Dry Eyes – Regulatory perspectives

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The views presented are personal and not necessarily the views of the SAWP, the CHMP or the MPA

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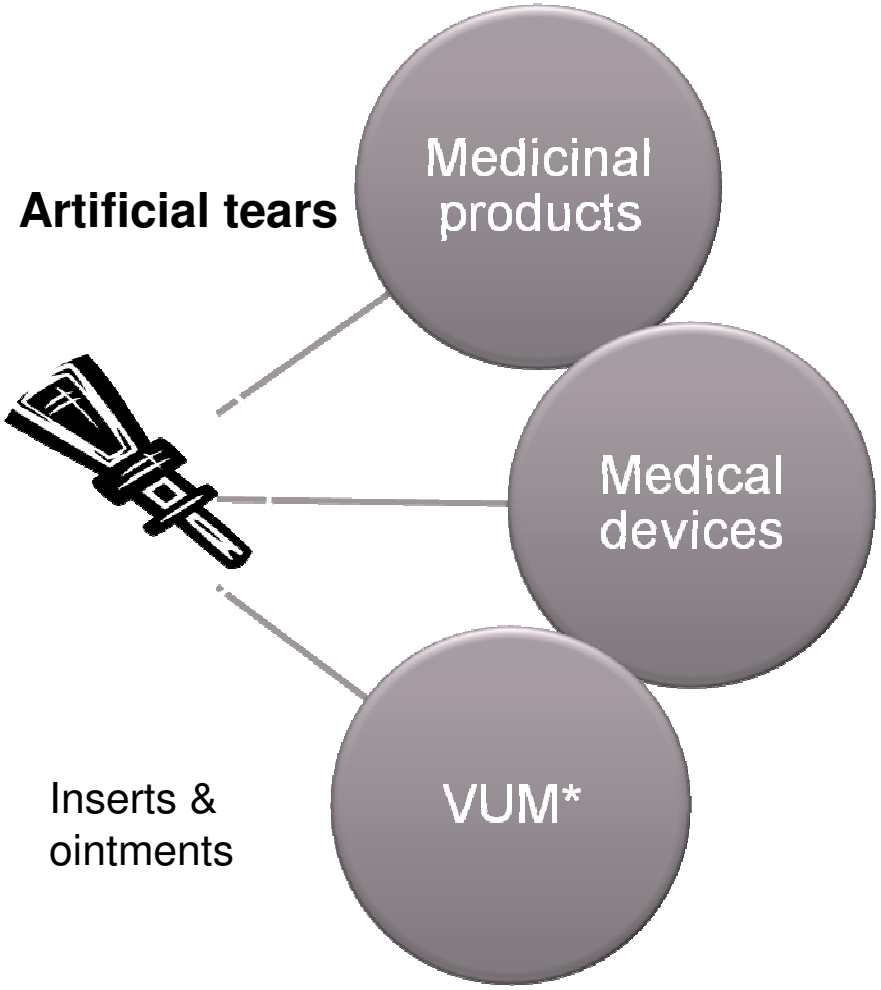
Give a regulatory view on frequently asked questions

- **For example,**
  - Study population
  - Endpoints
  - Comparator
  - Duration of studies
  - Adverse environment chamber
  - ...

No centrally approved pharmacological therapy in EU



- Approved (MRP)
  - Pilocarpine 5 mg tablets
    - Symptomatic treatment of dry eyes in Sjögren's syndrome
- Used (SE)
  - Bromhexine 8 mg
  - Evening primrose (*Oenothera glazioviana*)
  - …

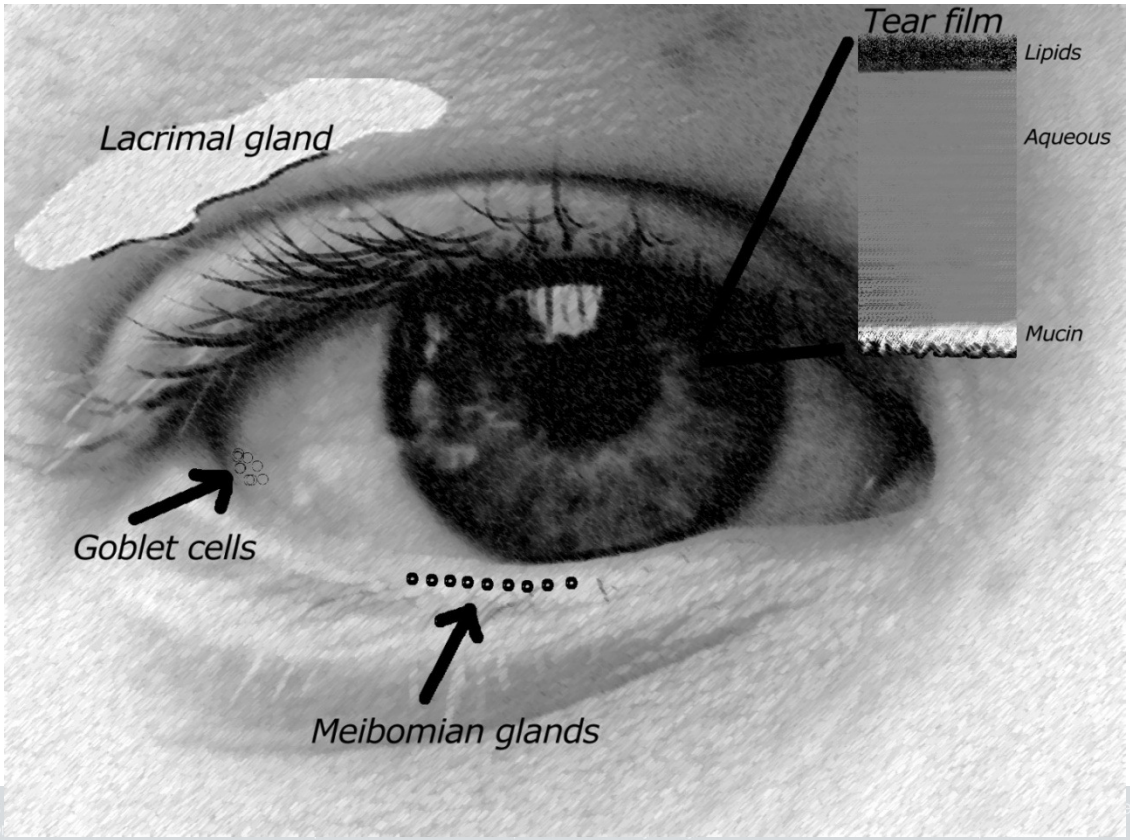
*Certain medicinal products for external use (specific for SE)

