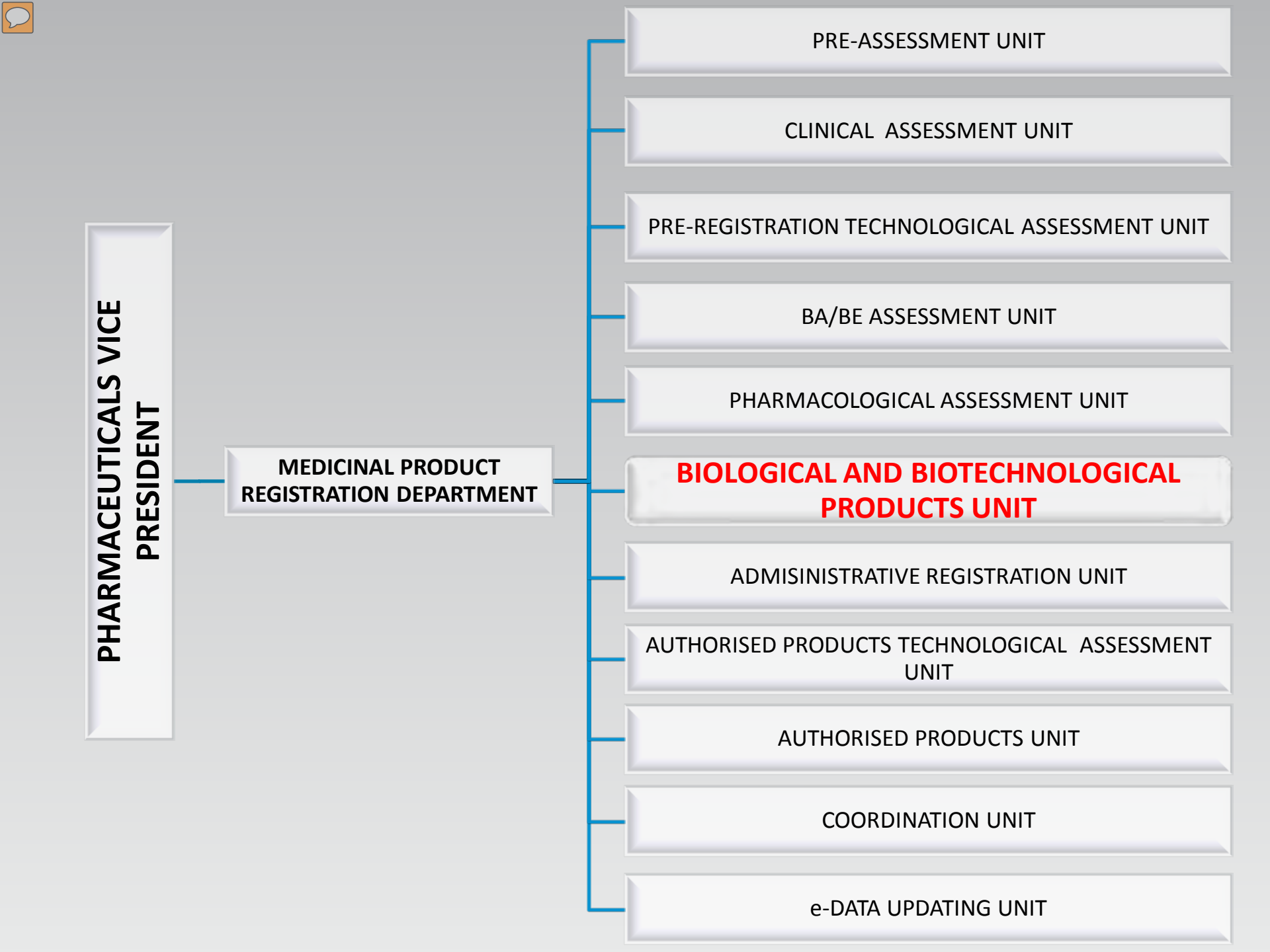
Tasks



- *Pharmaceutical product licensing*
- *Monitoring all phases of the supply chain*
- *Monitoring availability of pharmaceutical products in the market*
- *Providing patient access to medicines especially for life-saving conditions*
- *Preparing of Turkish Pharmacopeia*
- *Regulating and monitoring clinical studies*
- *Pharmacovigilance activities*
- *Pricing*

