# The EU-PAT Team and its activities

The evolving role of Process Analytical Technology

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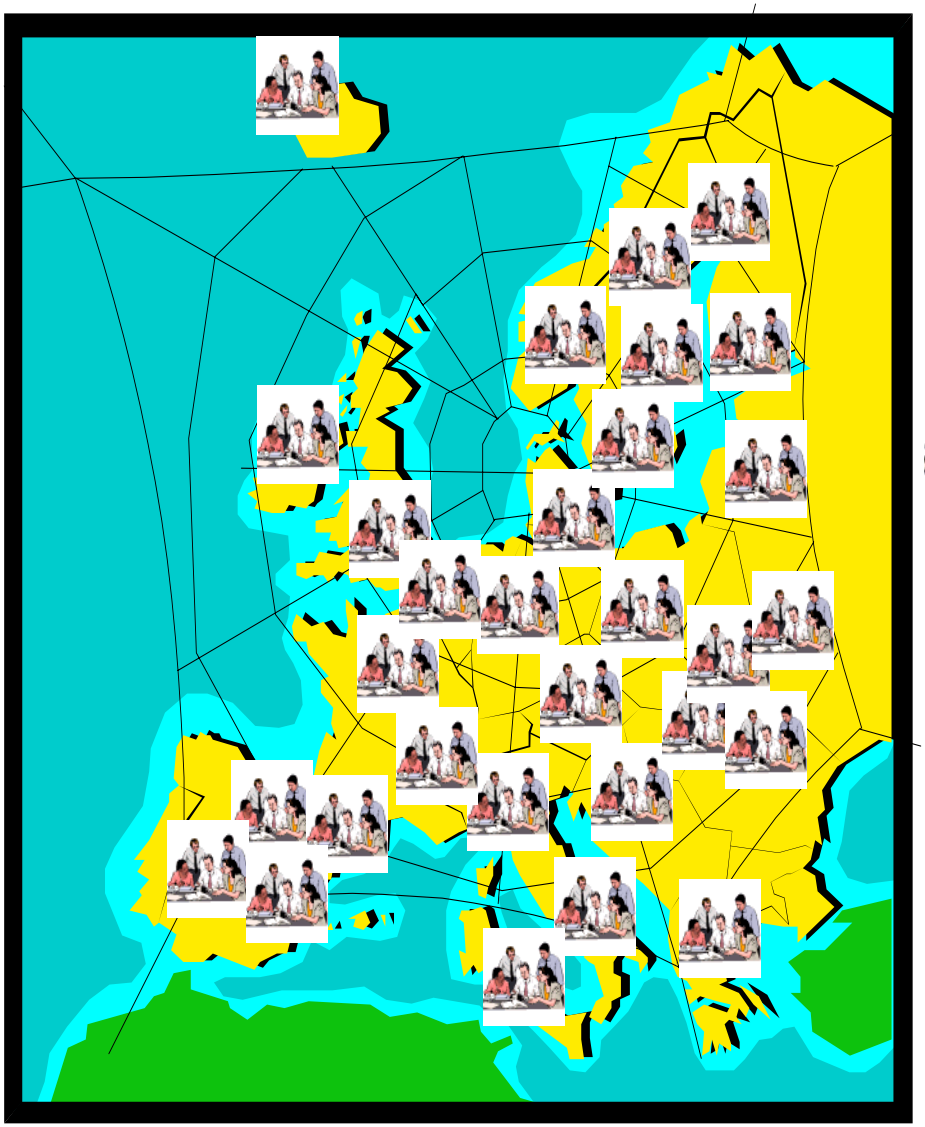


# EMEA: a virtual agency based on a network of the competent authorities of EU

# www.emea.eu.int/Inspections/PAT

EMEA PAT team created January 2004 to review implications and ensure that European regulatory framework and authorities are adequately prepared to conduct thorough and effective evaluations of PAT-based submissions.

# Concept clarifications

- PAT is not just new technologies. The important focus is process understanding. This applies for both drug substance and for drug product.

