R&D in the Next Decade

Santen's R&D Transformation

R&D Meeting

September 11, 2015

Today's agenda

Naveed Shams	Santen's R&D Transformation
Takeshi Matsugi	Non-Clinical Research
Masatsugu Nakamura	Disease Area Strategy
Kenji Morishima	Ocular Drug Delivery
Terri Phillips	Global Medical Affairs
Franz Buchholzer	Global Regulatory Affairs
Naveed Shams	Concluding Remarks

R&D in the next decade

Santen's R&D transformation

Naveed Shams MD Ph.D.
Senior Corporate Officer
Head Global R&D and Chief Scientific Officer
President & CEO Santen Inc, USA

September 11, 2015

Santen's corporate values

天機に参与する

Tenki ni sanyo suru

By focusing our efforts on ophthalmology and related areas, Santen develops scientific knowledge and organizational capabilities which are unique and original to Santen. We use our unique capabilities to contribute to patients and their loved ones, and consequently to society.

Global R&D leadership

Naveed Shams
Senior Corporate Officer & CSO, Head of R&D Division

Masatsugu Nakamura
Head of Global Ophthalmic Disease Area Strategy

Najam Sharif
Head of Global Biomedical Science, Santen Inc.

Yoshihito Tsukushi
Head of Global R&D Portfolio and Resource Planning

Tetsuo Kawaguchi
Head of Global Program Leaders

Elo Kent
Head of Innovation Office, Santen Inc.

Kenji Morishima
Corporate Officer, Head of Global Pharma Technology Development, Regional Rep., Asia

Takeshi Matsugi
Head of Global Non-Clinical Research

Yoshikazu Matsumoto
Head of Global Clinical Operations, Santen Inc.

Terri L. Phillips
Head of Global Medical Affairs, Santen Inc.

Franz Buchholzer
Head of Global Regulatory Affairs, Santen Switzerland SA

Yusuf Ali
Regional Representative, USA

Kazuyuki Nishioka
Regional Representative, Europe

(As of July 1, 2015)

A specialty pharmaceutical company with a global presence

Utilizing unique technologies and pathobiology understanding to develop differentiated products and drive global growth

Strong, stable position in Japan & Asia, pursuing growth in key regions

Aiming to become a global top-3 ophthalmology company

Transforming Santen R&D

- Reduce **time to launch**; Faster with focus on the right products to the right patients

TTL

- Significantly improve **probability of technical success** in all target disease areas

PTS

- Target and address region-specific **unmet medical needs**

UMN

Reducing time to launch

Pursuing first-in-man adaptive design

Early evaluation in man in regions of interest or feasibility

Rolling regional submissions

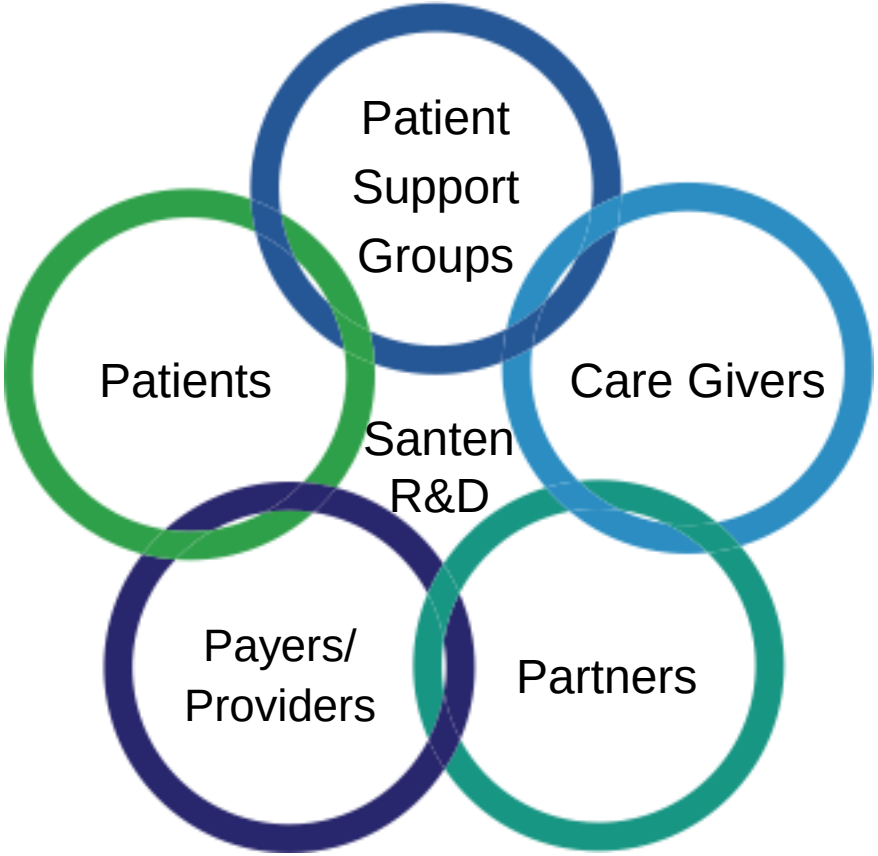
New indications/ adaption for better outcomes

Achieve 30% reduction in time to launch

Improving PTS

1	2	3	4
Disease knowledge via public domains	Understanding contextual pathophysiology	Testable Hypotheses	Early Human Studies
• Biology • Epidemiology • Genomics etc. • Other	• Disease subtype • Mechanisms • Targets • Biomarkers • Safety	Evidence to make the case • Targets • Molecular entities • Patient subpopulation • Disease-specific biomarkers • Efficacy biomarkers • Safety biomarkers	

Interaction and interface with customers in real time



Address UMN in specific regions

Addressing the needs of a changing world

Disease areas with region-specific needs

Asia	Developing world	Developed world	Worldwide
Myopia	Infectious disease	Age related diseases / dry eye Chronic illness / complications of diabetes	Rare diseases

Disease area strategy

- Focus on differentiated life-cycle management and GE products
- Improve PTS by developing deep understanding of pathobiology and unmet needs through translational research, biomarkers and diagnostics
- Boost productivity by prioritizing programs that can be Best-in-Class (BIC)*
- Pursue partnered R&D through clearly defined business development and in-licensing opportunities

*BIC: Any new product candidate that has POC in human with ophthalmic or other systemic indications

Non-Clinical Research

Takeshi Matsugi Ph.D.
Head of Global Non-Clinical Research

September 11, 2015

Santen's R&D Transformation

Santen's Non-Clinical Research organization and R&D capabilities

500+ R&D scientists developing innovative and differentiated products meeting global medical needs in Ophthalmology

Global Non-Clinical Research

Ophthalmic Pharmacology
- Pharmacology
- Translational Research

Toxicology and Pharmacokinetics
- Toxicology
- Pathology
- Pharmacokinetics

Santen HQ Japan

Santen SAS France

Santen Oy Finland

Santen Inc USA

Nara R&D Center Japan

Unique initiatives of Non-Clinical Research

New Pipeline Products

Filing of Differentiated Products
Focus on minimum Requirements for filing

Translational Research

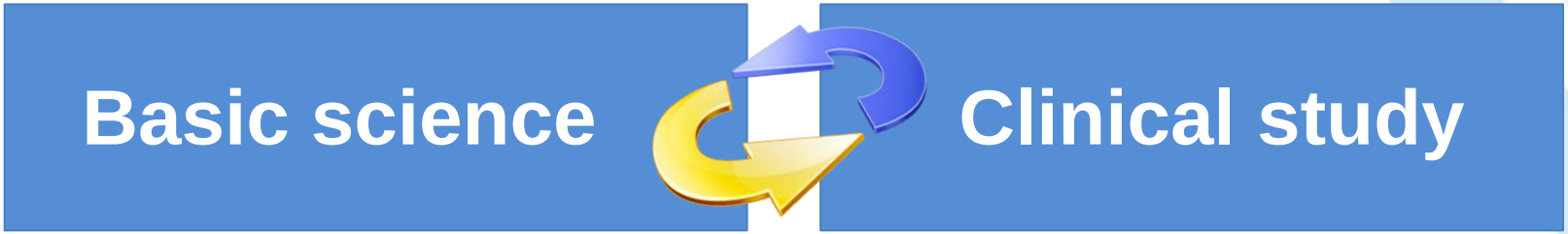
$$P \propto \frac{WIP \times V \times PTS}{C \times CT}$$