Organisation Chart




PHARMACEUTICALS VICE PRESIDENT
MEDICINAL PRODUCT REGISTRATION DEPARTMENT
PRE-ASSESSMENT UNIT
CLINICAL ASSESSMENT UNIT
PRE-REGISTRATION TECHNOLOGICAL ASSESSMENT UNIT
BA/BE ASSESSMENT UNIT
PHARMACOLOGICAL ASSESSMENT UNIT
BIOLOGICAL AND BIOTECHNOLOGICAL PRODUCTS UNIT
ADMISINISTRATIVE REGISTRATION UNIT
AUTHORISED PRODUCTS TECHNOLOGICAL ASSESSMENT UNIT
AUTHORISED PRODUCTS UNIT
COORDINATION UNIT
e-DATA UPDATING UNIT

Biosimilars

A Biosimilar product is a medicinal product which demonstrates similarity to a designated or retained reference biological product in terms of quality, safety and efficacy.

- The active substance of a biosimilar product is similar to a biological reference drug. (generally, same strength, indication, pharmaceutical form and route of administration)

- At first view, the trade name, appearance and labeling/packaging features can be considered as the only difference between a biosimilar drug and a biological product, but there are other allowable differences because the origin of these products is living organisms.

Biological Reference Product is a product which is registered with complete dossier including administrative, quality, pre-clinical and clinical data.

- Applicant must submit an “abridged” application which must demonstrate that there are no significant differences between the biosimilar product and a reference product in terms of quality, safety and efficacy .

- The standard generic approach is not appropriate in biosimilar products.

Biosimilars vs. Generics and New Products

	Classic Bioequivalent Products	Biosimilar Products	New Products (Full File)
Quality	✓ Comparison of Complete and Independent Product File Information with reference product	✓ Comprehensive comparison of Complete and Independent Product File Information with reference product	✓ Complete and Independent Product File Information
Pre-clinical	…….	✓ Abridged program, ✓ Subchronic toxicity studies according to complexity of molecule (4 weeks), ✓ Local tolerance, ✓ PK/PD studies	✓ Pre-Clinical Complete Studies
Clinical	✓ Bioequivalence studies	✓ Phase I; PK/PD studies ✓ No need for Phase II study ✓ Phase III study for each indication (If necessary) ✓ Risk Management Plan	✓ Phase I ✓ Phase II ✓ Phase III study in all indications ✓ Risk Management Plan

