Prequalification Team – Medicines (PQT/MED)

Update

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PQT Medicines 2024

- ✓ Updates
- ✓ Performance
- ✓ Biotherapeutics
- ✓ Current issues
- ✓ Coordinated Scientific Advice procedure (CSA)

So far in 2024…

- 41 finished products prequalified so far, including firsts such as cefiderocol, nicotine replacement therapies, additional generic rifapentine and bedaquiline products and pediatric TB and antimalarial formulations.
- 20 APIs prequalified
- Updated or new invitations (EOIs)
- Implementing a new pathway to increase insulin access
- Continued use of virtual platforms
  - Advisory/pre-submission meetings
  - Annual workshops for manufacturers (4-day quality workshop and biotherapeutics/biosimilar workshop, both in Sept)
- Increasing number of variations due to increasing number of prequalified products and requalification applications – *still PQT/MED is meeting its timelines*

EOIs - updated or new since January 2024

HIV/AIDS (1 Nov 2024) - *updated*

- Lenacapavir sol for sc inj 463.5mg/1.5 ml (309mg/ml)
- Lenacapavir tabl 300 mg
- Five TAF based 2- and 3-FDCs
- Emtricitabine/Tenofovir disoproxil fumarate/Levonorgestrel/Ethinylestradiol tabl 200mg/300 mg/0.15 mg/0.03 mg

Influenza (19 Aug 2024) - *updated*

- baloxavir marboxil tabl, granule for oral susp

NTD (15 Oct 2024) - *updated*

- Moxidectin 2mg tabl

TB (8 April 2024) - *updated*

- Isoniazid 75 mg/Rifapentine 300 mg/Moxifloxacin 100 mg/Pyrazinamide 375 mg tabl
- Isoniazid 75 mg/Rifapentine 300 mg/Moxifloxacin 100 mg tabl
- Sulfamethoxazole/Trimethoprim/Isoniazid/Pyridoxine (400 mg/80 mg/150 mg /12.5 mg scored tabl).
- Others

Treatment of apnoea in preterm infants (3 Oct 2024) - *New*

- Caffeine citrate; oral liquid; injection

PQT/MED scope

Priority medicines in 16 therapeutic areas

- ✓ HIV/AIDS
- ✓ Tuberculosis
- ✓ Malaria
- ✓ Reproductive health
- ✓ Influenza
- ✓ Neglected Tropical Diseases
- ✓ Diarrhoeal disease
- ✓ Hepatitis B and C
- ✓ Infections in newborn and young infants and childhood pneumonia
- ✓ Insulins and insulin analogues (BTPs)
- ✓ Certain cancers (BTPs)
- ✓ COVID-19 (BTPs and small molecules)
- ✓ Ebola Virus Disease (BTPs)
- ✓ Treatment of multi-drug resistant bacterial infections
- ✓ Products for cessation of tobacco use
- ✓ **Treatment of apnoea in preterm infants (2024)**
- ✓ *Priority formulations in children (azithromycin, amoxicillin clavulanate, nitrofurantoin)*
- ✓ *Childhood cancers*

Type of products

- ✓ Finished Pharmaceutical Products
- ✓ Active Pharmaceutical Ingredients
- ✓ Biotherapeutics, incl biosimilars

Pathways

- ✓ Full assessment of generics/biotherapeutics, including those that may be facilitated by access to SRA/WLA assessment reports
- ✓ Abridged pathway for innovator or generic/biosimilar products approved by an SRA, or in future ML4 WLA

Expert Review Panel (ERP) for FPPs and BTPs

PQT Medicines guidances

PQT/MED develops *and* updates guidances on an ongoing basis:

- ✓ **Product specific guidance,** eg Zinc products, DMPA inj
- ✓ **Therapeutic area specific guidance**, eg RH products
- ✓ **Common/frequent deficiencies in quality, or in BE protocols**
- ✓ **Q&As**
- ✓ **Screening checklist**
- ✓ **Comparator products lists**
- ✓ **BE study design advice (NDBS)**