P	=	Productivity
WiP	=	Work-in-Progress
V	=	Value
PTS	=	Probability of Technical Success
C	=	Invested cost
CT	=	Cycle Time

(Reference for Productivity formula: Nature Reviews, 2010; 9, 203-214)

Translational research / biomarkers

To optimize proof of concept and increase probability of technical success (PTS)



Our initiatives include translational research / biomarker exploration

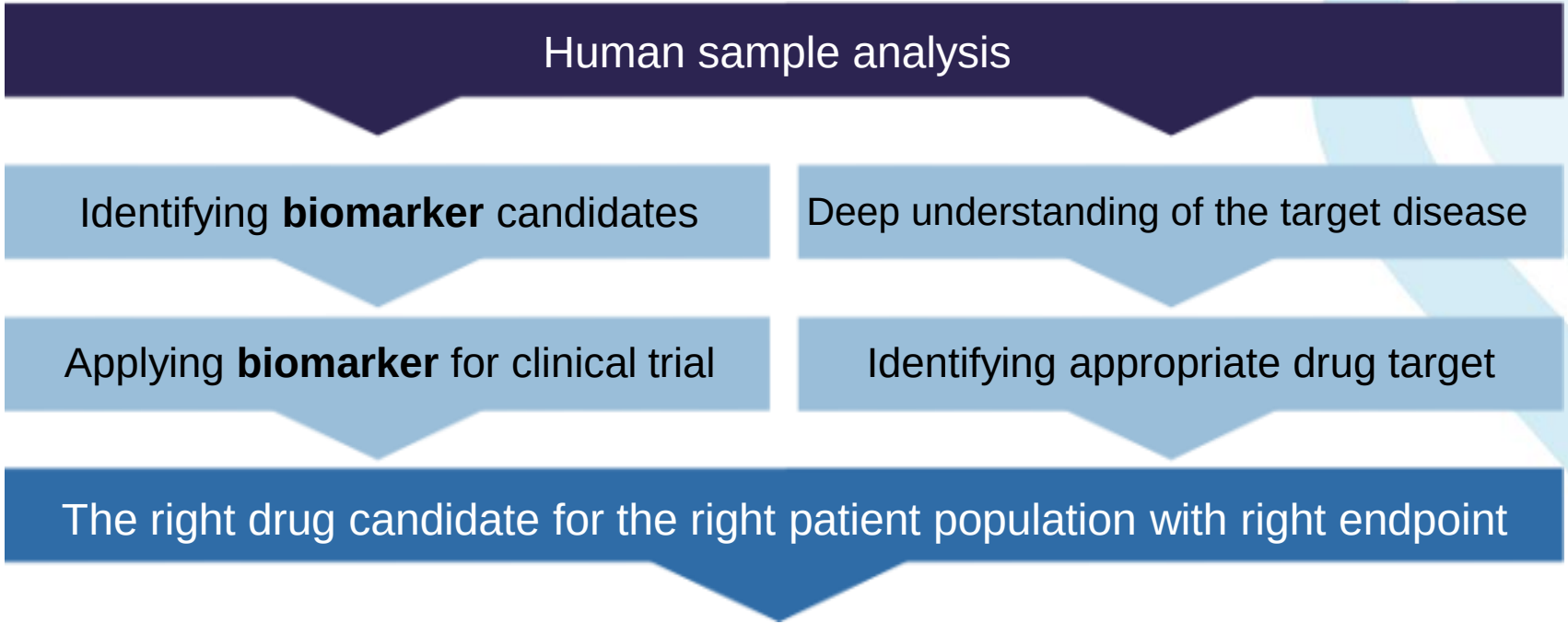
What are biomarkers?

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

(Biomarkers Definitions Working Group, Clin. Pharmacol. Ther. 2001; 69, 89–95)

The power of biomarkers

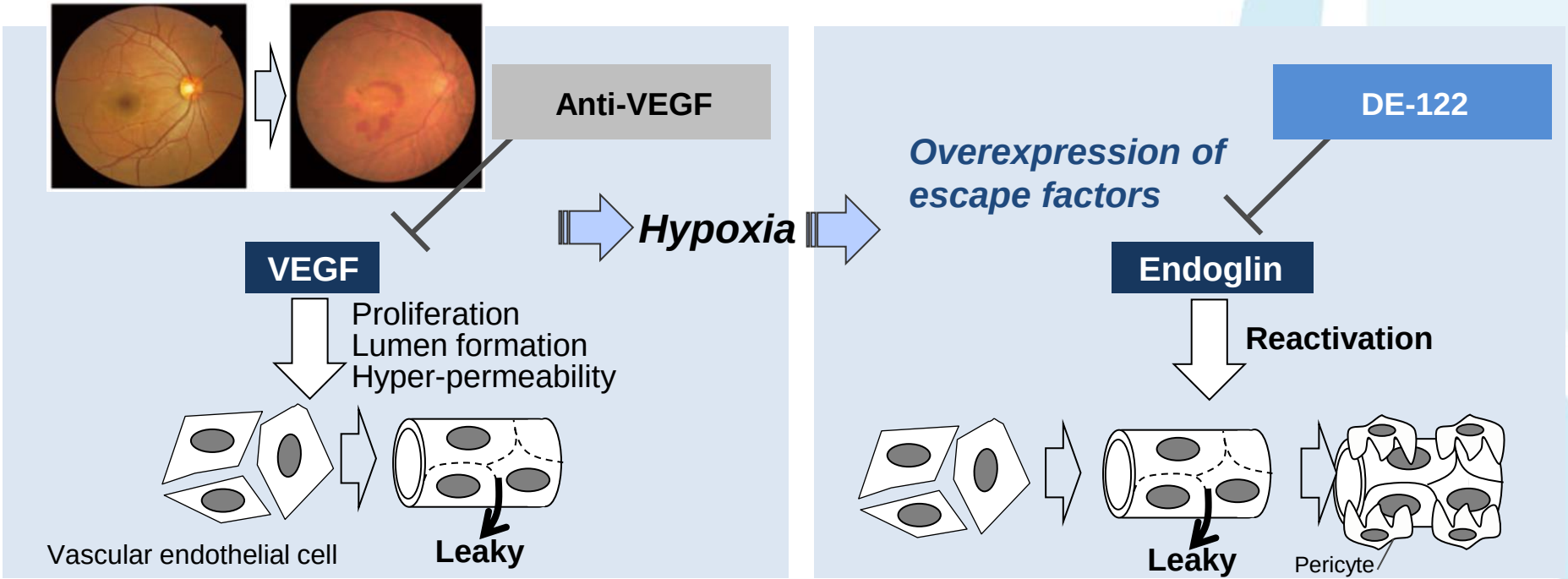
Biomarkers will help increase PTS and develop the best medicines for patients.



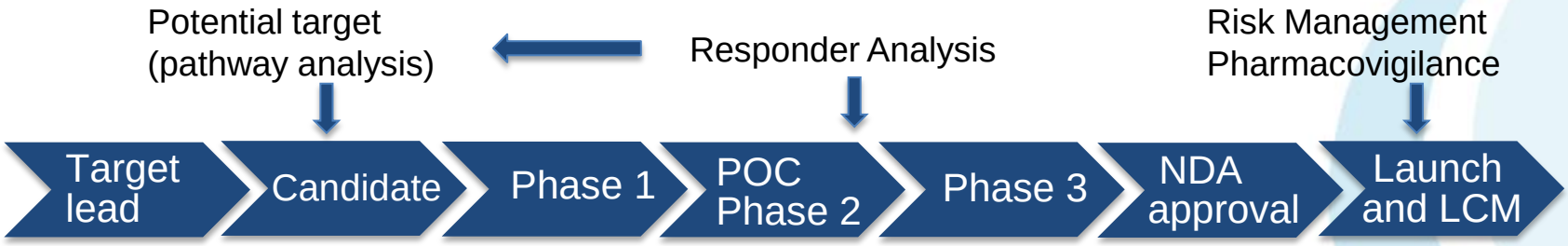
The power of biomarkers

Example:

DE-122 appears effective for Wet AMD patients with Endoglin over-expression in the retina



Ongoing translational research projects



Anti-Endoglin antibody IVT	DE-122	VEGF, Endoglin in serum and aqueous humor
VEGF, PDGF dual inhibitor IVT	DE-120	VEGF in serum
EP2 receptor agonist Eye drop	DE-117	DNA banking
mTOR inhibitor IVT	DE-109	DNA banking T-cell phenotype and function

IVT: Intravitreal Injection, LCM: Lifecycle management

Summary

- Translational research is key to improving PTS, thereby raising productivity
- We will deepen our exploration of biomarkers in humans to increase PTS and achieve early approval of products

Disease Area Strategy

Masatsugu Nakamura Ph.D.
Head of Global Ophthalmic Disease Area Strategy

September 11, 2015

Santen's R&D Transformation

Disease Area Strategy (DAS)

Global Disease Area Strategy

- Ophthalmic DAS Group
  FOTE, BOTE, Glaucoma
- Translational Research Team
- Research Planning & Networking Team

Disease Area Strategy

- Focus on differentiated life-cycle management and GE products
- Improve PTS by developing deep understanding of pathobiology and unmet needs through translational research, biomarkers and diagnostics
- Boost productivity by prioritizing programs that can be Best-in-Class (BIC)*
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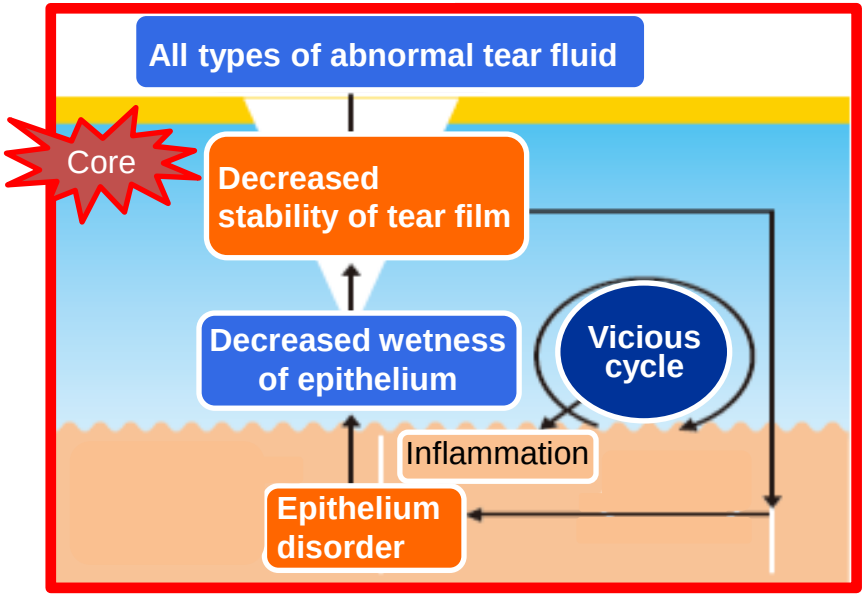
Targeting drivers of pathobiology / molecular pathways (1)

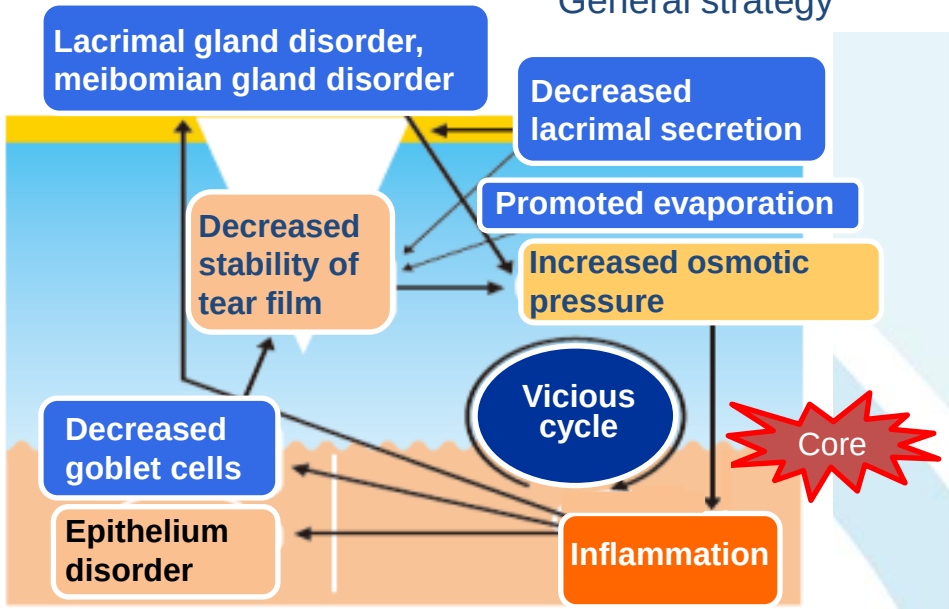
Dry Eye Strategy: Focus on tear film stability

Santen strategy



In Japan/Asia, tear film instability is the core mechanism of dry eye: TFOT (tear film oriented therapy) concept

General strategy

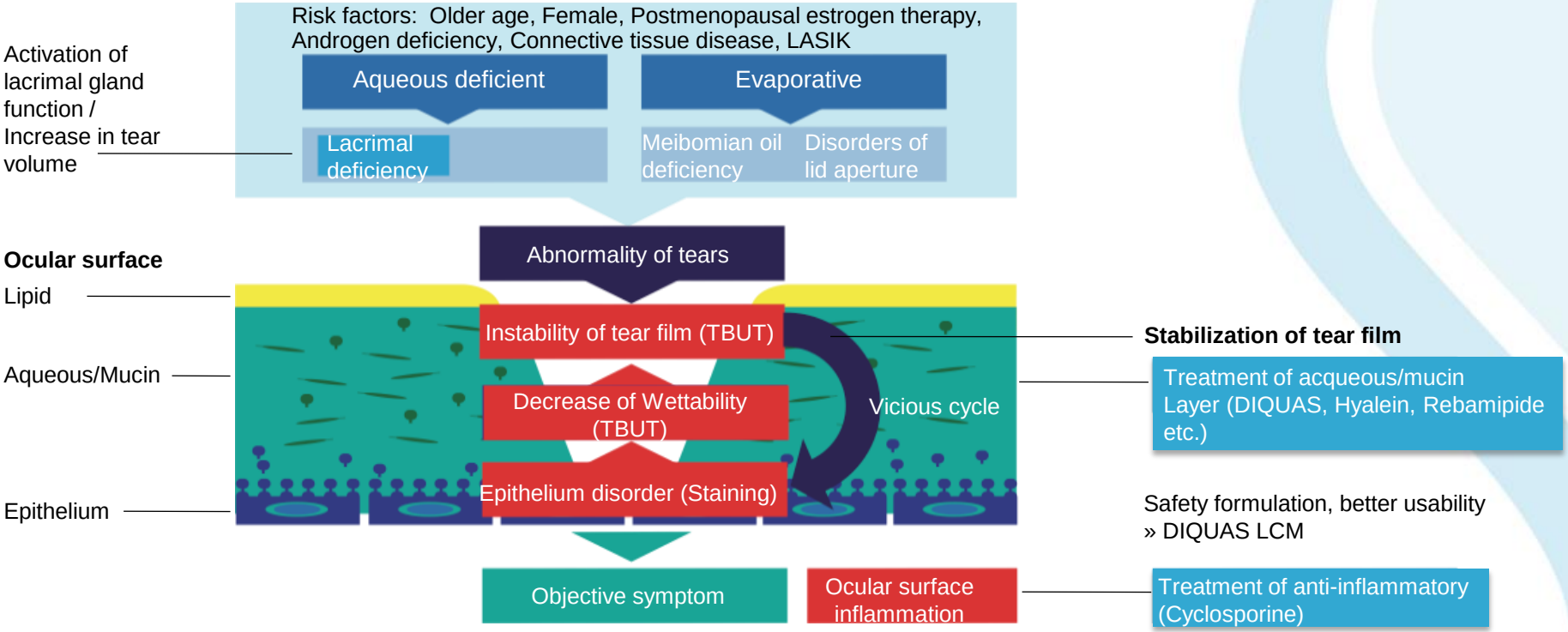


In the US, inflammation is the core mechanism of dry eye, but many candidates have failed in clinical trials