Registration Process

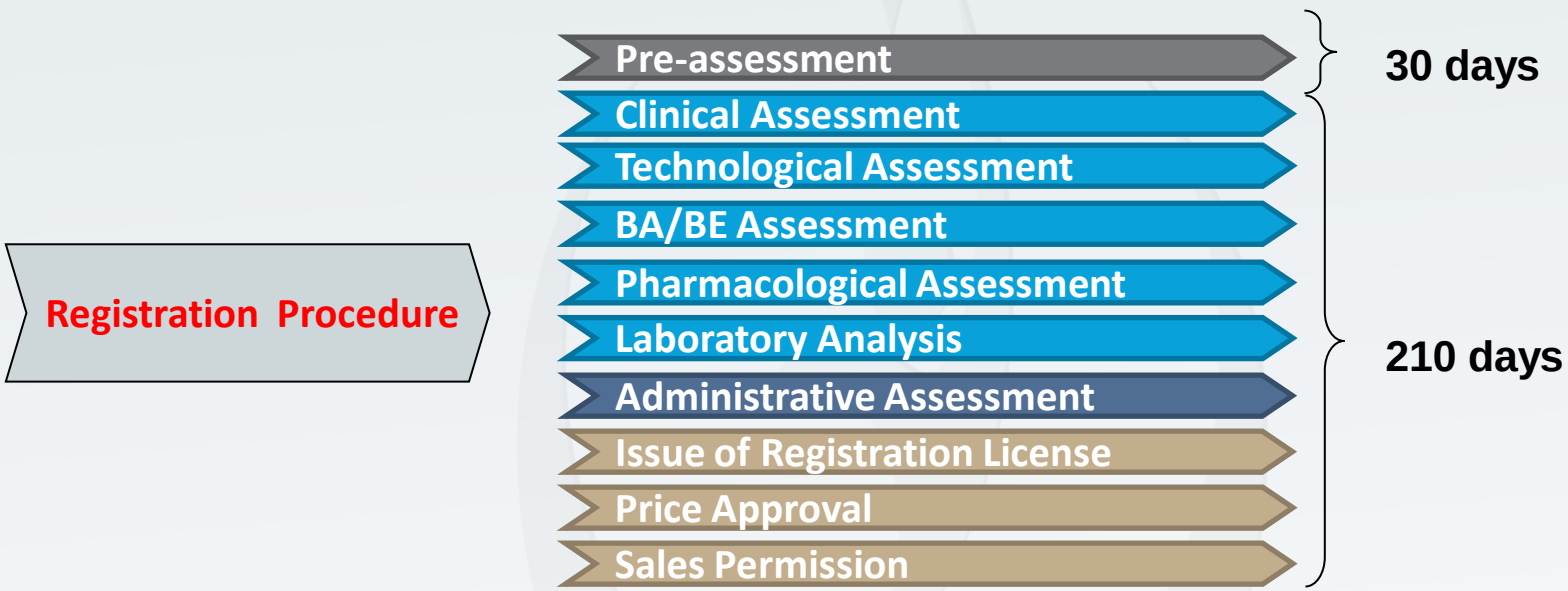
GMP Inspections

- Application for Inspection
- GMP Incpection
- Issue of GMP Certificate

Registration Procedure

- Pre-assessment
- Clinical Assessment
- Technological Assessment
- BA/BE Assessment
- Pharmacological Assessment
- Laboratory Analysis
- Administrative Assessment
- Issue of Registration License
- Price Approval
- Sales Permission

Timetable


Registration Procedure
Pre-assessment
Clinical Assessment
Technological Assessment
BA/BE Assessment
Pharmacological Assessment
Laboratory Analysis
Administrative Assessment
Issue of Registration License
Price Approval
Sales Permission
30 days
210 days

But;

If the product

- is first in treatment and diagnosis
- reduce the public expenditures
- is immediately required for public healthcare

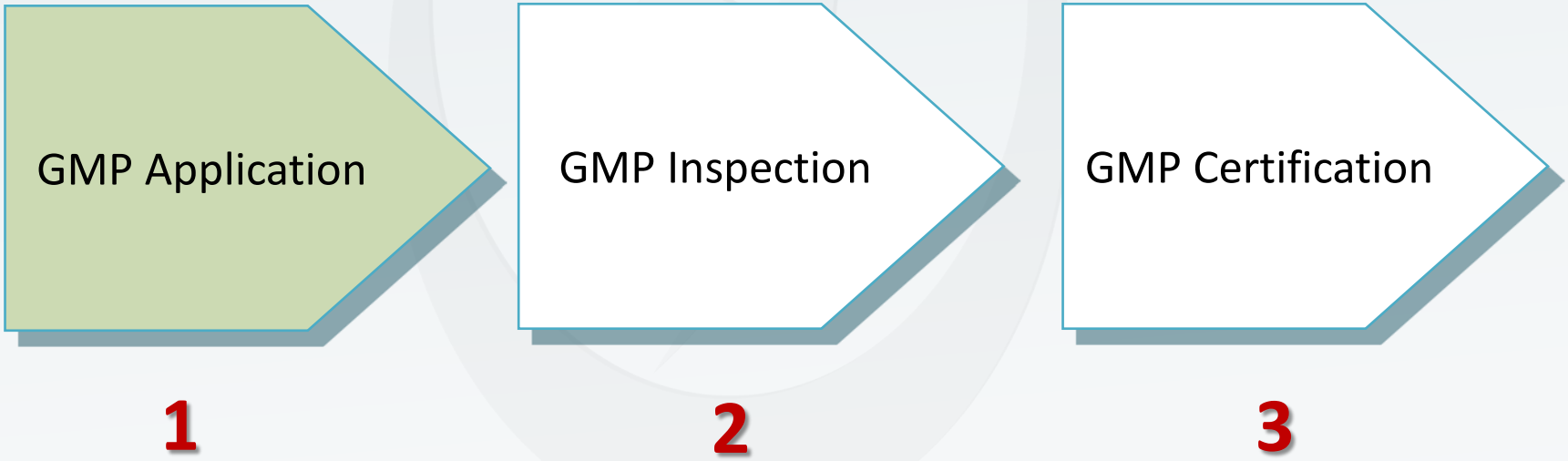
The process shall be completed in 180 days.

If the product is a part of co-marketing, the process shall be completed in 90 days.