Note, PQT/MED will review your final draft BE protocols, before study start (*most reg authorities do not do that*)

Pre-submission meetings

- Pre-submission meetings are mandatory for applicants new to PQT/MED
  - Generally, when the applicant has generated at least 1-2 months stability data on submission batches
  - Important to have early interaction to plan the pre-submission meeting, or to address specific questions
- Pre-submission meetings are encouraged for any applicant especially if unusual products/products with particular issues
- PQT/MED can provide advice at any stage before, or after submission – *PQT/MED is accessible. You should use this opportunity*

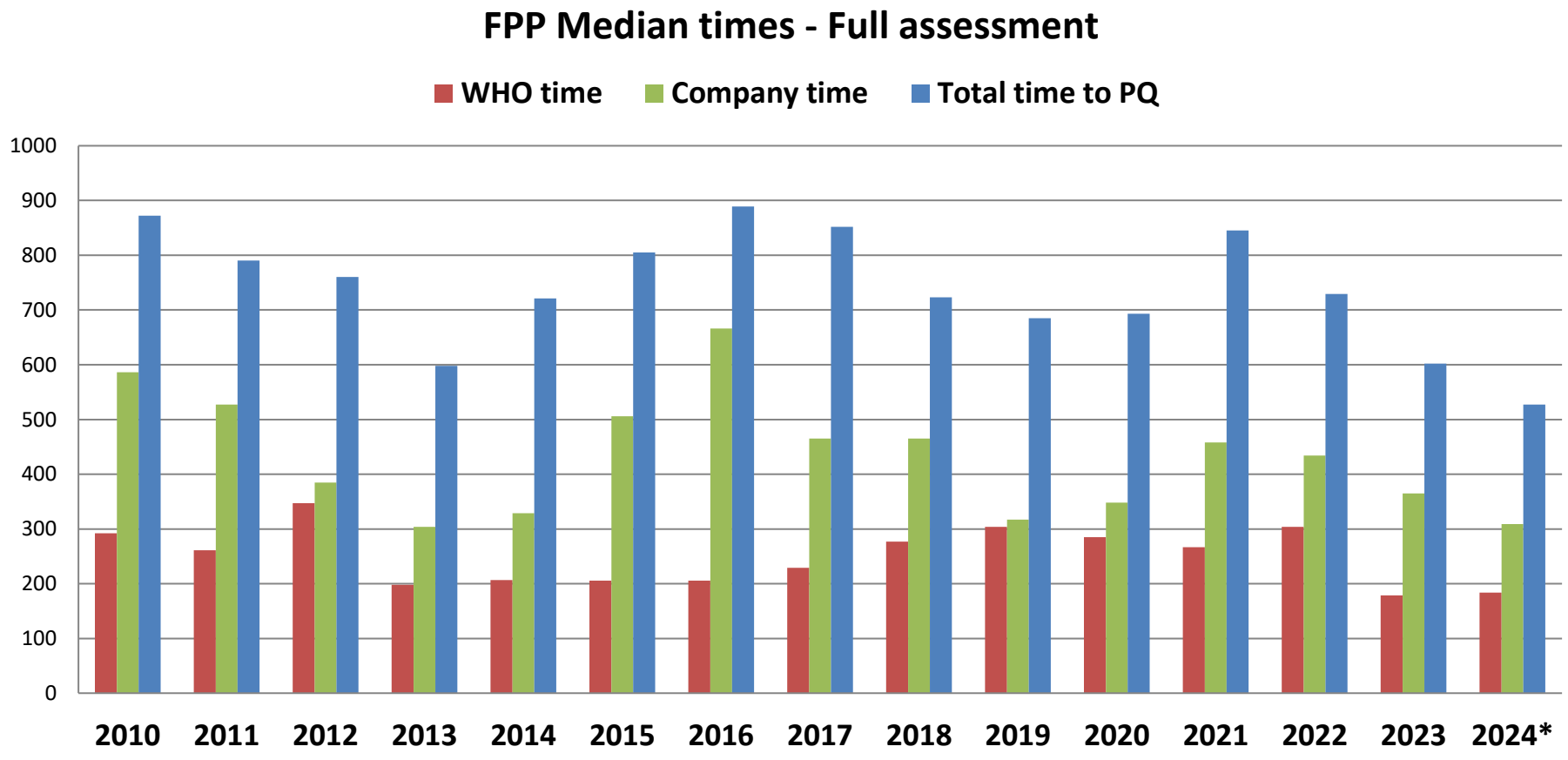
https://extranet.who.int/prequal/medicines/pre-submission-meetings

