BIOASSAY CHALLENGES EXPERIENCED IN THE PORTUGUESE OMCL

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INFARMED, I.P. (LISBON)

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3 -5 NOVEMBER 2020

REPÚBLICA PORTUGUESA
SAÚDE

SNS SERVIÇO NACIONAL DE SAÚDE

Infarmed
Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.

DISCLAIMER

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are possibly those of the individual presenter and

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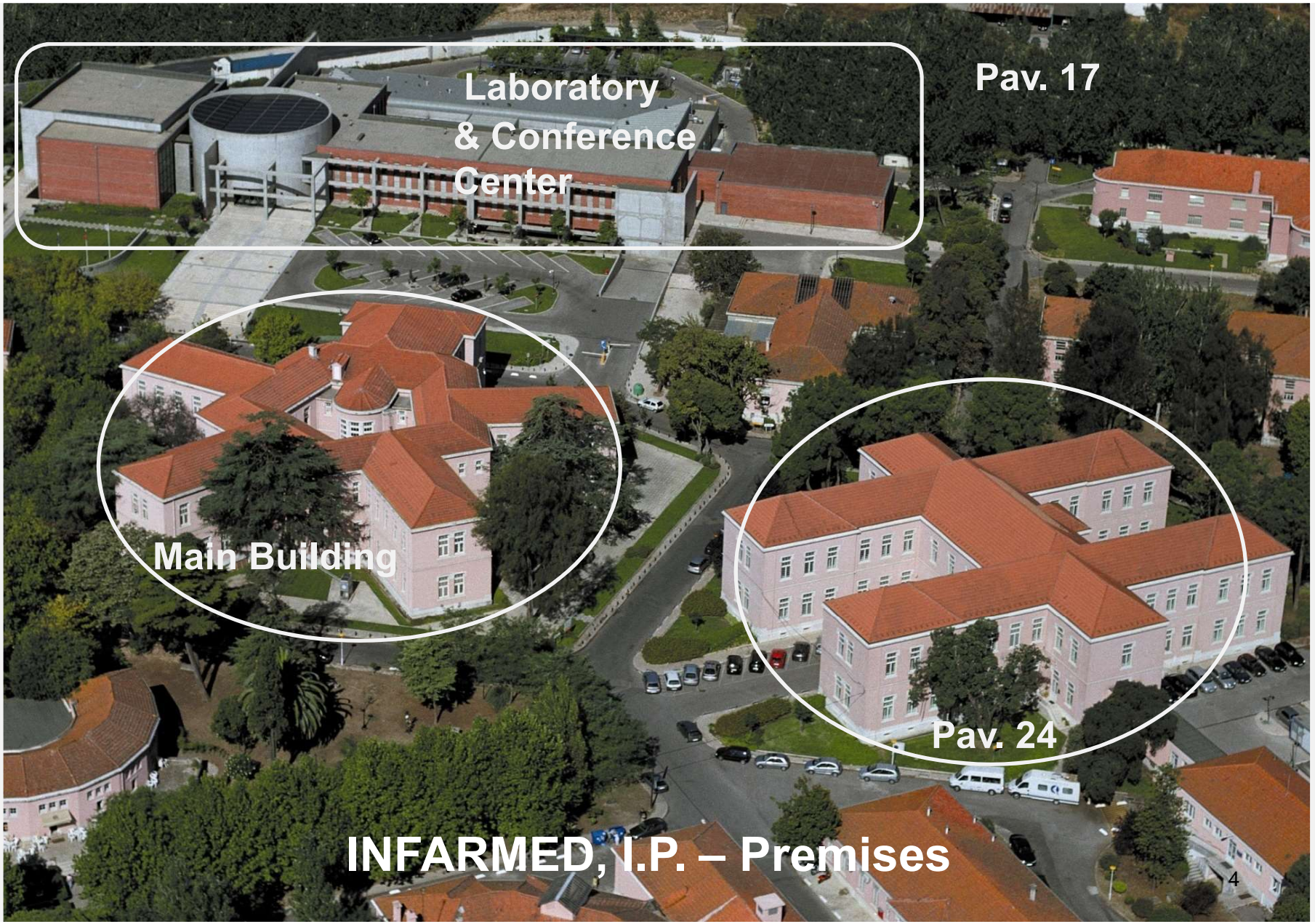
OUTLINE