- Analyzing includes chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner.

# Basic issue

In/on/at line process control
versus
testing of finished product

# EU´s PAT Team

- 4 GMP inspectors *(Denmark, Germany, Italy, UK)*
- 6 assessors of QWP and BWP *(Germany, Luxembourg, Sweden, The Netherlands, UK)*
- EDQM-observer
- EMEA secretariat

# General objective for EU´s PAT Team

- Forum for dialogue and understanding between assessors and inspectors

- Prepare a harmonised approach* within the EU for assessing applications and performing GMP-inspections.

**including new approaches to manufacturing and control of active substance/ medicinal product/ packaging material/ etc.*

# Specific objectives for EU´s PAT Team

- Review legal and procedural implications in EU
- Harmonize EU-approach with USA and Japan
- Identify training needs for assessors/inspectors*
- Develop Questions & Answers to be published on EMEA´s webside

* 3-days course for 60 inspectors/assessors Sept 2004; Course planned to be repeated December, 2005; Team has visited PAT sites;

# Specific objectives for EU´s PAT Team (cont.)

- Forum for ´informal´ presentations from drug companies
- Review ´mock´ submissions including PAT
- Develop procedure for assessment/inspection of PAT related applications

# Review of legal and procedural implications

- European Pharmacopoeia activities
- Revision of existing guidelines
- New guidelines
- Revision of assessment/inspection practices and quality system approaches
- Sampling and testing arrangements by OMCL´s

# Key guidelines to be developed*

- Pharmaceutical Development, (ICH Q8)
- Quality Risk Management (ICH Q9)
- Quality Systems (ICH Q10)

*No veterinary equivalents at the moment. However, VICH is considering Q9-10.

# ICH Q8 Pharmaceutical Development
## (Step 2, for consultation)

- Provides an opportunity to present risk management principles and to create opportunities for less restrictive regulatory approaches based on scientific understanding.
- Part 2 (discussed): Annexes relating to specific dosage forms and appropriate examples of risk management

# ICH Q9 Quality Risk Management
## (Step 2, for consultation)

A process* consisting of well defined steps which, when taken in sequence, support better decision making by contributing to a greater **insight into risks and their impacts.**

*includes assessment, control, communication and review of risk.