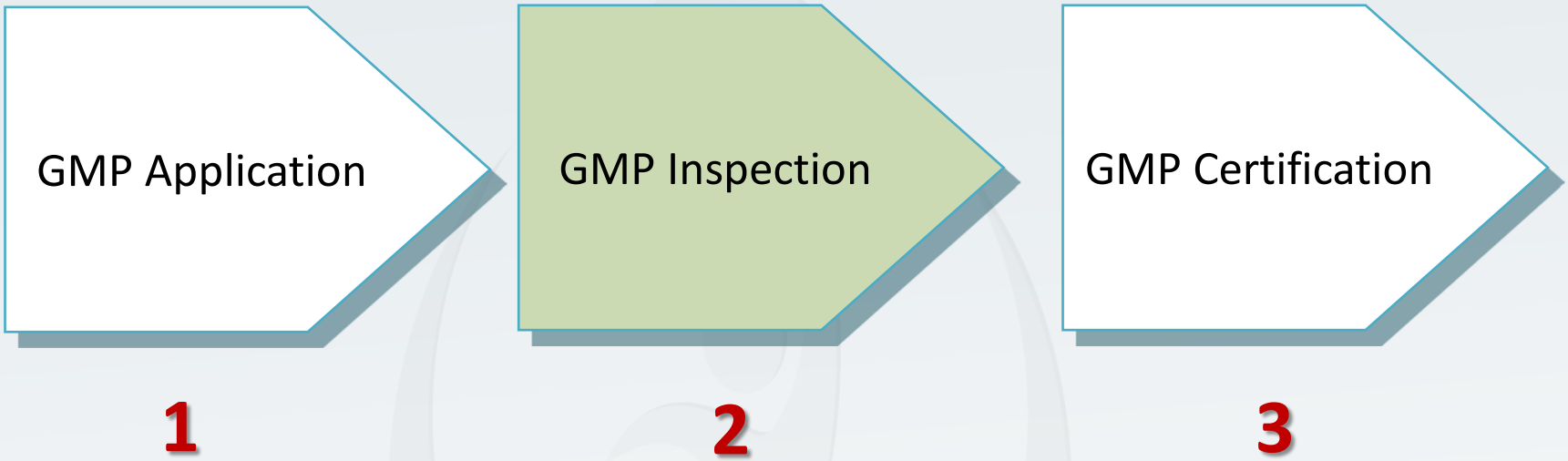
GMP Inspections

Finished product and API manufacturing site must have a valid **GMP certificate issued by the Agency**.

- ✓ The applicant have to make an application to the Agency for GMP inspection and submit the relevant data in a dossier.



GMP Inspection Process



- Guidance on The Good Manufacturing Practices For Pharmaceutical Products

« If the manufacturing facility of active substance and the finished product are different from each other, both of them must be inspected by the Agency. »

GMP Inspection Process

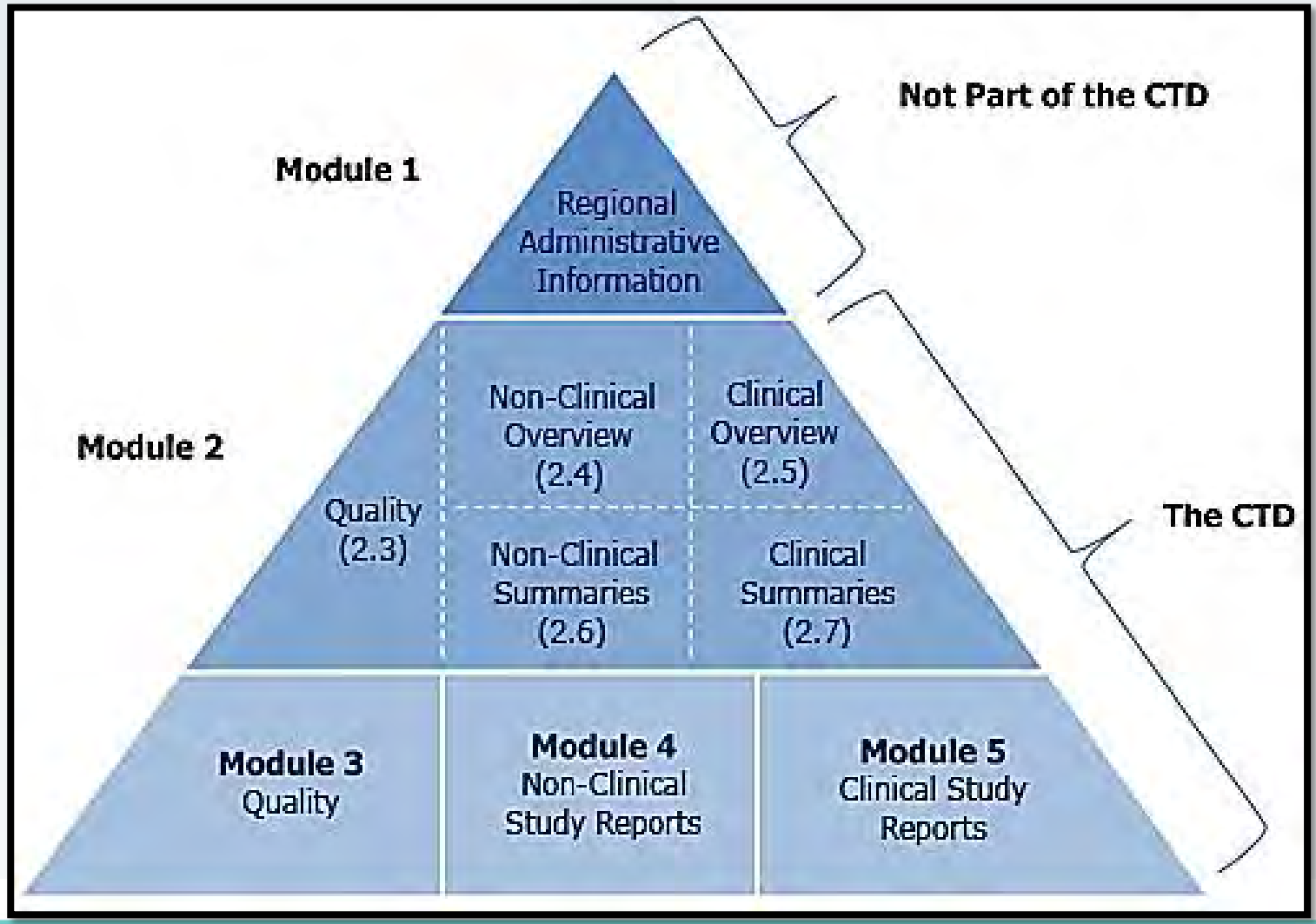
❑ For registration of biological and biotechnological products having a GMP Certificate is an obligation.