INFARMED, I.P. – Premises

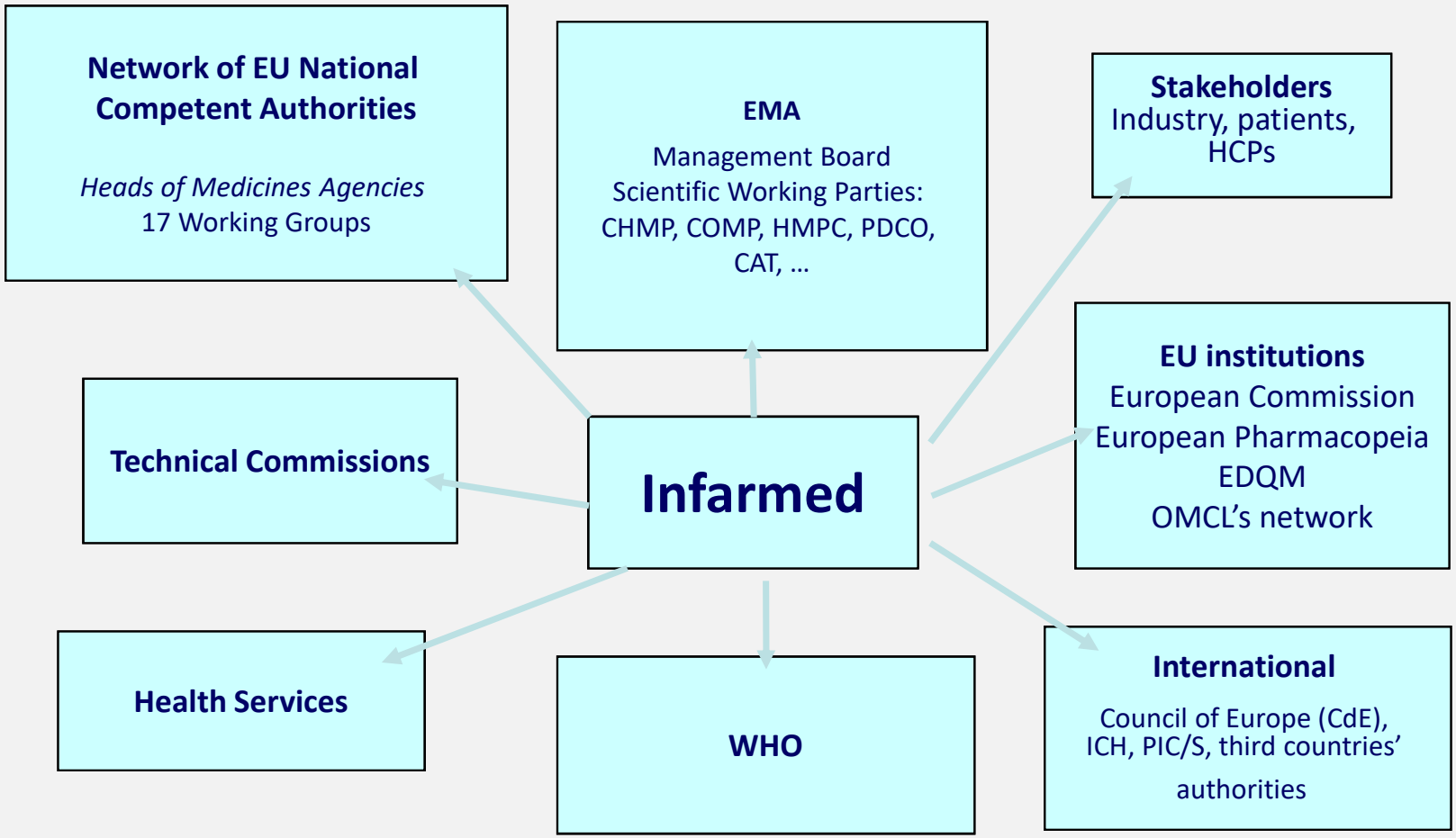
INFARMED – NATIONAL AUTHORITY OF MEDICINES AND HEALTH PRODUCTS, I.P.