# ICH Q10 Quality Systems
## (Drafting group)

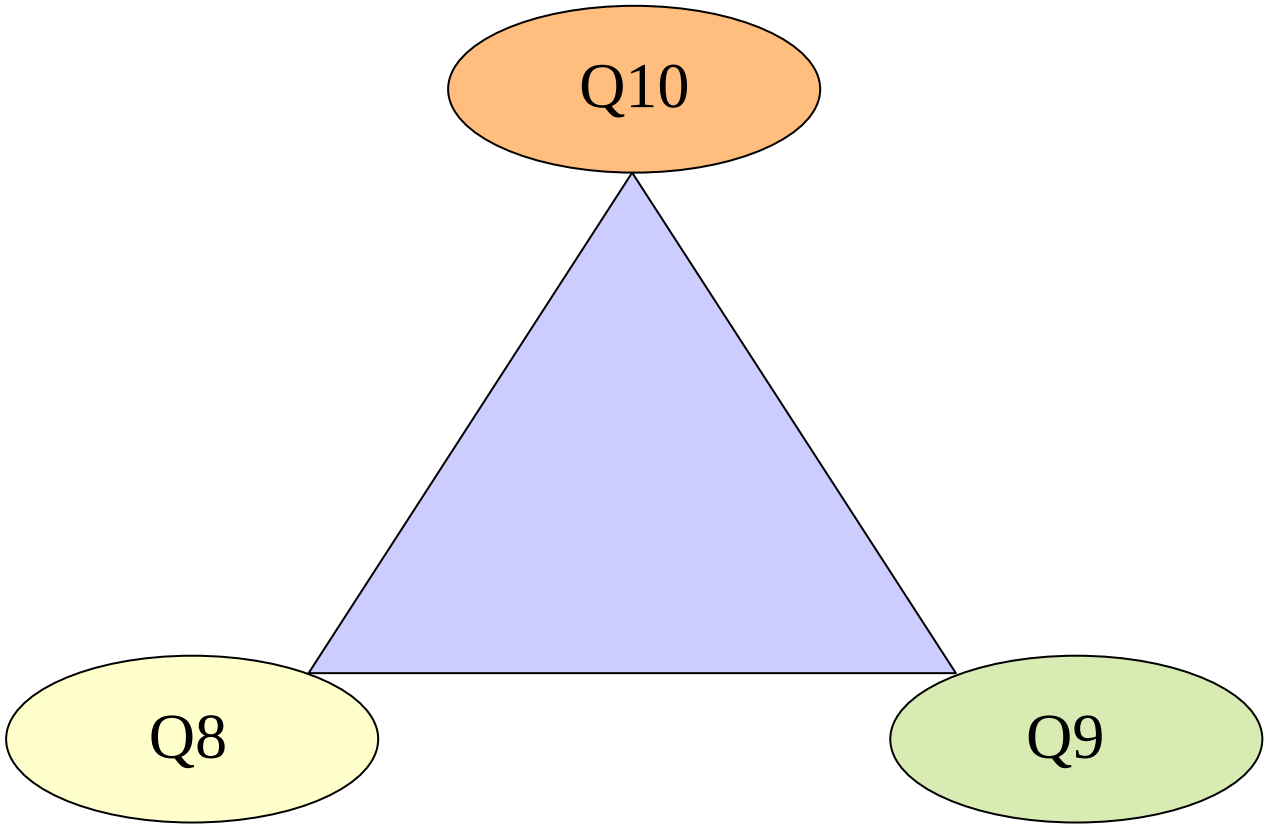
Continuous improvements: ISO 9004:2000

- Quality system structure

*versus*

- Changes in manufacturing procedures (*at present variations*)

# ICH guidelines simplifying regulatory implementation of PAT



- Following discussions with industries and organisations some new concepts need clarification.
- Items in the following points 1-6 thus are in a communication phase and no decisions are taken.

# Some new concepts for discussion/clarification

1. Design space
2. Process signature
3. Real-time release
4. Process specification
5. Comparability protocols
6. Quality system of continuous improvements

# 1. Design space (ICH Q8)

Established multidimensional range of process parameters/formulation attributes) demonstrated to provide guaranteed quality

based on

- formal experimental design
- experimental results (positive/negative)
- lifecycle knowledge

# Examples on possible controlling/interacting parts in a space

- **Starting materials** (e.g. by NIR): identification including particle size distribution, specific surface area or other functionality-related characteristics, ratio of ingredients to each other, etc.
- **Process operations** (e.g. by NIR, acoustics): water content of mass/granule over time, blending profile over time, etc.
- **Machine parameters**: weight discharged by blender, feedback control of compression force, etc

# 1. Design space (ICH Q8), cont.

- Working within design space (multidimensional region) not generally considered as a change
- Movement out of design space is a change → regulatory process

*Question 1:*

# When PAT is implemented will the manufacturer be allowed to make changes to the process without need for regulatory "approval"?

On the assumption

- understanding of variables that affect product quality attributes, methods to monitor and control
- process control strategy falls within the boundaries of knowledge i.e. in established design space

↓

Adjustments possible without need of variation submission

# 2. Process signature

*Proposal for comments before 31 August*:*

"A collection of batch specific information that shows a batch has been produced within the design space for the product."

* www.emea.eu.int/Inspections/PAT

# ASTM definition of Process signature

"A single or multi-dimensional signal indicative of the attributes of the process."

(Compare: "A collection of batch specific information that shows a batch has been produced within the design space for the product.")