Pre-Assessment

- Pre-assessment contains formal control of documents.

- The application dossier shall be prepared accordingly Common Technical Documents (CTD) format which is determined by International Conference on Harmonization (ICH) and is an international standard.

Pre- Assessment



Scientific Assessment

- Scientific assessment contains the assessment of application by committees which consist of academicians, clinicians and senior agency personnel.

- Committees assess the application, in terms of efficacy, quality and safety.

Scientific Assessment

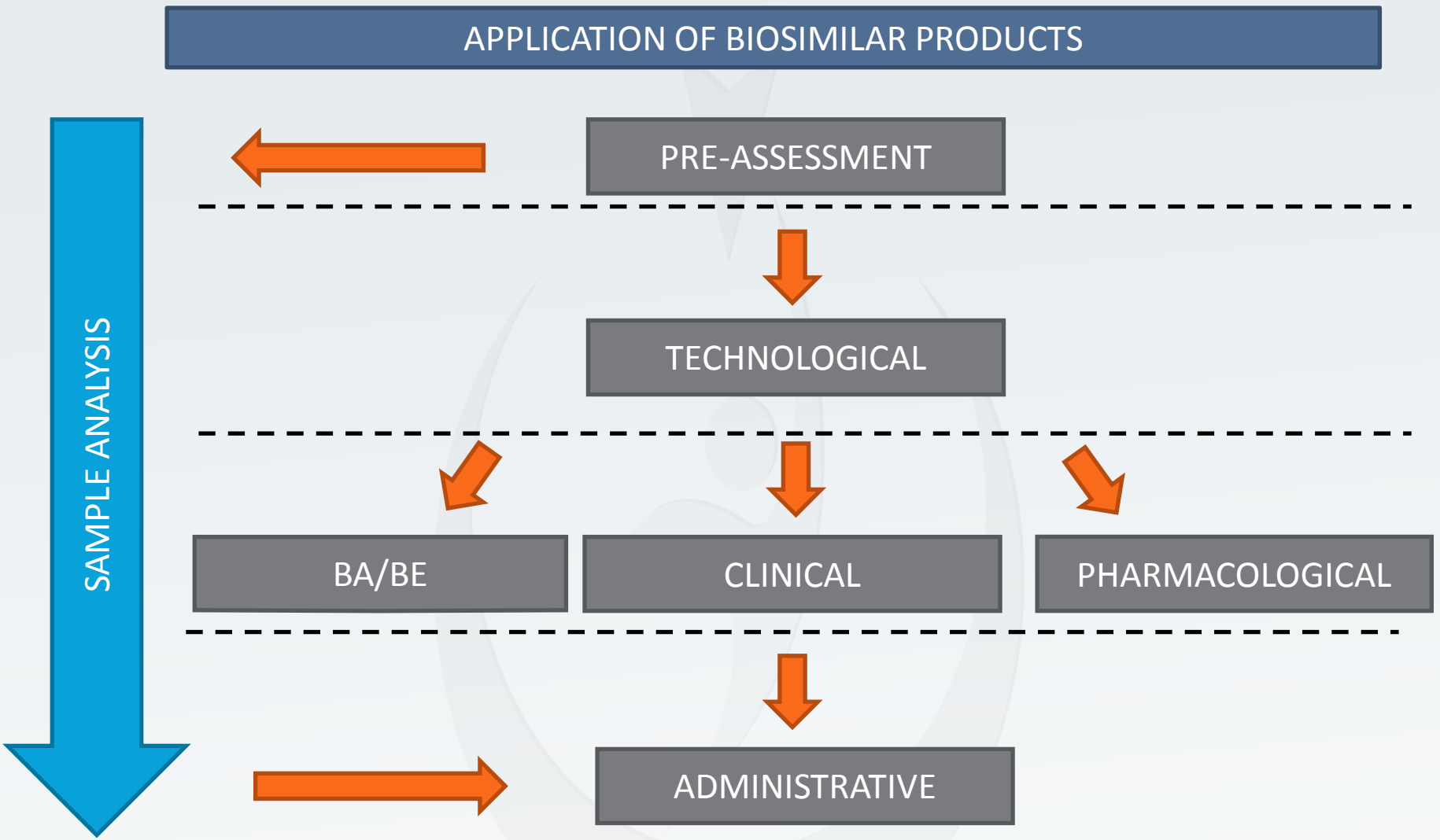
Committees

- Clinical Assessment Committee: (Mostly clinicians)
- Technological Assessment Committee
- BA/BE Assessment Committee