Mission: quality, efficacy and safety of medicines on the Portuguese market

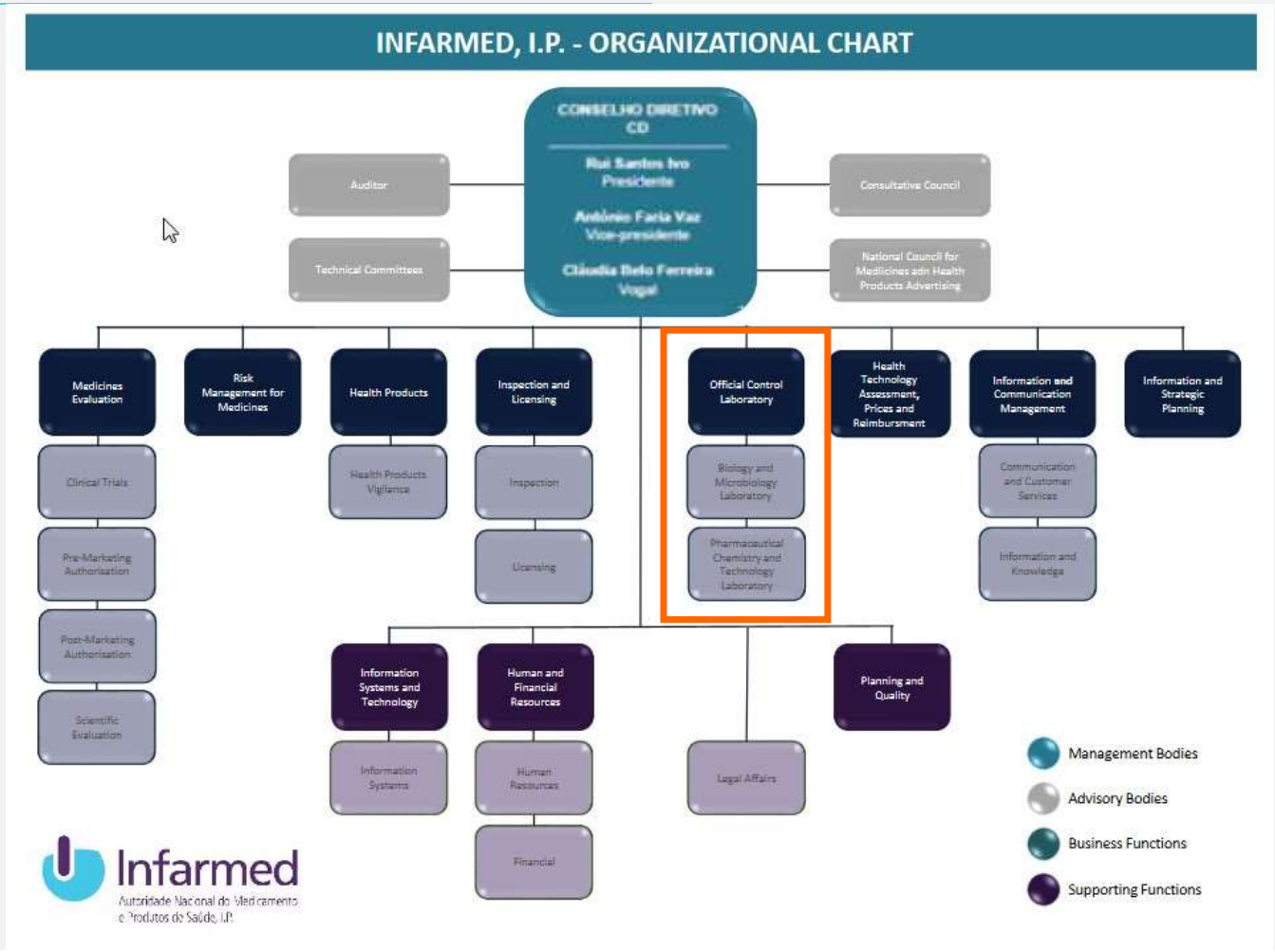
- Permanent staff: 350
- External experts: 250
- Collaboration with academia
- Cooperation with other National Authorities (authority for economic activities and food security, ASAE), customs, police, Portuguese speaking African countries (PALOP: Angola, Cape Verde, Brazil, Mozambique, São Tomé e Príncipe, Guinea Bissau)

INFARMED, I.P.

INTERNATIONAL COOPERATION



INFARMED – NATIONAL AUTHORITY OF MEDICINES AND HEALTH PRODUCTS, I.P.