PQT/MED: Key performance targets met

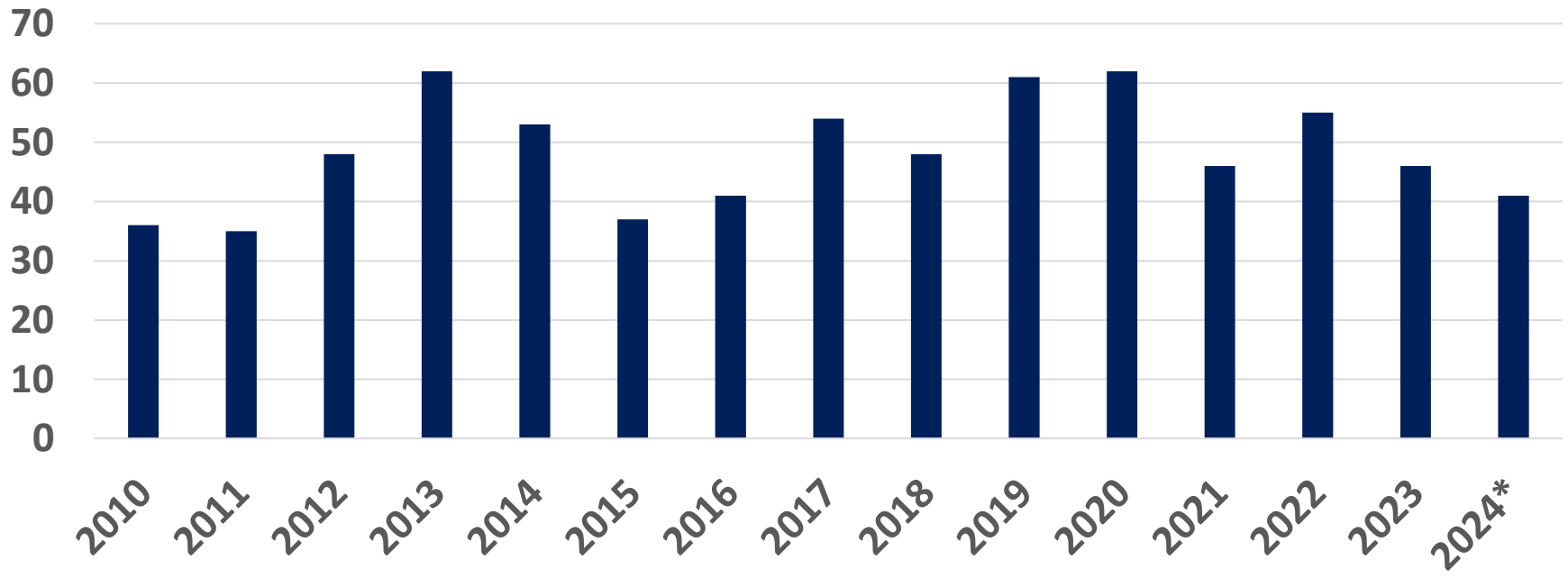
- ✓ Screening – 80% of applications screened within 30 days (*target: 80%*)
- ✓ WHO time to PQ for FPPs (full) – less than 270 days for 76% of FPPs (*target: 50%)*
- ✓ WHO time to PQ for FPPs (abridged) – less than 100 days for 100% of FPPs (*target: 90%*)
- ✓ WHO time to PQ for APIs – less than 270 days for 50%* of APIs (*target: 40%*)
- ✓ First action for variations to FPPs – completed for 91-100% within the timelines stated (*target 80%*)

**backlog due to Covid-19 and other priority applications is being cleared*

Time (days) to prequalification of medicines (FPPs, median, full assessment) 2010 – *21 Nov 2024*



Number of prequalified products (FPPs) per year since 2010 (*as of 21 Nov 2024*)



PQT/MED maintenance activities (*Jan - Nov*)

- 354 new variation applications. Nearly 100% assessed within target timelines.