Yokoi, Norihiko and others, Journal of the Eye, 2 9:291-297, 2012

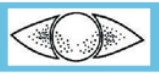
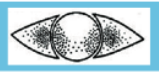
Targeting drivers of pathobiology / molecular pathways (2)

Pathogenesis of dry eye and UMNs

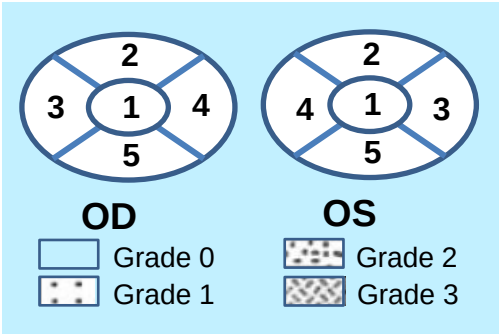


Improving productivity: Biomarker identification / validation

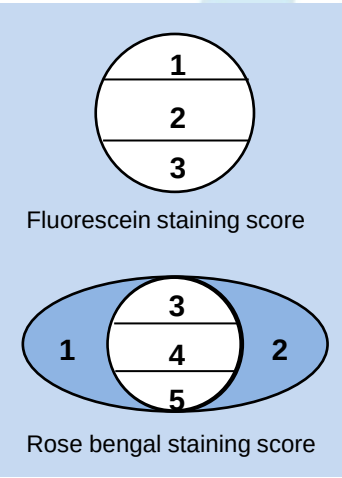
Imaging for FOTE: evaluation of vital staining

Panel	Grade	Criteria
A 	0	Equal to or less than panel A
B 	I	Equal to or less than panel B, greater than A
C 	II	Equal to or less than panel C, greater than B
D 	III	Equal to or less than panel D, greater than C
E 	IV	Equal to or less than panel E, greater than D
>E	V	Greater than panel E

The Oxford grading scale (Oxford)



The grading system recommended by the NEI Workshop (NEI)



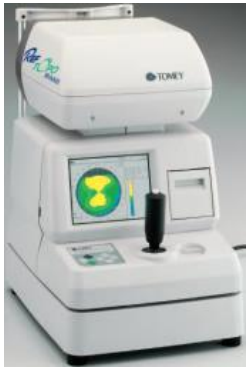
Grading scale used in Santen clinical trial

Establish grading system of keratoconjunctival damage

Improving productivity: Biomarker identification / validation

Imaging for FOTE: evaluation of tear film stability

DR-1



TSAS

Keratograph

Establish quantitative evaluation with standardized methods

Improving productivity: Biomarker identification / validation

Selection of appropriate patients for dry eye

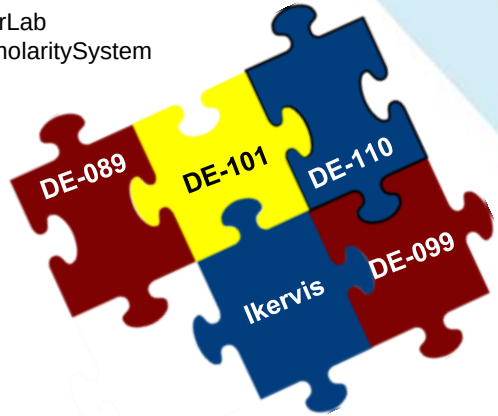
■Identify appropriate patients for treatment using biomarkers

- Santen is exploring innovations including development of our own biomarkers and modification of use of existing systems (such as those below)

Schirmer Test

InflammaDry®

TearLab OsmolaritySystem



■Search for dry-eye specific symptoms

- Meta-analysis using Santen's clinical data

Improving productivity: Open innovation / network strategy

Joint activity with associations

Strategic joint research with academia




Partnerships with systemic pharmaceutical companies: BIC strategy

エーザイ株式会社

Summary

Critical elements for Santen Vision 2020 and beyond:

- Focus on differentiation
- Expand geographic network
- **Focus on disease drivers**
- **Improve probability of success**
- **Improve productivity**
- Enhance business development & licensing activities

Ocular Drug Delivery

Kenji Morishima
Corporate Officer, Head of Global Pharmaceutical Technology Development

September 11, 2015

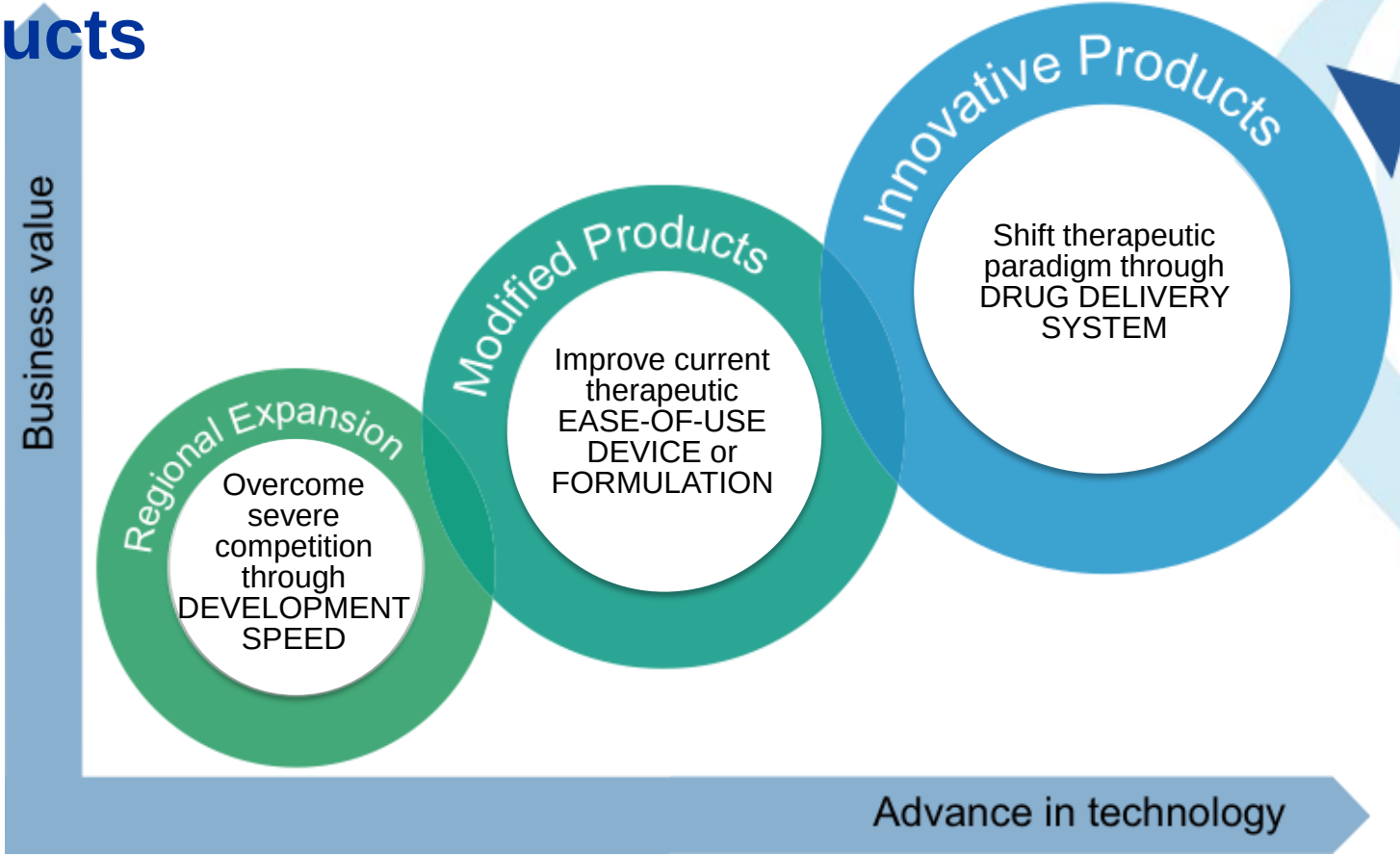
Santen's R&D Transformation

Global Pharmaceutical Technology

Global Pharmaceutical Technology

- Advanced technology
- Pharmaceutical development
- Analytical and Synthetic Chemistry
- Process development and transfer

Aggressive Life Cycle Management of marketed products



Unmet medical needs as DDS targets

Drug Delivery System (DDS): Formulation technology engineered to deliver the right amount of the drug to hit the right target at the right time.