PORTUGUESE OMCL

Dir: MARIA JOÃO PORTELA

Staff: total 31

Pharmaceutical Chemistry and Technology Laboratory,

Staff: 12

Head: (recruitment ongoing)

Biology and Microbiology Laboratory,

Staff: 11

Head: Monica Miranda

PORTUGUESE OMCL

DIREÇÃO DE COMPROVAÇÃO DA QUALIDADE

- Accreditation according to ISO/IEC 17025 since 2007 by the National Accreditation Body (IPAC)

  81 analytical methods accredited

- Mutual Joint Audit (MJA) by General European OMCL Network (GEON) for all methods performed since 2008

- WHO Prequalification Programme Quality Control Laboratories since 2010

PORTUGUESE OMCL

MAIN ACTIVITIES

Post-marketing surveillance

- 500 medicines: national authorization / mutual recognition procedure / decentralized / centralized procedure
- 20 API
- 180 health products: cosmetics / medical devices
- Quality alerts
- 140 falsified medicines / suspicious food supplements

Official Control Authority Batch Release (OCABR) for Blood Products

- 470 batches for EU
- 360 batches for Non-EU countries

BIOLOGY AND MICROBIOLOGY LABORATORY

ACTIVITIES

Biology

- European/ non-EU Official Batch Release (OCABR) for blood products
- Testing of medicines authorized by the centralized procedure (CAP programme, EMA/EDQM)
- Collaborative studies (establishment of reference preparations and international standards, BSP, WHO)

Microbiology

- Sterility
- Non-sterile products
- LAL
- Antibiotic assays

CAP PROGRAMME

EU MARKETING AUTHORIZATION

- Centrally Authorized Products, community marketing authorization granted by the Commission of the EU.
- Co-ordinated European approach to quality control: yearly sampling and testing organized by the EMA with EDQM and the OMCL Network.

Roles

- EMA is the sponsor and has overall responsibility for the programme, whereas
- EDQM coordinates the sampling and testing operations.
- National Inspection Services draw products from the market.
- OMCL Network provide expertise and resources testing the samples.
- MAH provide control sample, reference material, qualified reagents, approved SOP.