- Biological Products Committee
- Biotechnological Products Committee
- Pharmacological Assessment Committee

Administrative Assessment

- Administrative assessment contains a final assessment about SPC/PIL, labeling/packaging and last checking of documents and Committee decisions.

- Quality and Administrative Assessment is considering in Biological and Biotechnological Products Unit together.


APPLICATION OF BIOSIMILAR PRODUCTS
PRE-ASSESSMENT
TECHNOLOGICAL
BA/BE
CLINICAL
PHARMACOLOGICAL
ADMINISTRATIVE
SAMPLE ANALYSIS

Numbers

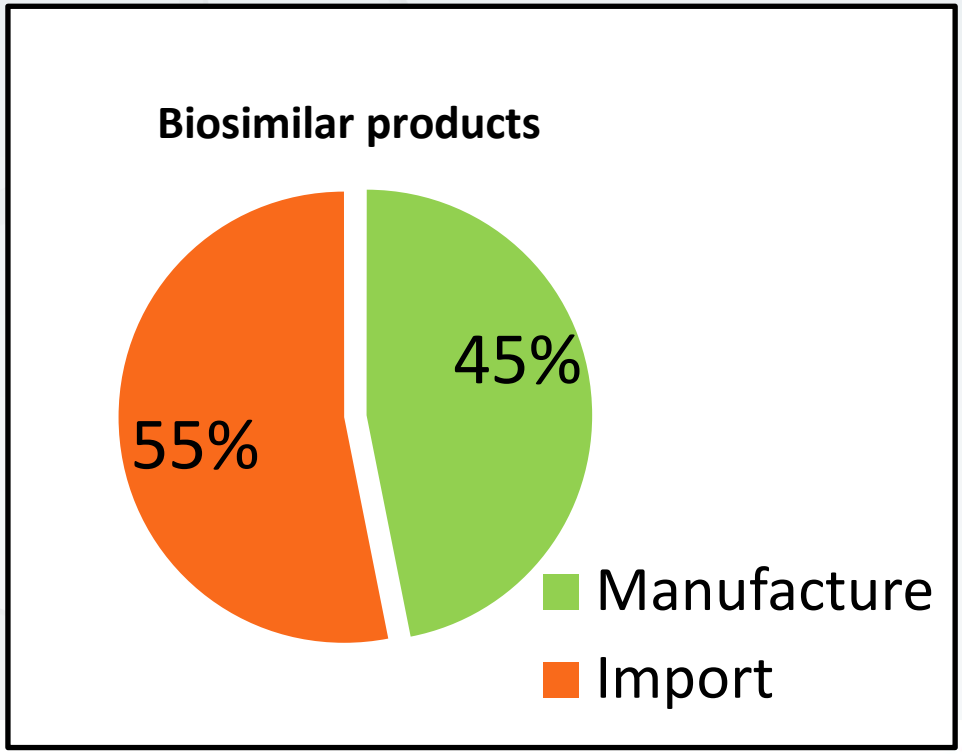
Registered Biosimilar Products

Turkey currently has **262** registered biotechnological products with their different strengths. **29** of them are biosimiliars.