Front of the eye

- Improve adherence
- Reduce frequency of instillation
- Reduce systemic and topical adverse events

Glaucoma

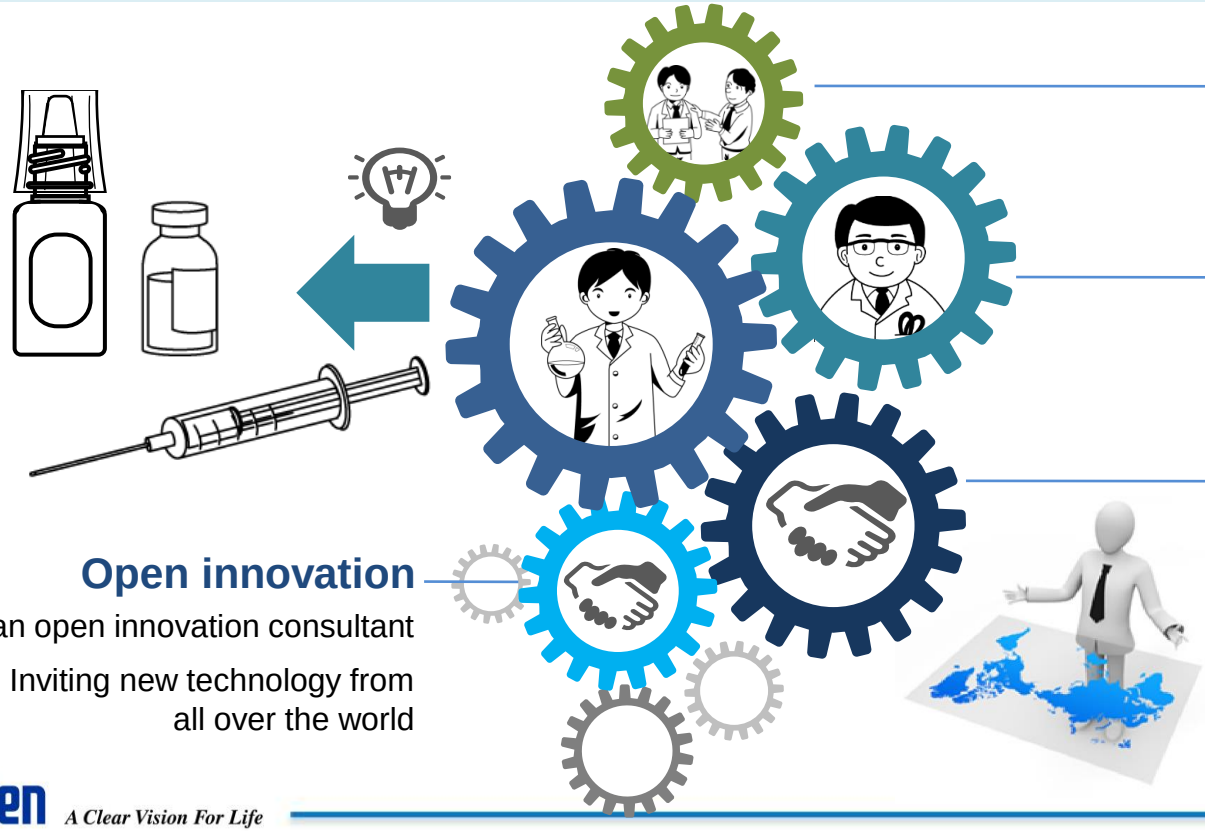
- Strong intraocular pressure (IOP) reduction over Latanoprost
- Improve adherence
- Reduce frequency of instillation
- Reduce systemic and topical adverse events
- Mid-term sustained delivery

Back of the eye

- Long-term sustained delivery
- Strong efficacy over ranibizumab and aflibercept
- Reduce frequency of instillation

Network-based development at Santen

Connect (unmet medical needs + external technologies) **and Develop**



KOL field visits
Field Visits
Questionnaires

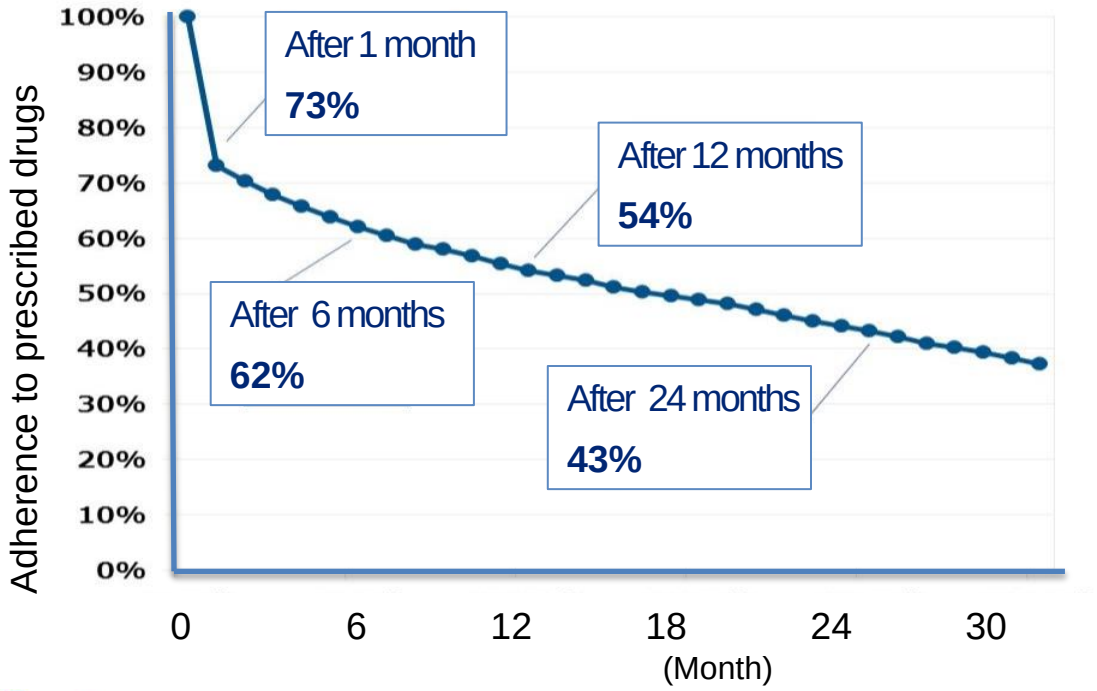
Advisory panel
Drug Delivery
Advisory Panel

Global partnerships
Academia
Research Institutes
Start-up company

Open innovation
Utilize an open innovation consultant
Inviting new technology from all over the world

Benefits of DDS: improving adherence through ease of use

Adherence among new glaucoma patients is significantly low



Source: ©2015 IMS Health
Calculated based on IMS-NPA 2009-11
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Recent examples of ease of use