CAP PROGRAMME

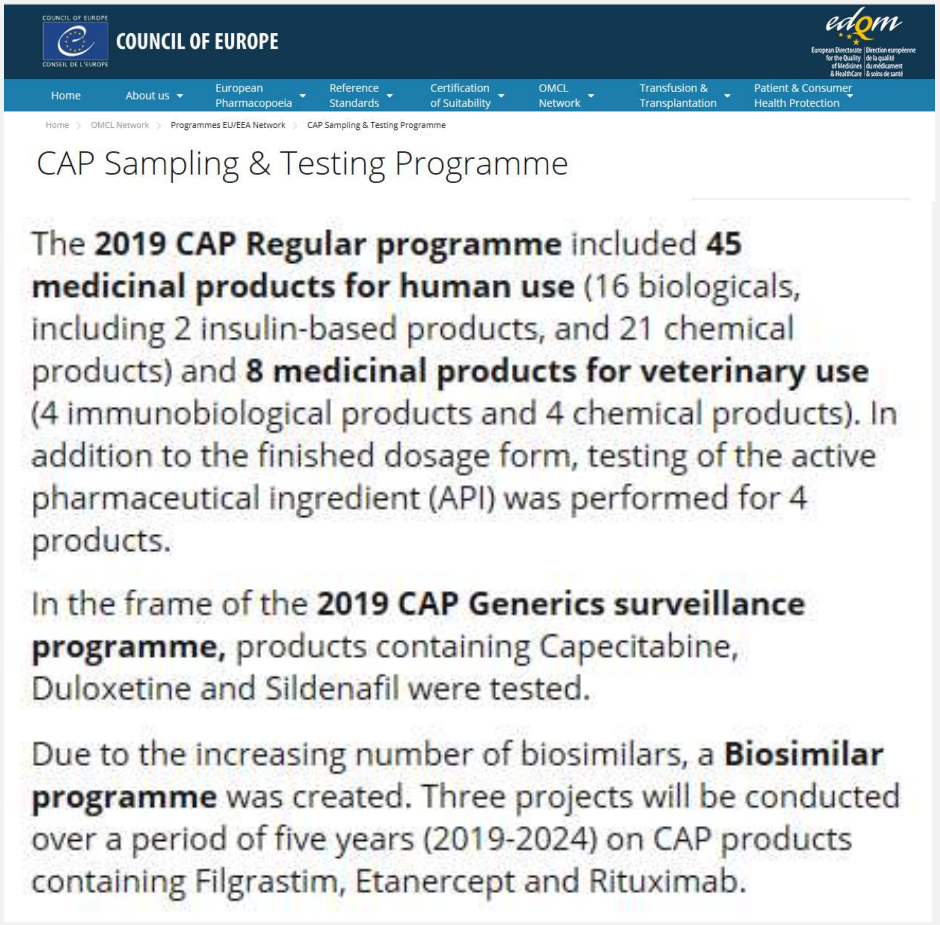
PURPOSE

- Supervise the quality of centrally authorized medicinal products that are placed on the EU/EEA market, in all parts of the distribution chain, by testing their compliance with their authorized specifications.

- Check that the authorized control methods are suitable for their intended use.

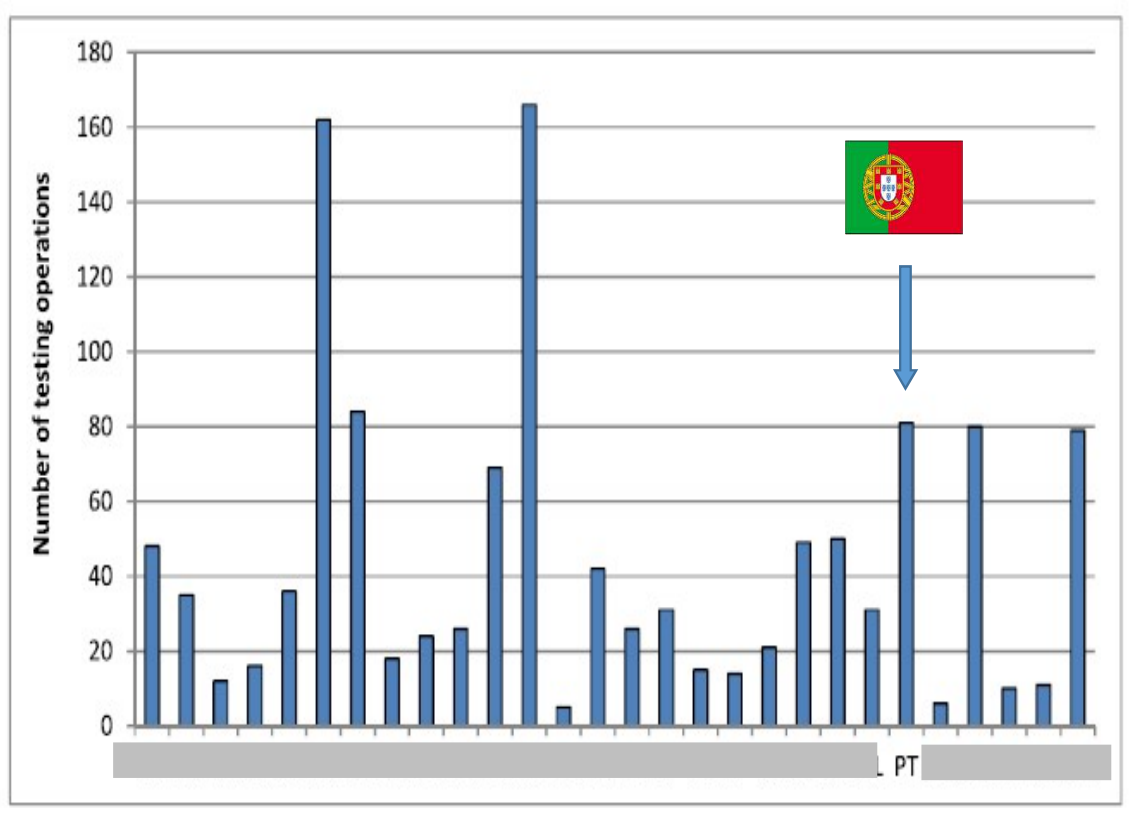
CAP PROGRAMME
NUMBERS

- 1998- 2017, more than 700 products were tested.
- Usually, 15 to 20 biological products are tested every year (including insulins) which is in line with the current capacity of the Network; according to the adopted testing scheme, each biological product is tested in 2 OMCLs
- The number of authorized biosimilar products has also been increasing so a programme on CAP Biosimilars was created. Filgrastim-containing products were selected for a pilot study.