29 Biosimilar

16 Imported

13 Manufactured in **Turkey**



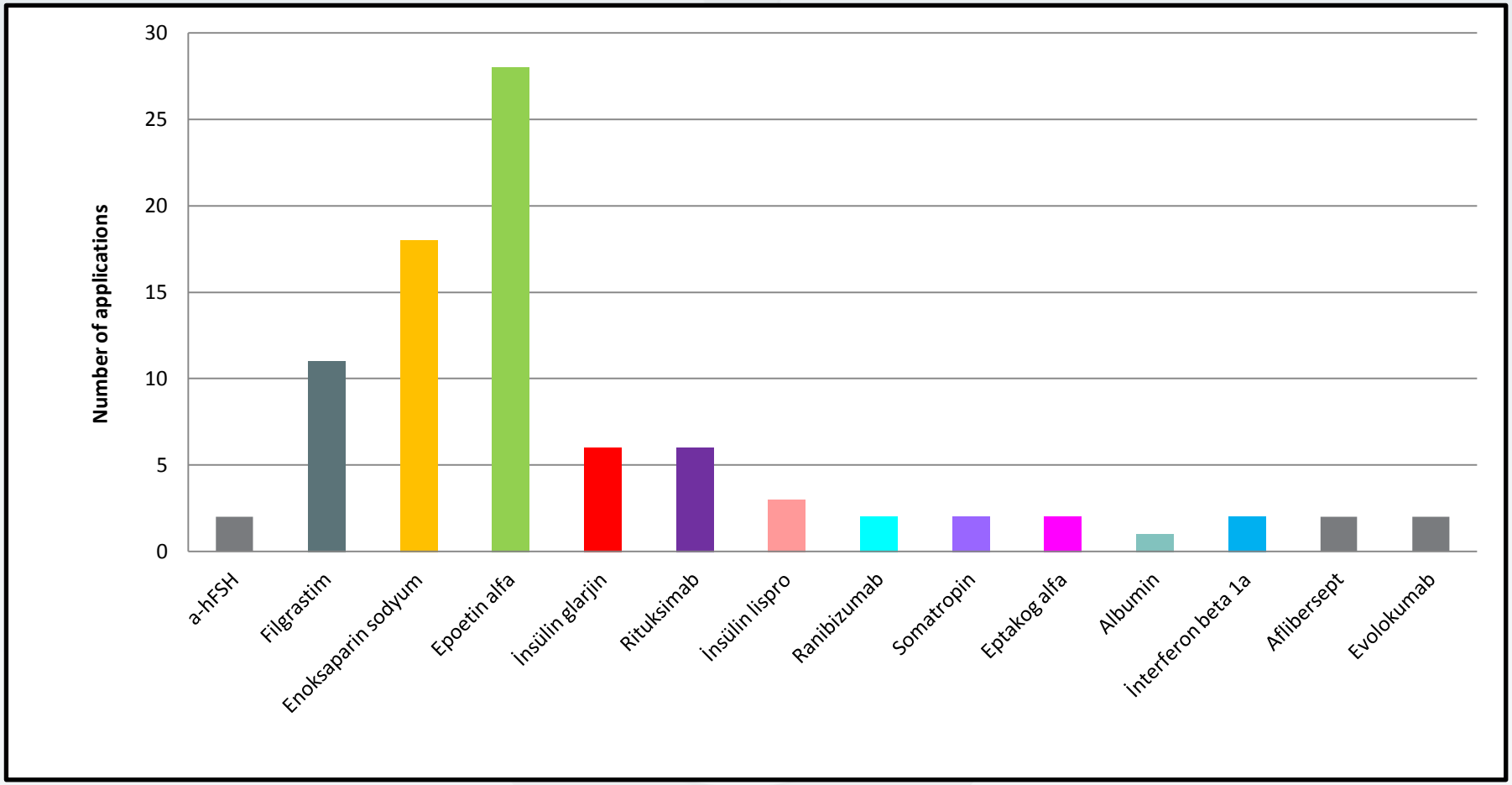
Sağlık Bakanlığı

Registered Biosimilar Products

Name of Product	Active Ingredient	Manufactured in	Registration Year
Tevagrastim (2)*	Filgrastim	Mexico	2015
Remsima	İnfliximab	Turkey	2015
Dropoetin (3)*	Epoetin alfa	Turkey	2013
Enox (5)*	Enoxaparin sodium	Turkey	2013
Epoplus (2)*	Epoetin alfa	Cuba	2013-2015**
Leukoplus	Filgrastim	Cuba	2014
Oksapar (6)*	Enoxaparin sodium	Turkey	2012-2013**
Omnitrope (2)*	Somatropin	Austria	2011
Eporon (3)*	Epoetin alfa	South Korea	2011
Epobel (5)*	Epoetin zeta	Germany	2009
Leucostim (2)*	Filgrastim	South Korea	2009