Unit Dose

Original products

60 ampules

Preservative-Free
Multi Dose

New dosage form

1 bottle

Original products

5 min. interval between drops

New dosage form

Combination Product

If drug A is followed by drug B within 30 secs,
50% of drug A is washed out

and less frequency

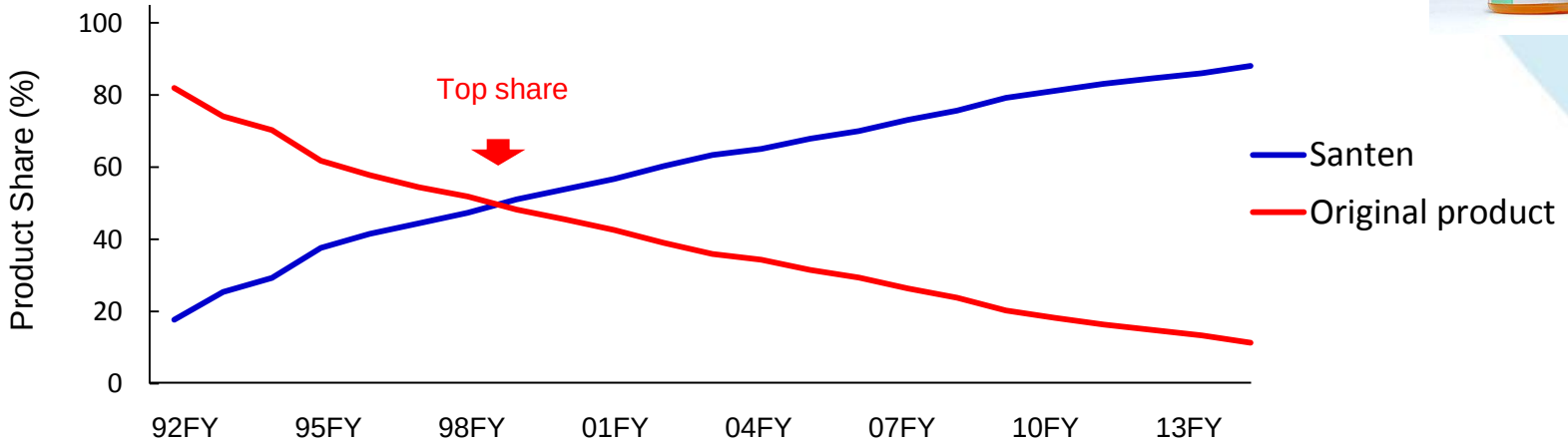
Increased market share through ease of use

Original product

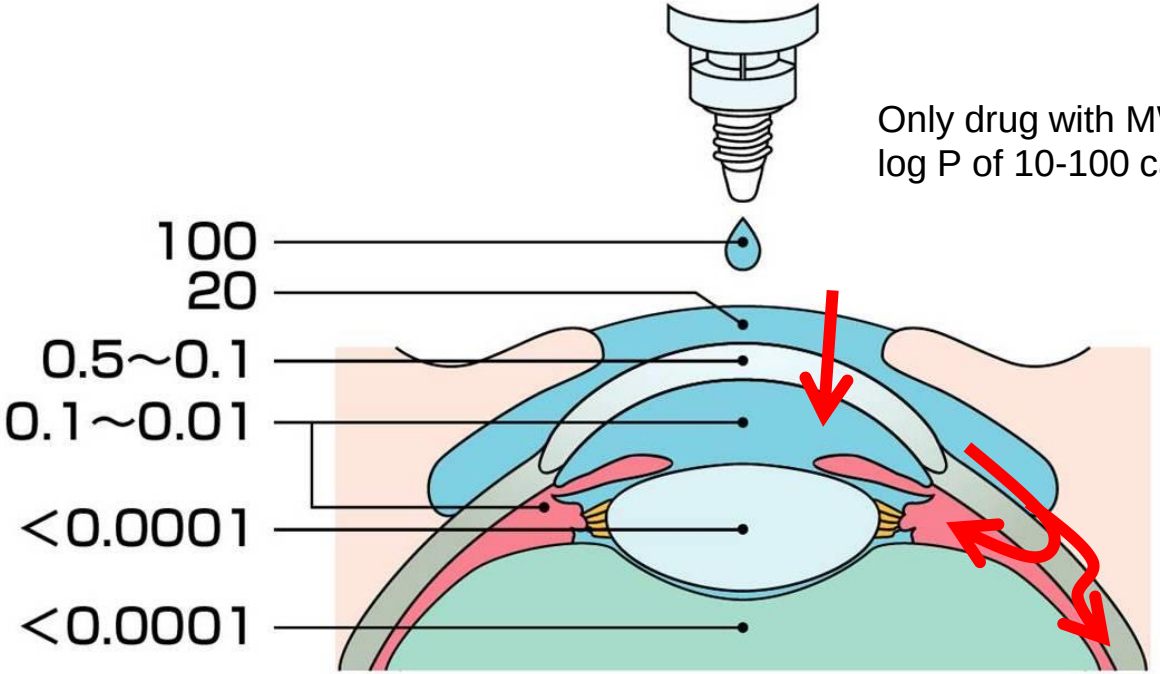
Must be mixed and dissolved before use

New dosage form

Need only be shaken before use



Benefits of DDS development: Overcoming transport barrier



Only drug with MW <5kDa and
log P of 10-100 can pass through cornea

Nano particles
Liposomes
Nano-emulsions
etc.

Dr. Makoto Araie, 1994

Benefits of DDS development: Overcoming transport barrier

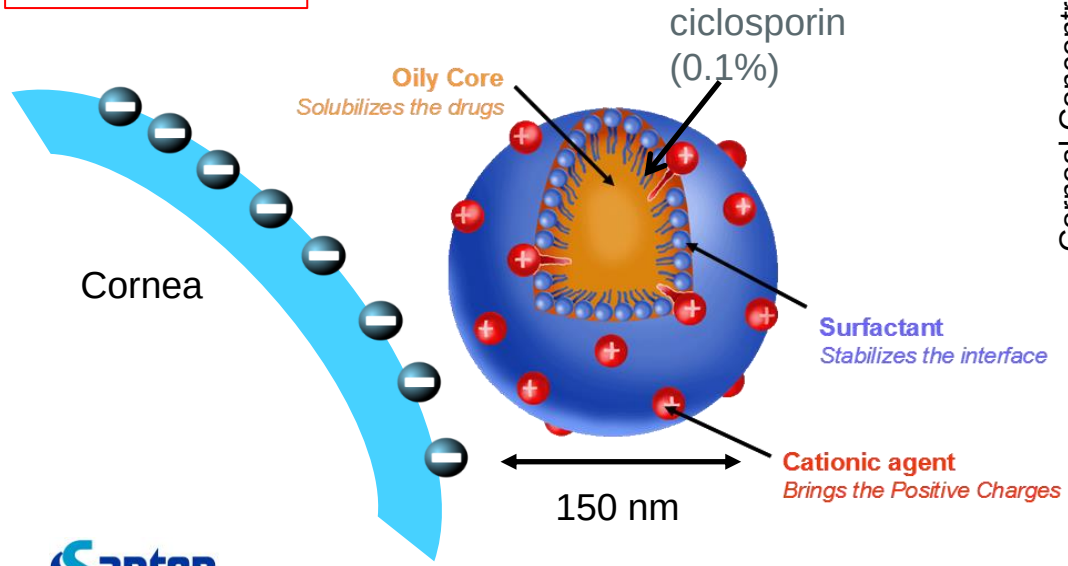
Ordinary formulation

Twice a day

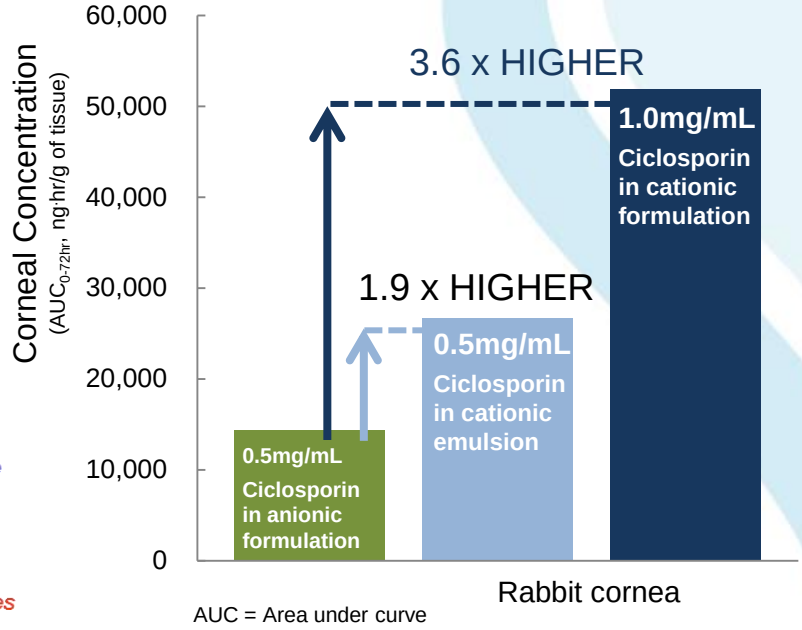
Higher corneal delivery (Novasorb)

