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New galenical approaches to reach the anterior segment of the eye

17. Jahreskongress für Klinische Pharmakologie
1. – 2. Oktober 2015, Köln

How to achieve prolonged release ?

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Drugs intended for systemic availability

- oral modified release formulations up to 24 hours
  - classical matrix MR products
  - zero-Order release as perfect aim (e.g. OROS®) etc ..
- other prolonged release systems up to several days / weeks
  - transdermal therapeutic systems
  - transdermal depot formulations / implants

Drugs intended for local availability

- locally applied modified release formulations
  - target organ allows such an approach
  - often the difficulty of limited residence time
- sophisticated drug / device combinations
  - anatomy of target organ allows insertion (e.g. vagina)

Systemic availability still remains a safety topic !

Local MR – the “old-fashioned” way

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Example pilocarpine: viscous gel

PILOPINE HS®
(pilocarpine hydrochloride ophthalmic gel) 4% -
Each Gram Contains:
Active: pilocarpine hydrochloride 4% (40 mg).
Preservative: benzalkonium chloride 0.008%.
Inactives: carbopol 940, edetate disodium, hydrochloric acid and/or sodium hydroxide (to adjust pH) and purified water.

- patient´s regular application needed – what does this mean?

Disadvantages in daily life

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Daily application of gel

- difficult handling
- especially for the elderlies
- visual blurring after administration
- compliance often not the best

Number of days without therapy (out of 365 days)

Age range	Number of days (out of 365)
66 – 74 (n = 695)	118.4 (± 109.9)
75 – 84 (n = 970)	109.5 (± 112.4)
85 + y (n = 775)	109.7 (± 112.7)

Source: Gurwitz et al. Am J Publ Health, 1993

Why drug-device combinations ?

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Potential reasons for drug-device combinations

- intended local application for locally acting drugs
- intended drug targeting due to
  - improved therapeutic effect when the site of action is difficult to reach
  - improved tolerability when the side-effect pattern constrains regular systemic administration
- necessity to overcome drug substance limitations
  - high–first pass metabolism
  - poor absorption due to solubility problems or molecule size
- therapeutic necessity for (local) prolonged release
  - the-flatter-the-better concept applicable
  - either for systemic or for local administration

Ocusert® – prolonged release device

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Galenic principle

- a pilocarpine reservoir surrounded by an annular ring for visibility/ handling
- once weekly administration
- at bedtime due to initial blurred vision

Compliance related difficulties

- need for instruction
- need for reliability of the patient
- risk of unaware device loss
- occasional side effect of cutting sensation
- transient blurred vision
- high costs

Therapeutic progress: Ocusert®

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Approved pilocarpine containing system established since decades

- increased ocular residence
- release at a slow and constant rate
- accurate dosing (contrary to eye drops)
- reduction of systemic absorption
- lower incidence of visual and systemic side-effects
- better patient compliance
- possibility of targeting internal ocular tissues through non-corneal (conjunctival scleral) routes
- no preservatives needed

Device suitable also for other drugs ...

New inserts: what to test prior to FIM?

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Interplay of drug and formulation

- In-vitro studies to predict the in-vivo-behaviour in the eye
  - swelling index in physiological buffer over time
  - Scanning Electron Microscopy for morphological characterisation of the surface and to detect cristals
  - drug content
  - content uniformity
  - in-vitro drug release (Franz Cell System)

Animal studies

- comparative biodistribution studies (vs. eye drops)
- experimental model of HA induced glaucoma

Predictive value ? Guideline Recommendation ?

Source: Franca et al.: PLOS online, 2014

MIGS – better regulatory situation !

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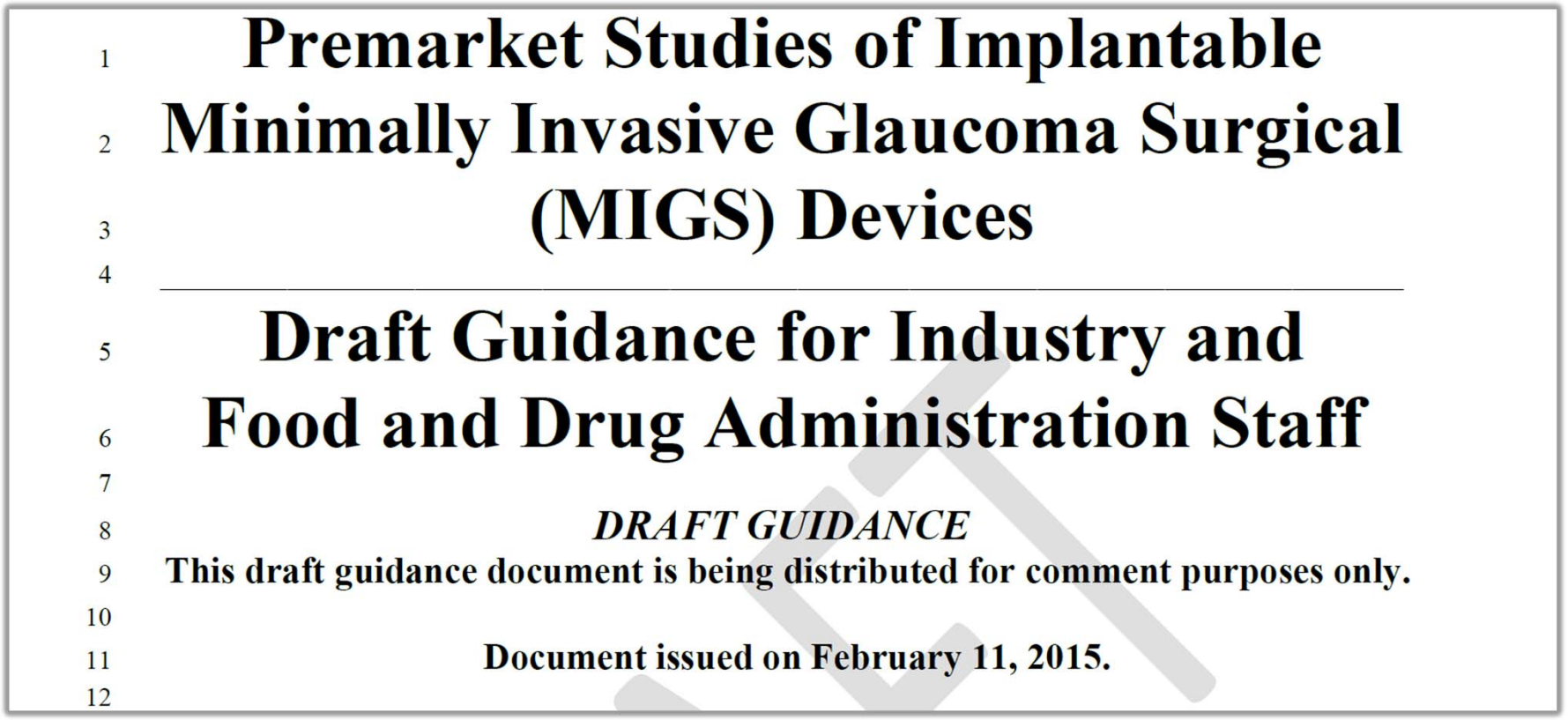
Implantable Invasive Glaucoma Surgical Devices