# 2. Process signature, cont.

- Operating within design space
- No unique process signature
- Family of process signatures with common characteristics (salient features)

# 2. Process signature, cont.

**Process signature** e.g. amount of water added in relation to time *(wet massing)*, air flow rate and bed temperature during fall rate drying *(fluidized bed drying)*

**(Compare in-process control points:** end-point limits for e.g. granule moisture content)

# 3. Real-time release (RTR) instead of finished product testing?

- RTR control based on prediction modelling of finished product quality attributes.
- Current EU legislation requires two specifications: release and end of shelf-life.
- Does RTR mean a third specification?

*Question 2:*

**Is it possible for a product to have two specifications-one for real-time release based on on-line measurements and another for end-of-life testing?**

- At present release and shelf-life specifications taking account to relevant monographs of the Ph.Eur.
- How to ensure compliance to release specification is open but has to be described in submission → a third specification?

cont.

# *Question 2, cont.*

**Release decisions made on a third specification:**

- Relationship between process measurements & controls and release specifications key issue in submission
- *After release*: Compliance to shelf life specifications (conventional methods)

# Examples on finished product tests which are shown possible to be replaced by RTR

- Identification of active substance/excipients (including functionality properties)
- Water content
- Uniformity of mass
- Uniformity of content
- Dissolution

# 4. Process specification

- *Proposal*:

  Recognises the interrelationship between various process parameters and describes ranges within which the process needs to be operated.

- Compare RTR, a third specification?

*Question 3:*

**Will it be possible to widen the limits for an approved product and process specification" if, post-approval, such changes are found to have no significant effect on product quality**

- Process specifications are not finished product specifications
- Adjustments within "design space" possible without further variation application
- Changes to finished product specification → variation regulations

# Compliance with European Pharmacopoeia (Ph.Eur.)

…does not imply that performance of all tests in a monograph is necessarily a prerequisite for a manufacturer in assessing compliance with the Ph.Eur. before release of a product. The manufacturer may obtain assurance that a product is of Ph.Eur. quality from data derived, e.g. from validation studies of the manufacturing process and from in-process controls.

..results of in process tests and controls may constitute sufficient grounds for batch release and provide greater assurance of the finished tablet meeting certain criteria in the specification without the tests being repeated on a sample of the finished product...

Note for Guidance on Parametric Release (CPMP/QWP/3015/99)

# Commission directive 2003/94/EC

## (Principles and guidelines of GMP in respect of medicinal products for human use…)

*Transposition to*

Swedish regulation LVFS 2004:

**§21 Quality control**

……

When a manufacturer has applied and has got approval from MPA to apply another means (than results from tests on final product etc.) like parametric release or real-time release, the approval from MPA will describe how the requirements in this paragraph should be applied.

