DISCLAIMER

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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

Network of EU National Competent Authorities
- Heads of Medicines Agencies
- 17 Working Groups

Technical Commissions

Health Services

EMA
- Management Board
- Scientific Working Parties: CHMP, COMP, HMPC, PDCO, CAT, ...

WHO

Stakeholders
- Industry, patients, HCPs

EU institutions
- European Commission
- European Pharmacopeia
- EDQM
- OMCL's network

International
- Council of Europe (CdE), ICH, PIC/S, third countries' authorities
INFARMED – NATIONAL AUTHORITY OF MEDICINES AND HEALTH PRODUCTS, I.P.
Pharmaceutical Chemistry and Technology Laboratory,
Staff: 12
Head: (recruitment ongoing)

Biology and Microbiology Laboratory,
Staff: 11
Head: Monica Miranda

PORTUGUESE OMCL
Dir: MARIA JOÃO PORTELA
Staff: total 31
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.

The **2019 CAP Regular programme** included **45 medicinal products for human use** (16 biologicals, including 2 insulin-based products, and 21 chemical products) and **8 medicinal products for veterinary use** (4 immunobiological products and 4 chemical products). In addition to the finished dosage form, testing of the active pharmaceutical ingredient (API) was performed for 4 products.

In the frame of the **2019 CAP Generics surveillance programme**, products containing Capecitabine, Duloxetine and Sildenafil were tested.

Due to the increasing number of biosimilars, a **Biosimilar programme** was created. Three projects will be conducted over a period of five years (2019-2024) on CAP products containing Filgrastim, Etanercept and Rituximab.
CAP PROGRAMME
TESTING PARTICIPATION 1999-2019

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 → Data analysis → Read-out
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 $\geq 0.35$ 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 $\geq 0.035$ 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 ≤ 0.01)
6. The term for non-parallelism is not significant (p ≥ 0.05)
7. The term for non-linearity is not significant (p ≥ 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%
CELL BASED ASSAYS METHOD TRANSFER
DATA ANALYSIS

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 1<sup>ST</sup> WHO-IS PARTICIPATION

Benefits:

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

2019: Adalimumab

2020: Trastuzumab
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’

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 (2925).

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.
QUESTIONS
OBRIGADO
THANK YOU