- US – Draft Guidance for Industry recently published



Premarket Studies of Implantable Minimally Invasive Glaucoma Surgical (MIGS) Devices

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Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on February 11, 2015.

MIGS – better regulatory situation !

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Detailed guidance on tests to be performed in vitro

- biocompatibility Tests
  - e.g. cytotoxicity, sensitization, ocular irritation, systemic toxicity, sub-chronic toxicity, genotoxicity, carcinogenicity, pyrogens testing
  - physico-chemical tests (extractables, hydrolytic stability, leachables, insoluble inorganics)
  - biological response from mechanical failure
  - sample preparation (e.g. polar and non-polar extraction procedure)
- physical and mechanical testing
  - validation of dimensional tolerances
  - surface and edge quality
  - structural intergrity
  - insertion testing if delivered from an injector system
  - specific tests for coated devices and metallic devices
- sterility/package integrity; shelf life/shipping stability ... etc

MIGS – better regulatory situation !

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Detailed guidance on clinical testing

- study design
  - 12 to 24 months follow-up prior to submission
  - patients with defined early or moderate open angle glaucoma
  - wash-out phase necessary
- endpoint
  - baseline IOP to be determined after wash-out
  - percentage of patients with reduction of at least 20% mean diurnal IOP from baseline
  - additional analysis prespecified including diurnal fluctuation
- safety outcome
  - hypotony as early (within 2 weeks after surgery) or late adverse event with predefined conditions
  - substantial visual field loss
  - chronic anterior uveitis

Next generation: drug implants

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Bimatoprost SR: currently under development

- injector with implant intended for injection into anterior chamber
- sustained-release prostamide-loaded implant
- bioerodible
- to be done at the ophthalmologist's office
- τ = 4 to 6 months

First-in-Class technology of Allergan

Bimatoprost SR: current clinical studies

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currently running phase-III-trials

- sponsor: Allergan
- 2 studies in parallel in different regions
- start August 2015 – status: currently recruiting
- 600 patients with open-angle glaucoma/ocular hypertension
- design of :
  - double-blind, double-dummy
  - reference: standard treatment (timolol eye drops)
  - using sham inserts and placebo eye-drops
  - 2 different bimatoprost doses tested
- total duration 20 months
  - 12 months treatment, 8 months follow-up
- primary endpoint: IOP change from baseline over time

Source: www.clinicaltrials.gov

Bimatoprost SR: current clinical studies

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currently planned phase-III-trial by Allergan

- reference: selective laser trabeculoplasty
- start August 2015 – status: planned
- 160 patients with open-angle glaucoma/ocular hypertension
- design:
  - sham SLT on Day 1 followed by Bimatoprost SR Dose A administered on Day 4, Weeks 16 and 32 in the primary eye
  - SLT on Day 1 followed by Sham Bimatoprost SR administered on Day 4, Weeks 16 and 32 in the other eye
- total duration 20 months
  - 12 months treatment, 8 months follow-up
- primary endpoint: IOP change from baseline over time

Source: https://www.clinicaltrials.gov

New Endpoints introduced

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commonly applied endpoints in glaucoma trials

- reduction of intraocular pressure
- visual function (e.g. by Humphrey Field analyser)

alternative approaches discussed since 2008

- FDA is open to use structural endpoints as surrogate ...
- ... asks for proof of predictivity for (future) visual function
- potential advantages
  - more consistent
  - less variable
  - shorter duration of the trials
  - lower costs
  - less trials

Fits into FDA critical path initiative !

Source: Weinreb and Kaufman, iovs 2011

New Endpoints introduced

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potential alternative methods

- optical coherence tomography (OCT)
  - retinal nerve fibre layer (RNFL): greater sensitivity for progress assumed and correspondence to function expected
- stereoscopic optic disc photography
  - optic disc: changes are strongly predictive for function, but qualitatively only (high level of subjectivity)
- scanning laser polarimetry
  - peripapillary RNFL thickness: structure/function relationship demonstrated
- confocal scanning laser ophthalmoscopy
  - optic disc surface topography: age-related changes in normal control

Source: Weinreb and Kaufman, iovs 2011

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Concepts in Drug Research and Development

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