Heterogeneous disease

- **Reason for dry eye?**
  - Impaired tear function, meibomian gland dysfunction (MGD), mucin deficiency, extrinsic factors, a mix

Evaporative

Tear deficient



Define target population!

- **Reasons for dry eye**
- **Well-documented history of DED**
  - Persistence of symptoms
- **Severity**
  - Reasonable to target a more severe population for pharmacological therapy
    - (Mild), moderate, severe?
    - Based on signs and symptoms
- **Duration of disease**
  - Affect corneal sensitivity (symptoms)?
  - Affect severity?

Endpoints - Requirements

- **Which weight are they given?**
- **What are the associated claims?**
- **All data will be considered**
- **Benefits in relation to risks**

Endpoints

- **Signs and symptoms**
  - Normally significant differences both in symptoms and signs required (co-primary endpoint)
  - Significant effect in sign or symptoms with a strong trend in the other
    - Multiplicity

Signs (I)

- **Consider target population**
  - Selection of one sign over the other guided by
    - disease aetiology
    - underlying mechanism of action of the compound
    - phase II data

- **Frequently used**
  - Corneal staining (Oxford, NEI)
    - Justify validity of other scales
  - Schirmer
  - Tear break up time
    - generally a secondary endpoint, of importance in MGD

Signs (II)

- **Upcoming**
  - Tear osmolarity
    - Option if supported with validated evidence
  - Ocular protection index?
    - Limited info

- **In MGD**
  - Appearance of lid margin abnormalities/redness and/or gland obstruction/drop out
    - Standardised grading and evaluation system not available
  - Composition of meibum?

Symptoms

- **Symptomatic disease!**
- **Composite measure recommended**
  - Validated questionnaire
  - MGD - no specific questionnaire available

- **Use of one single worst symptom discouraged**
  - Subjectivity and variability limit usefulness
    - Adequate marker of a subjective clinical benefit??
  - Changes in other symptoms may not parallel worst symptom over time
  - Multiplicity!

In addition

- **Address the intended mode of action of the compound**
  - Tear production
  - Marker of mucin secretion
  - Meibum composition
  - Marker of ocular surface inflammation

Effect size

- **Statistical significance not all…**
  - Relevant effect size!
  - The effects size needs to be supported for the chosen endpoint
- **Include evaluation of mean changes and responder analyses**
  - Difference between the means must be clinically relevant
  - Predefined relevant definition of responders

Comparator (I)

- **Vehicle**
  - Straight forward
  - Addresses potential effect/intolerance of vehicle

- **Artificial tears**
  - If target population already regular users (more severe population)
  - If composition of vehicle similar to what is included in artificial tears

Comparator (II)

- **In MGD**
  - Vs. best standard of care?
    - Best standard of care not defined
      - lid hygiene/warm compresses/lid massage
      - artificial tears/topical lipid supplements
      - (topical antibiotics/tetracycline p.o.)
  - Masking and compliance with lid hygiene an issue!

Concomitant use of artificial tears

- **May be necessary to prevent a large drop-out (in vehicle group)**
  - if infrequent administration

- **Must be documented**
- **Address extent of use as a secondary outcome**

Duration of studies

- **Pharmacological treatment**
  - Efficacy
    - When chronic treatment foreseen, primary evaluation at 6 months to confirm that effect is maintained
  - Safety
    - Generally 12 months (ICH E1 Population Exposure)
  - If (chronic) intermittent use foreseen, consider randomised withdrawal to evaluate maintenance.
- **Artificial tears**
  - If new composition, 3 months generally sufficient for efficacy.
  - Longer safety follow up needed.

Controlled adverse environment

- **Useful in exploratory trials**
  - Proof of concept
  - Aid in dose selection
  - Evaluate biomarkers
- **Not acceptable as pivotal trial without environmental study**
  - selects an enriched patient population
    - questioned whether this population is representative for target population
  - lose real life heterogeneity
    - overestimation of effect

Inflammation

- **Several anti-inflammatory products in development**

- **2ndary manifestation**
- **Need to address in PD studies (biomarkers)**
- **Exploratory marker in pivotal studies**
- **Duration of effect after discontinuation of treatment?**

Studies in general

- **Superiority trials**
  - Lack of comparator in EU
  - If available, assay sensitivity still an issue

- **History of failures, two confirmatory studies recommended**
  - Don't have to be replicates
  - One pivotal trial
    - A clinically convincing and statistically compelling outcome needed (PtC One Pivotal study CPMP/EWP/2330/99)

In conclusion

- **Sign & symptoms stage**
- **Need to learn more about the disease(s)**
- **Need to get a better understanding of**
  - the relevance and usefulness of different outcome measures
  - the strengths and weaknesses of the symptom scales and visual function quality of life questionnaires

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