CAP PROGRAMME

TESTING PARTICIPATION 1999-2019



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

edqm

PT: 4th position out of 28

Source: EMA

CELL BASED ASSAYS METHOD TRANSFER

CAP PROGRAM

Features…

- No routine (2 – 4 samples)
- MAH validated analytical procedure
- Method verification based on system suitability criteria, integral part of potency methods, ensure good data quality and reliable potency results

CELL BASED ASSAYS METHOD TRANSFER

BIOASSAY TYPICAL SCHEME

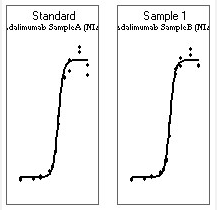

Culture of cells

Distribution of cells on microplates


Addition of titrating dilutions of reference standard, controls, samples

Incubation 37°C, CO2, humidity



Read-out

Data analysis

CELL BASED ASSAYS METHOD TRANSFER

METHOD TRANSFER

Critical aspects

- Shipment of frozen cells
- SOPs from MAH
- Qualified reagents
- Equipment for readout (specifications)
- Calculation software for the statistical analysis of data (Ph. Eur. 5.3)

CELL BASED ASSAYS METHOD TRANSFER

SYSTEM SUITABILITY CRITERIA, AN EXAMPLE

Readout, Spectrophotometry

1. Cell growth control to cell death control (max to min) amplitude ≥0,35 OD units.
2. The net average readings for each sample should be within 0,100 OD units from the net average maximum OD reading.
3. The mean OD difference between 2 dose levels is at least ≥0,035 OD units.
4. The mean OD difference between 2 unspecific molecule dose levels is < 0,035 OD units.

Equipment specifications dependent

- System suitability tests 1 – 4 based on OD are dependent on the specifications of the spectrophotometer
- Criterion 1: approx. 0,9 OD (3x)
- Criterion 2: not fulfilled, probably as a consequence of high sensitivity
- Criterion 3: fulfilled
- Criterion 4: not fulfilled, probably as a consequence of high sensitivity

- Deviations reported to EDQM/EMA

CELL BASED ASSAYS METHOD TRANSFER

SYSTEM SUITABILITY CRITERIA, AN EXAMPLE

ANOVA

5. The linear regression is significant ($p \leq 0,01$)
6. The term for non-parallelism is not significant ($p \geq 0,05$)
7. The term for non-linearity is not significant ($p \geq 0,05$)
8. The relative 95% confidence interval should be < 30%

Statistical data analysis

- Software used by MAH *versus* CombiStats (equivalent)
- Criteria 5 – 8 all fulfilled with a probability of 95%

Model: Parallel lines
Design: Completely randomised
Transformation: y' = y
Variance: Observed residuals

Common slope(factor) = 0.242795 (0.223158 to 0.262432)
Correlation | r |: 0.981628