- 45 products requalified so far in 2024. This concerns products prequalified based on full assessment. For products prequalified based on SRA approval there is a requalification process called “SRA verification” – 21 products have been “SRA verified” so far in 2024.

Support to CRP

PQT/MED has shared assessment reports for 34 products in the context of CRP so far in 2024 (57 products in 2023).

Cumulatively, reports for 306 prequalified products have been shared in CRP; and 1096 registrations have been completed in the 67 participating NRAs and 1 Regional Economic community (CARICOM – composed of 15 countries).

Biotherapeutics/biosimilars

Work on prequalification of trastuzumab/rituximab (16 products prequalified 2019-2021) established a platform for prequalification of other biotherapeutics

- Therapeutics against COVID-19 (IL-6 inhibitors and neutralizing antibodies): 3 tocilizumab products prequalified in Feb 2022.
- Therapeutics against Ebola Virus Disease: two products prequalified in Nov 2023
- Human insulin and insulin analogues: 4 human insulin dossiers prequalified (2 fast-acting and 2 intermediate acting) and 2 insulin analogue (Insulin glargine) products prequalified in May 2023. *Further analogue submissions expected*.
- The human insulin Master File procedure (h-IMF) is an innovative pathway launched in Aug 2023 to facilitate access to h-insulin. *Manufacturers are now actively preparing dossiers.*
- Expert Review Panel (ERP) mechanism for biotherapeutics *recently cleared Serum Institute's TB skin test to detect Mtb allowing GDF to add this test to its portfolio.*
- TB skin tests – "medicines for diagnostic purpose", will soon be invited to PQ.

Current issues

Rifampicin API shortage

Proactive engagement with potential new and existing API manufacturers. Prioritized assessment of dossiers and inspection of sites. ERP as an interim measure.

Nitrosamines

- Actively working with manufacturers to ensure affected/suspected products are tested based on priority. Risk mitigation strategies when impurities are confirmed + regulatory decisions based on risk-benefit to prevent shortages of critical products.
- NITWG, NISG, ICH

Coordinated scientific advisory procedure (CSA)

- Coordinated by the WHO Science Division
- Advice to product developers on the generation of robust data for future evaluation towards a WHO policy recommendation and product prequalification in areas of unmet public health needs.
- Advice provided jointly by WHO PQT/MED and the corresponding WHO clinical department
- Applies to new, not yet invited, products, or new/additional data on existing products
- PQT/MED participates in *all* CSA procedures for medicines

CSA

- The CSA process has been well-received by applicants and may accelerate introduction of therapies particularly relevant to LMICs.

- A total of 12 requests for advice have been received; 10 procedures completed and 2 rejected as not eligible for full advice.

New products

- An NCE for malaria that would address malaria drug resistance
- An FDC single pill product for HIV prevention and contraception
- A product for treatment of a debilitating invasive fungal NTD

Improvements from existing therapy

- A product to shorten leprosy treatment
- A product with improved PK to allow more convenient dosing for MDA for filariae.
- An antimalarial product with more favourable PK, possibly lessening resistance
- A triple-drug treatment for malaria, possibly lessening resistance

New IT platform (ePQS)

- The ePQS database has been used internally for over a year.
- We have started piloting the ePQS portal.
- We are anticipating opening the portal to all users Jan/Feb 2025.
- User Acceptance Testing is about to commence for eCTD facility.
- Go live of eCTD is expected Feb 2025.

Meeting PQT/MED?