* The number next to product shows different strenghts of product
** The 1.dosage of Epoplus was licensed in 2013, while 2. dosage was licensed in 2015
** 4 dosage of Oksapar were licensed in 2012 while 2 dosages were licensed in 2013

Biosimilar products applications which are in registration process



For 87 different Biosimilar products license applications have been made and are being evaluated.

Superior Policy Documents

1. 10th Development Plan
   - Healthcare Related Industries Structural Transformation Program

2. Turkey Biotechnology Strategy And Action Plan (2015-2018)

3. Turkey Medicine Sector Strategy Certificate And Action Plan (2015-2018)

4. National Biotechnology R-d And Innovation Strategy Certificate And Action Plan(2015-2019) - Draft

10th Development Plan

In the **10th Development Plan - Healthcare Related Industries Structural Transformation Program** approved by **Higher Projection Council** on 16 February 2015. There are 4 components and the program covers all of them.

Healthcare Related Industries Structural Transformation Program

Components of the Program / Component Liables

1. Strengthening of the Public Guidance Capacity / *Ministry of Health*

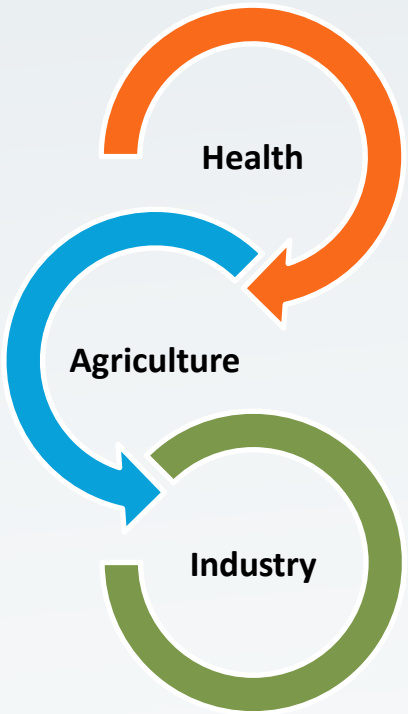
2. Improving R-D and Innovation Area / *Ministry of Science, Industry and Technology*

3. Improving Work and Enterprise Ecosystem / *Ministry of Science, Industry and Technology*

4. Supporting Production and Exports / *Ministry of Economy*

Turkey Biotechnology Strategy And Action Plan (2015-2018)

Main Biotechnology Implementation areas



Aim:

Increasing the technological knowledge and the value-added production and becoming one of the world's leading countries in the Biotechnology area.

Making our county, a center in the Biotechnology area, that can produce technology, that is innovative, with high value-added and **is able to manufacture products within the norms of global competition.**

Turkey Medicine Sector Strategy Certificate And Action Plan (2015-2018)

Aim:

Taking into account Turkey's targets in it's industrial perspective, the action plan is prepared in order to support the government's public health and development targets, to form a sustainable and effective structure for the medicinal sector of our country.

Medicinal Sector Strategy and Action Plan consists of five main sections:

- Current status of the medicinal sector
- A status analysis made together by the partners that took role in preparing the strategy
- Medicinal sector perspective, main aim and targets decided by all the partners
- Implementation, monitoring and evaluation
- Action plan

National Biotechnology R-d And Innovation Strategy Certificate And Action Plan(2015-2019)

National Biotechnology R-d And Innovation Strategy Certificate And Action Plan(2015-2019) draft has been published by the Turkish Republic, Science, Industry and Technology Ministry and studies are continuing.

What is our goal as TİTCK ?

The most commonly used biological - biotechnological products are diabetes (insulins) products, which are placed on the top, antineoplastic, immunosuppressants and immunostimulatory products follow them respectively.

According to the current datas; biotechnological products constitutes approximately 20% of the world medicine market and it is estimated the percentage will continue to increase in the near future.

The Turkey Medicinal Product Market is the 17th biggest market in the World and in the frame of all the strategy and action plans our target as a regulatory authority to carry Turkey one step further in the market by revising our legislations, approval standards and practice according to international and scientific standards in line with EU Harmonization Process.

Thank you

Teşekkürler

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