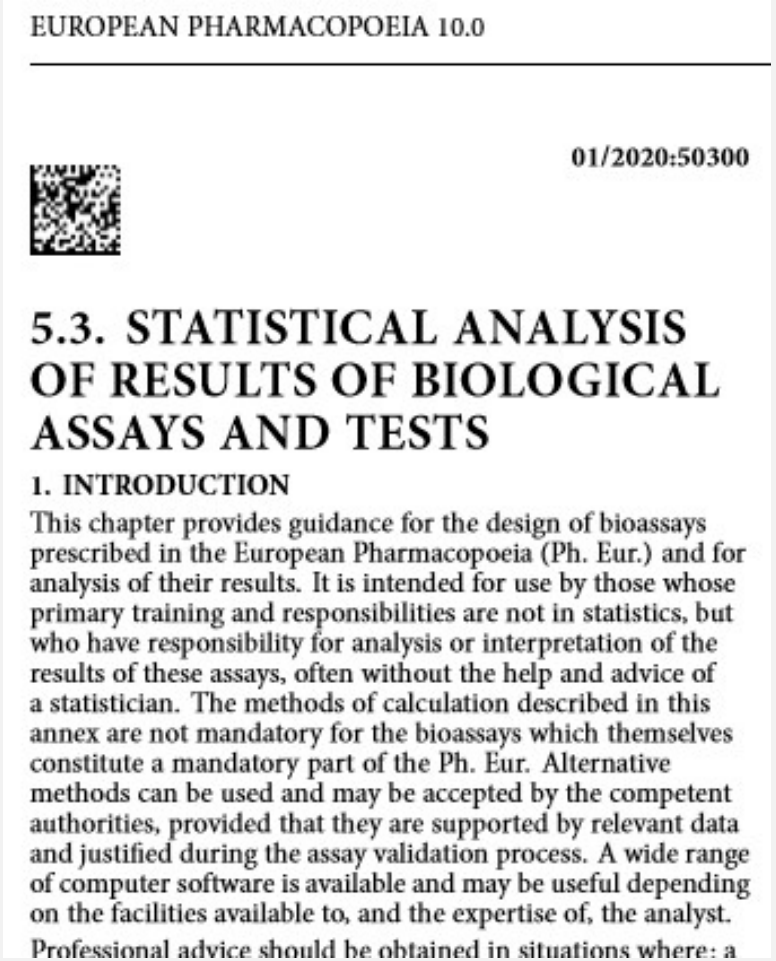
Source of variation	Degrees of freedom	Sum of squares	Mean square	F-ratio	Probability
Preparations	3	0.00730639	0.00243546	11.076	0.001 (***)
Regression	1	0.106782	0.106782	485.608	0.000 (***)
Non-parallelism	3	0.000912117	0.000304039	1.383	0.295
Non-linearity	4	0.000759556	0.000189889	0.864	0.513
Standard	1	2.00083E-06	2.00083E-06	0.009	0.926
Sample 1	1	0.000521401	0.000521401	2.371	0.150
Sample 2	1	0.000235853	0.000235853	1.073	0.321
Sample 3	1	3.00833E-07	3.00833E-07	0.001	0.971
Treatments	11	0.115760	0.0105236	47.858	0.000 (***)
Residual error	12	0.00263872	0.000219893		
Total	23	0.118399	0.00514777		

Sample 1			
Id.	CTS		
(mg/ml)	Lower limit	Estimate	Upper limit
Potency	193.568	209.026	226.074
Rel. to Ass.	100.3%	108.3%	117.1%
Rel. to Est.	92.6%	100.0%	108.2%

Sample 2			
Id.	sampleA		
(mg/ml)	Lower limit	Estimate	Upper limit
Potency	220.471	238.203	258.221
Rel. to Ass.	109.7%	118.5%	128.5%
Rel. to Est.	92.6%	100.0%	108.4%

CELL BASED ASSAYS METHOD TRANSFER

DATA ANALYSIS



EUROPEAN PHARMACOPOEIA 10.0

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5.3. STATISTICAL ANALYSIS OF RESULTS OF BIOLOGICAL ASSAYS AND TESTS

1. INTRODUCTION

This chapter provides guidance for the design of bioassays prescribed in the European Pharmacopoeia (Ph. Eur.) and for analysis of their results. It is intended for use by those whose primary training and responsibilities are not in statistics, but who have responsibility for analysis or interpretation of the results of these assays, often without the help and advice of a statistician. The methods of calculation described in this annex are not mandatory for the bioassays which themselves constitute a mandatory part of the Ph. Eur. Alternative methods can be used and may be accepted by the competent authorities, provided that they are supported by relevant data and justified during the assay validation process. A wide range of computer software is available and may be useful depending on the facilities available to, and the expertise of, the analyst. Professional advice should be obtained in situations where: a

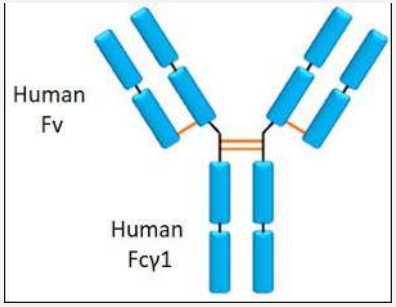
CombiStats

- Calculation software developed by EDQM for statistical analysis of data from biological dilution assays
- Parallel line analysis,
- Slope ratio analysis,
- Probit analysis,
- ED50 determination
- 4-/ 5-parameter logistic analysis (sigmoid curves),
- Limit testing of single dose
- Combination of results (geometric)