- ✓ Coordinated Scientific Advice, early point of contact
- ✓ Advisory meetings anytime (before or after submission) https://extranet.who.int/prequal/medicines/technical-advice
- ✓ Pre-submission meetings
- ✓ Annual workshops for manufacturers, usually in Sept.
- ✓ During industry gatherings (e.g., CPHI, procurer organized meetings)
- ✓ *Any questions, e-mail me (stahlm@who.int)*

Thank you!

Biotherapeutics/biosimilars

- Prequalification of trastuzumab/rituximab (16 products prequalified 2019-2021) created a platform for prequalification of other biotherapeutics, as well as ERP:
  - Therapeutics against COVID-19 (IL-6 inhibitors and neutralizing antibodies): 3 tocilizumab products prequalified in Feb 2022.
  - Therapeutics against Ebola Virus Disease: two products prequalified in Nov 2023
  - Human insulin and insulin analogues: 4 human insulin dossiers prequalified (2 fast-acting and 2 intermediate acting) and 2 insulin analogue (Insulin glargine) products prequalified in May 2023. *Further analogue submissions expected*.
  - The human insulin Master File procedure (h-IMF) is an innovative pathway launched in Aug 2023 to facilitate access to h-insulin. *Manufacturers are now actively preparing dossiers.*
  - TB skin tests – medicines for diagnostic purpose. *EOI soon to be established*
  - Expert Review Panel (ERP) mechanism for biotherapeutics recently cleared Serum Institute's TB skin test to detect Mtb allowing GDF to add this test to its portfolio.

PQT/MED collaboration with WHO clinical departments

- Interaction with WHO treatment programmes (EOIs)
- The Coordinated Scientific Advice procedure (CSA) "*…voluntary…to provide advice to product developers on the generation of robust data for future evaluation towards a WHO policy recommendation and product prequalification, in areas of unmet public health needs*" (https://www.who.int/activities/optimizing-research-and-development-processes-for-accelerated-access-to-health-products/who-coordinated-scientific-advice-for-health-product-r-d)

  The CSA procedure applies to new products, or new/additional data on existing products
- "*Coordination between WHO Living Guidelines and WHO EUL and PQ processes for Therapeutics in the context of COVID-19*" https://extranet.who.int/pqweb/key-resources/documents/coordination-between-who-living-guidelines-and-who-eul-and-pq-processes

  ✓ Invitations for PQ (or EUL) can be issued before a recommendation for use, if data exist that may support a positive WHO recommendation. PQ (or EUL) assessment can then proceed in parallel with the analysis of the totality of the evidence.

  ✓ PQ (or EUL) will not be granted until a guideline recommendation has been made.

Abridge route to prequalification

The following products were the first (and thus far the only) in their class to be prequalified:

Integrase Inhibitors:

- Cabotegravir (as sodium) 30 mg film-coated tablets (HA788)
- Cabotegravir 600 mg/3 mL prolonged-release suspension for injection (HA789)

For treatment of multi-drug resistant bacterial infections:

- Cefiderocol Powder for concentrate for solution for infusion 1g/vial (MR001)

For treatment of disorders caused by use of tobacco:

- Medicated nicotine chewing gums: 2 strengths (TD001 and TD002)
- Nicotine patches: 3 strengths (TD003, TD004 and TD005)

For treatment of neglected tropical diseases:

- Azithromycin 500mg film-coated tablets (NT019)

Antimalarial medicines (*to be prequalified*)

- Tafenoquine (as succinate) 150 mg film-coated tablets
- Tafenoquine (as succinate) 50 mg dispersible tablets

New pathways/procedures

New pathways for products approved by WLAs, ML3/ML4 NRAs or regulatory networks

A draft document outlining how PQT/MED intends to interact with the new WLAs/ML3/ML4 NRAs, is ready for consultation.