# 5. Comparability protocols

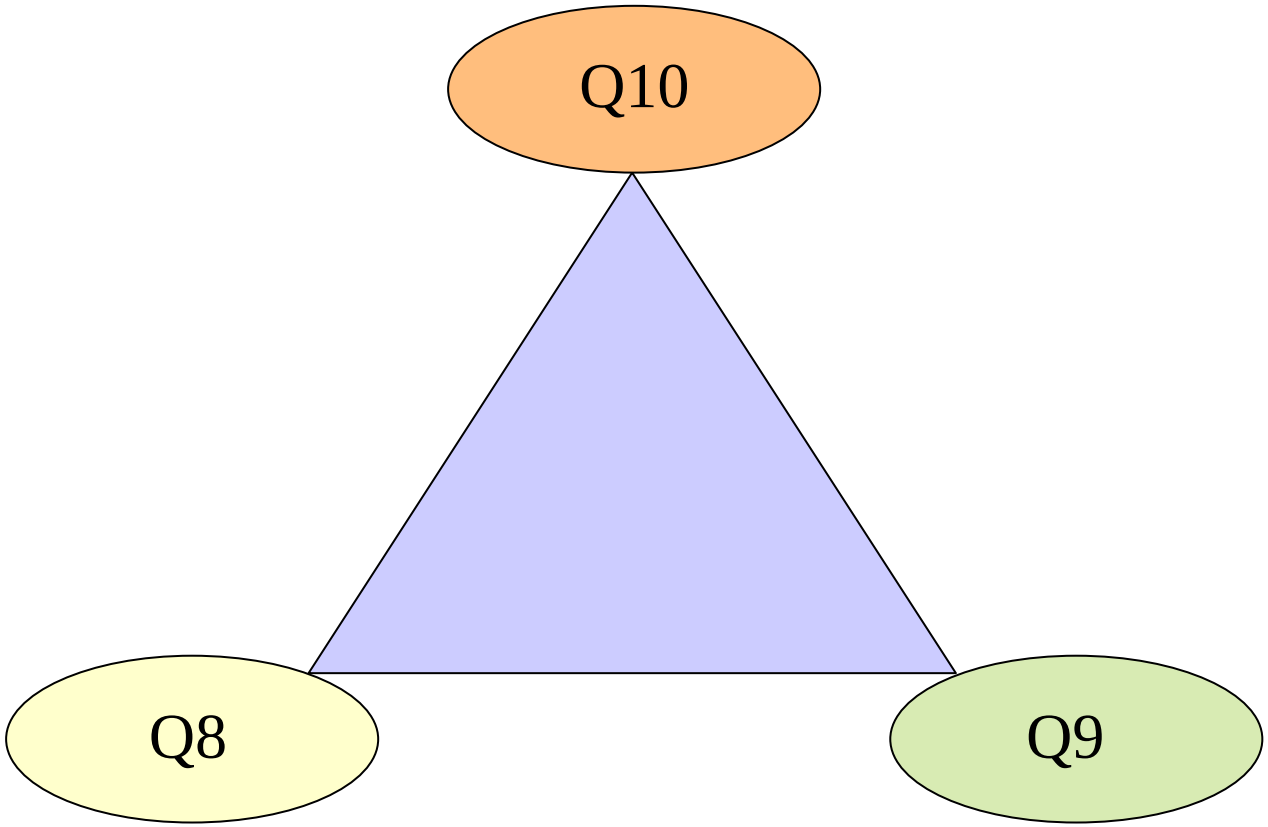
- Not part of EU regulatory system.
- Current EC regulations concerning variations to marketing authorisation (No 1084/2003; 1085/2003) are valid.

# 6. Quality system (ICH Q10)

Develop a harmonized pharmaceutical quality system applicable across the life cycle of the product emphasizing an integrated approach to quality risk management and science.

(ICH meeting 2003, Brüssel)