COLLABORATIVE STUDY FOR ESTABLISHMENT OF 1ST WHO-IS PARTICIPATION

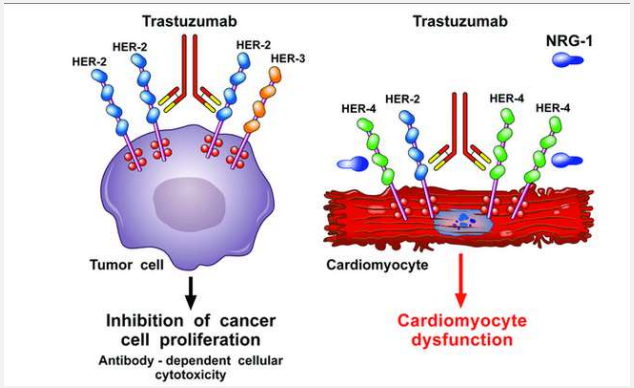
Benefits:

- Ensuring the validity of results
- Assessment of performance (z-score)
- Qualification of technicians



2019: Adalimumab

2020: Trastuzumab

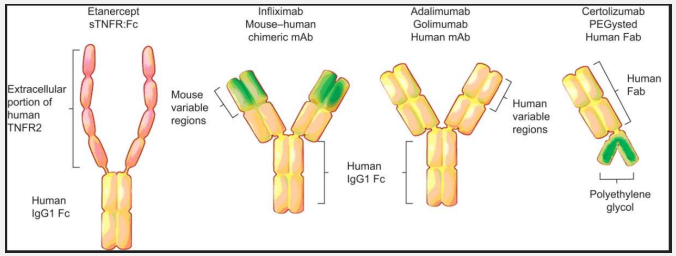


PH. EUR. MAB WORKING PARTY

PUBLIC STANDARDS, MONOGRAPHS

Setting of public standards for therapeutic MAB, started 2014 with a pilot phase:

- Development of general methodologies applied to a wide range of MAB
- Elaboration of product-specific monographs for MAB
- Bottom-up approach: from product-specific monographs to general texts for MAB (and fusion proteins)
- Infliximab as case study for the investigation of the feasibility (PoC)
- Continuation of the pilot phase with new MAB
- Elaboration of a Ph. Eur. General chapter on‘cell-based assays for potency determination of TNF-alpha antagonists’



PH. EUR. MAB WORKING PARTY

NOV 2017: MILESTONE IN SETTING QUALITY STANDARDS

COUNCIL OF EUROPE
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COUNCIL OF EUROPE

edqm
European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

Home | About us | European Pharmacopoeia | Reference Standards | Certification of Suitability | OMCL Network | Transfusion & Transplantation | Patient & Consumer Health Protection

Home > About us > Newsroom > New monograph for Infliximab concentrated solution: the first monograph on a monoclonal antibody in the Ph. Eur.

New monograph for Infliximab concentrated solution: the first monograph on a monoclonal antibody in the Ph. Eur.

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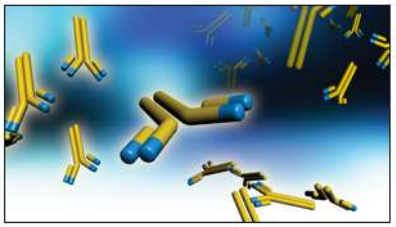
EUROPEAN PHARMACOPOEIA MONOGRAPH | NEWS | 14 DECEMBER 2017 | STRASBOURG, FRANCE



The European Pharmacopoeia (Ph. Eur.) Commission has achieved an important milestone in the field of biotherapeutic products at its 159th Session, held in Strasbourg on 21-22 November 2017, with the adoption of the monograph for *Infliximab concentrated solution (2928)*.

The Ph. Eur. Commission embarked upon the setting of public standards for therapeutic monoclonal antibodies (mAbs) in 2014 with a pilot phase and following extensive consultation with its stakeholders. A 'bottom-up' approach has been undertaken, that started with an investigation of the feasibility of establishing individual monographs (using Infliximab as a case study), building on knowledge and exploring areas for the development of general Ph. Eur. texts applicable to mAbs.

AGENDA

20 FEBRUARY 2020
STRASBOURG, FRANCE
Don't miss out! Join us for the Meet the World Pharmacopo...

01 APRIL 2020 TO 02 APRIL 2020
STRASBOURG, FRANCE
NEW: Training on the Management of Extraneous Agents in I...

21 APRIL 2020 TO 23 APRIL 2020
STRASBOURG, FRANCE
Keeping up with Reality and Quality: A Challenge for Euro...

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QUESTIONS

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OBRIGADO
THANK YOU

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