Pilot procedure to enable CRP of products prequalified via the abridged procedure, ~~and~~
~~Pilot procedure to enable prequalification of EUM4All and Swissmedic approved products via abridged procedure and to further support CRP for these products as prequalified products~~

A draft guideline for piloting these procedures is ready for consultation

Some of our priorities for 2025 and beyond I

- ✓ Continue to collaborate with WHO clinical departments to implement development of treatment recommendations in parallel with prequalification for promising products to promote faster access (as applied for COVID-19 therapeutics), maybe gaining 6-12 months or more.
- ✓ Continue to engage with WHO clinical departments, procurers and partners to expand into new therapeutic areas as per set priorities – *additional expertise needed?*
- ✓ Continue to collaborate with WHO Science division and clinical departments in the WHO Coordinated Scientific Advice (CSA) Procedure for new priority products or new uses of existing products – *additional expertise needed? Collaboration with SRAs?*
- ✓ Pilot an extension of the abridged procedure to allow prequalification of SRA/WLA approved products (EMA Art 58, Swissmedic's MAGHP and other access programmes) and facilitate their national registrations via CRP

Some of our priorities for 2025 and beyond II

- ✓ Continue to collaborate with the AMA as they establish assessment procedures and practices
- ✓ Continue to collaborate with USFDA to expand the CRP lite pilot
- ✓ Pilot the new abridged procedures to enable CRP of products approved by WLAs/SRAs (as a prequalified product)
- ✓ Pilot procedures for prequalification of products approved by ~~PQT/MED can use the decision/outputs of~~ new WLAs/tWLAs (ML3/ML4 NRAs) ~~in its assessments~~ – ~~*how*~~ *to ensure harmonized standards across products to reassure procurers and countries.*
- ✓ Continue to implement the new approach to increase availability of quality-assured human insulin: human insulin master file procedure
- ✓ ~~Expand the pipeline on the web to include additional details (as for COVID-19 therapeutics)~~
- ✓ Continue collaborations to promote local production

Parallel guideline development and prequalification procedure

- A procedure for medicines not yet included in the WHO treatment guidelines
- Instead of a sequential approach prequalification assessment of the product dossier may proceed in parallel with development of treatment recommendations, thereby gaining time
- This will potentially allow prequalification of the product at the time when the treatment recommendations are finalized
- Piloted successfully for certain COVID-19 therapies
- Expected to be extended to all therapeutic areas

Biotherapeutics/biosimilars

Currently 27 have been prequalified including

- trastuzumab and rituximab for cancer indications,
- human insulin (h-insulin) and long-acting insulin analogues for the treatment of diabetes, and
- neutralizing monoclonal antibodies for the treatment of Ebola virus disease and COVID-19.

Collaborations

- Collaborations with WHO Science division and clinical departments (e.g., CSA; updates to EOIs or launching of new EOIs)
- Collaborations with NRAs and regional networks (CRP, participation in PQT assessments; trainings to regulators; joint assessments)
- Collaborations with SRAs (e.g. CRP-lite; EMA; EDQM)
- International collaborations (ICH working groups e.g., M13, Q1 revision; IPRP; NISG/NITWG; USP)
- Collaborations with procurers and related agencies (ERP, regulatory and QA advice to procurers; MPP)
- Industry bodies (IFPMA, IGBA)

Coordinated scientific advice (CSA)

- To provide advice to product developers regarding generation of robust data for future evaluation towards a WHO policy recommendation and product prequalification in areas of unmet public health needs.
- Applies to new products, or new/additional data on existing products
  - For medicines: for example, new chemical entities and new dosage forms/new combinations/new indications for existing molecules
- Advice on quality, non-clinical, clinical aspects
- So far seven CSA sessions completed for medicines. Two ongoing currently

PQT/MED Workshops for Manufacturers

- Two PQT Medicines workshops for manufacturers held in 2024
  - PQT Medicines 7th Annual Medicines Quality Workshop for Manufacturers - 23-26 September 2024
  - PQT Medicines 3rd Biotherapeutic Product (BTP) and Similar Biotherapeutic Product (SBP) Workshop for Manufacturers – 27 September 2024
- Close to 250 participants
- Similar workshops planned for 2025 (*dates to be announced on the web*)