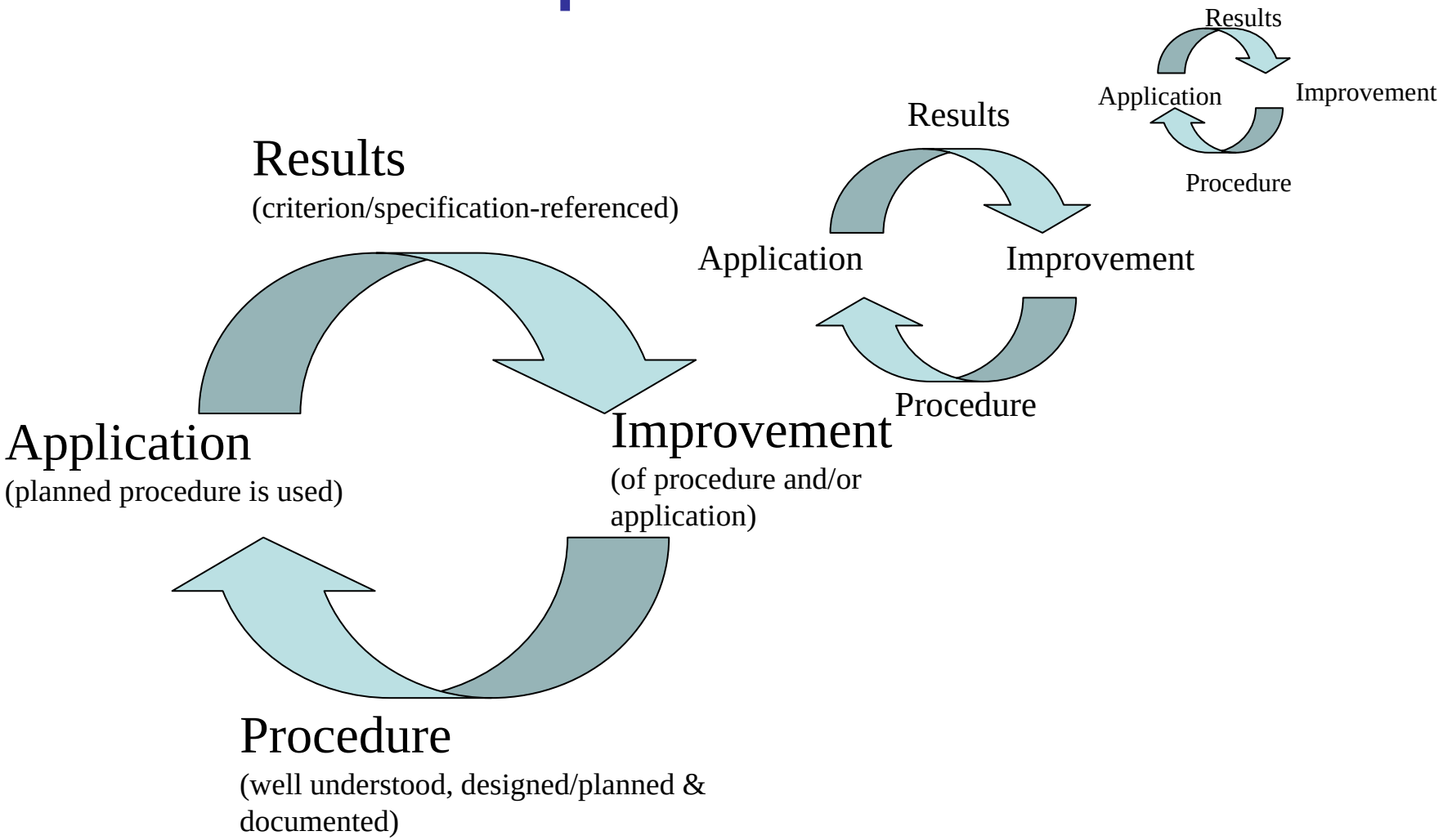
# ICH guidelines simplifying regulatory implementation of PAT



# Quality System (ICH 10)

- Key elements from ISO 9001:2000 and ISO 9004 to complement existing GMPs (active substance, products)
- To promote continual improvements over the life-cycle of the product

# 6. Quality system for continuous improvements



# 6. Quality system of continuous improvements

**Following approval – lifecycle perspective:**

- Within design space → Regulatory relief
- Outside design space → Regulatory process
- Continuous change of design space →
  → Regulatory process

# Challenges for Industry

- Amount/level of information to present to regulators (e.g. chemometrics/statistics)
- Validation of association between measurements during manufacture versus release testing according to specification → basis for release of batch

# Challenges for Regulators

- Change in review process
- Enhanced collaboration between assessors and inspectors:
  - at submission and during lifecycle
  - clarification of respective responsibility
- New definitions and specifications (?)

# EU PAT Team - Reflections

- Lot of activity in the area
- Companies using different approaches and philosophies and are at different stage of progress
- Internal discussions within companies are key factor

# Present tripartite discussions

- ICH Q8-9 guidelines – following step 2 consultation
- ICH Q8, Annex
- ICH Q10 – draft for step 2 consultation
- PAT and biological products

EU PAT Team is actively working to ensure that regulators and inspectors across EU are ready to assess any PAT related submission.

So, please, take the initiative and submit PAT-applications.

# EMEA Contact details

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