New formulation

Once a day



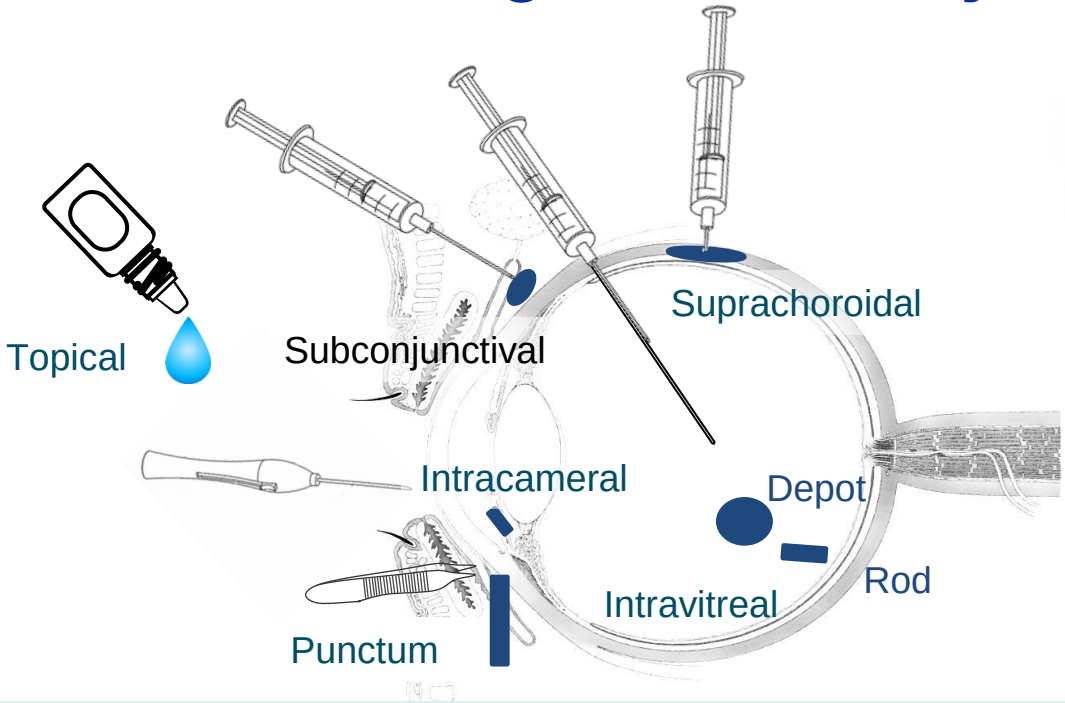
CORNEAL CONCENTRATION
(Results of animal model)



AUC = Area under curve

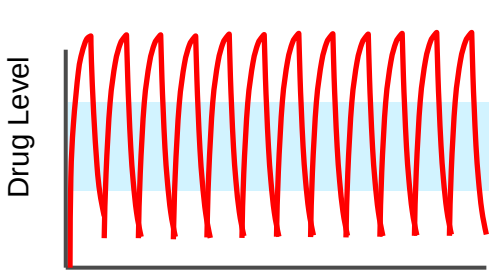
Santen A Clear Vision For Life

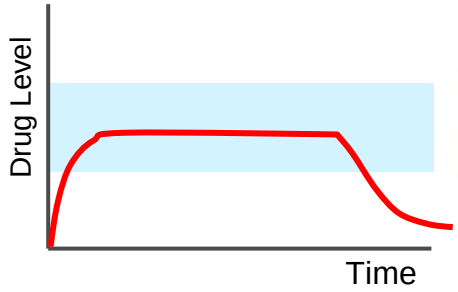
Benefits of DDS development: Diversified routes for targeted delivery



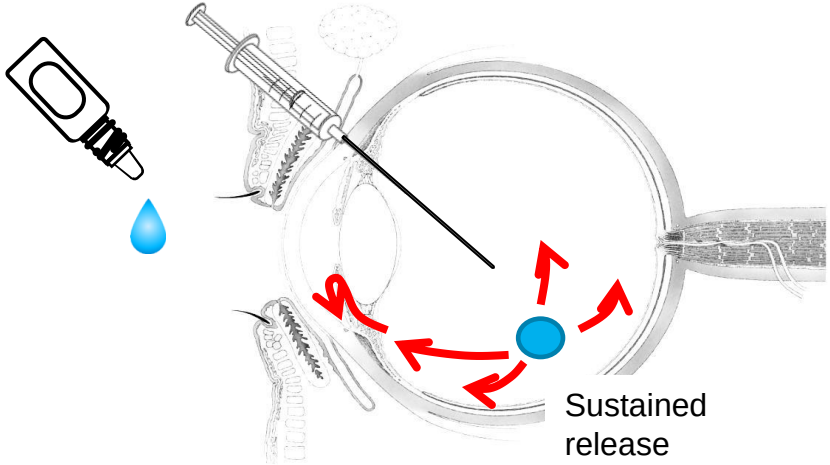
Santen is going beyond being an “eye-drop” company

DDS: Driving paradigm shift in ophthalmic therapy



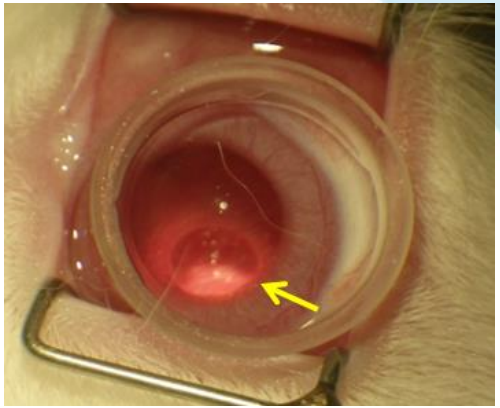


Therapeutic range



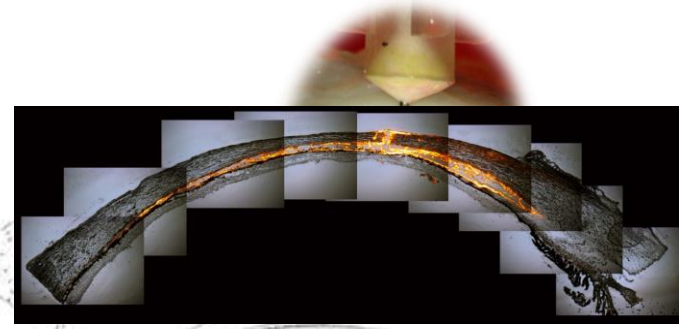
Sustained release from Depot

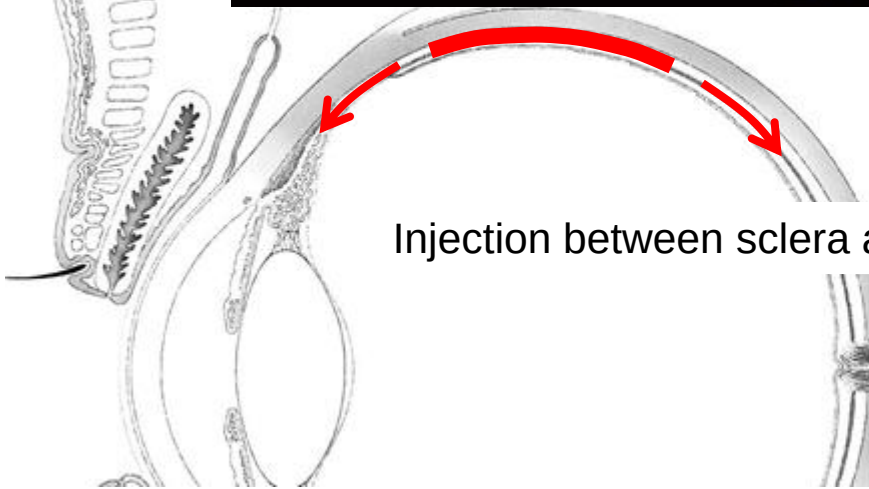
with DURECT



Benefits of DDS development: Ease of access to choroid

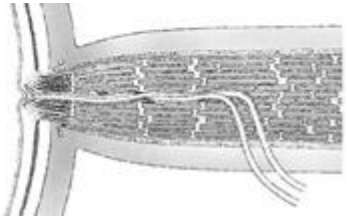
Suprachoroidal Delivery





with CLEARSIDE™ BIOMEDICAL

Injection between sclera and choroid



Summary

Santen is changing ophthalmic therapy by:

- Increasing the PTS (probability of technical success) by connecting unmet medical needs with external technologies
- Accelerating regional expansion through rapid development
- Improving adherence through easy-to-use devices and formulations
- Innovating DDS development

Global Medical Affairs

Terri L. Phillips MD
Head of Global Medical Affairs

September 11, 2015

Santen's R&D Transformation

Global Medical Affairs: Mission and organization

- Head, Global Medical Affairs
  - Director, U.S.
  - General Manager, Japan
  - Director, Korea
  - Director, Singapore
  - Director, China
  - Director, Europe
  - Senior Global Medical Director

Mission: Create value for Santen and all stakeholders and help realize Vision 2020

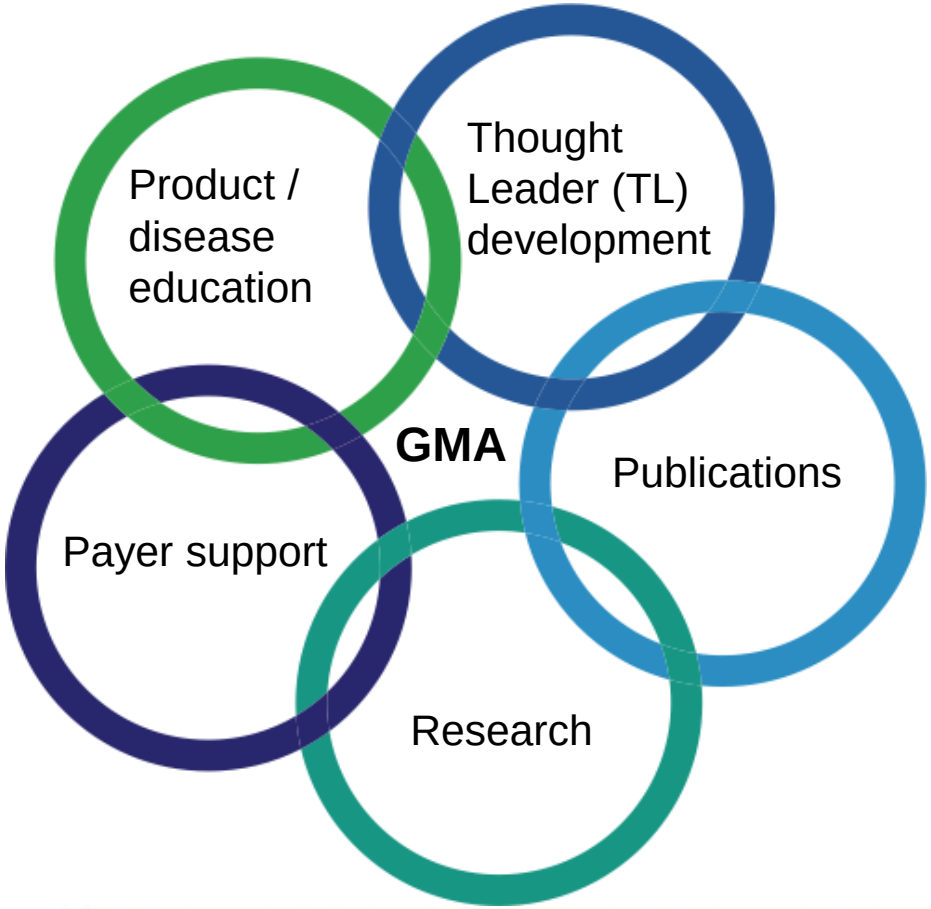
Organization: Creating a Medical Affairs capability that is global, efficient and supports the realization of Global 2020

Transforming Santen Medical Affairs for the 21st century

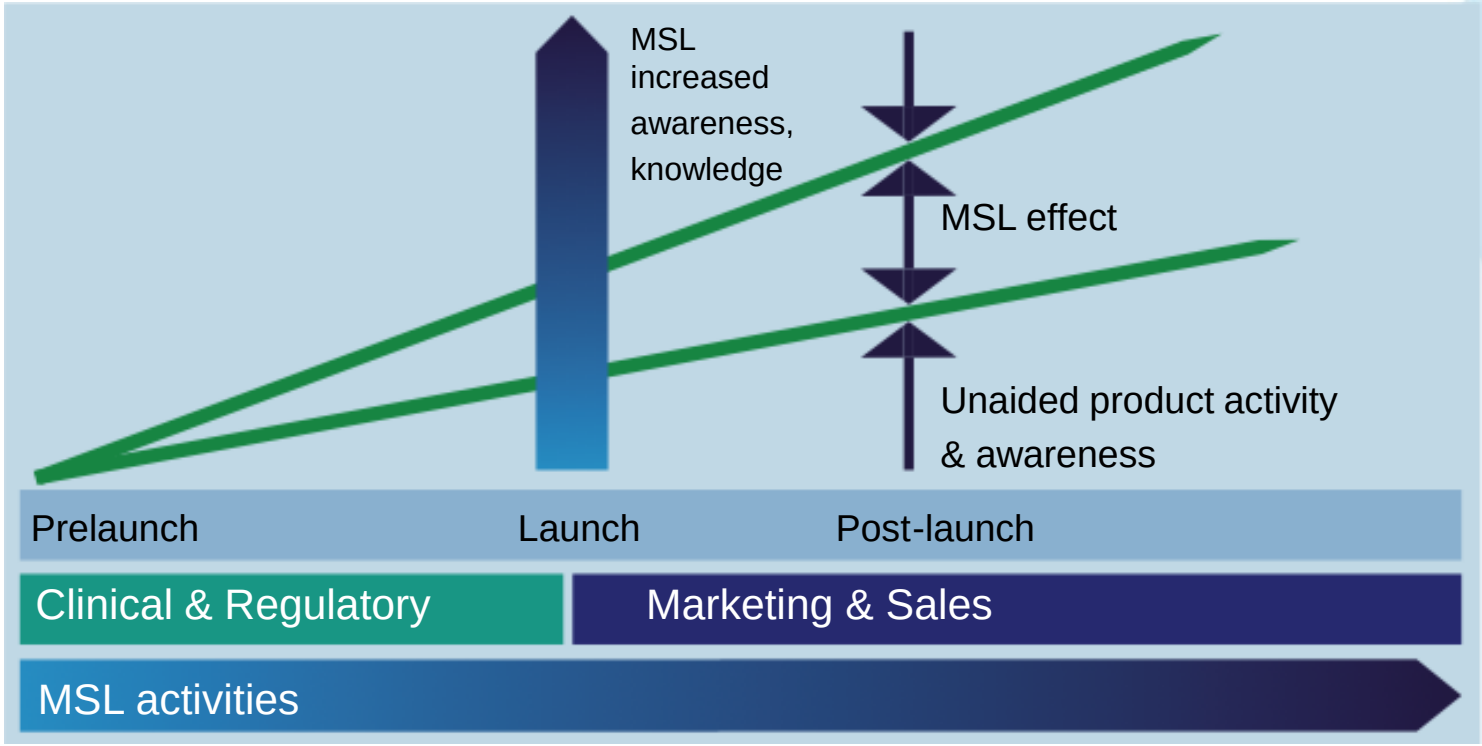
Developing GMA: Proactive, value-generating, global

- Healthcare stakeholders worldwide are demanding evidence based, real world, comparative effectiveness data
- Increasing number and sophistication of medical stakeholders
- Increasing demand for data transparency

Key elements of GMA support



Medical scientific liaison (MSL) activities impact the slope of product awareness



Coordinated and timed MA activities will support successful product launch

Early Market (T-24 m)	Pre-launch (T-12-24m)
• Identify and engage TLs • Provide disease education • Publish clinical data, burden of illness, MOA • Qualify and communicate treatment landscape and UMN	• Expand TL awareness of data • Understand payer perceptions of UMN and value • Present pivotal data • Prepare medical information • Define further research needs • Train country teams

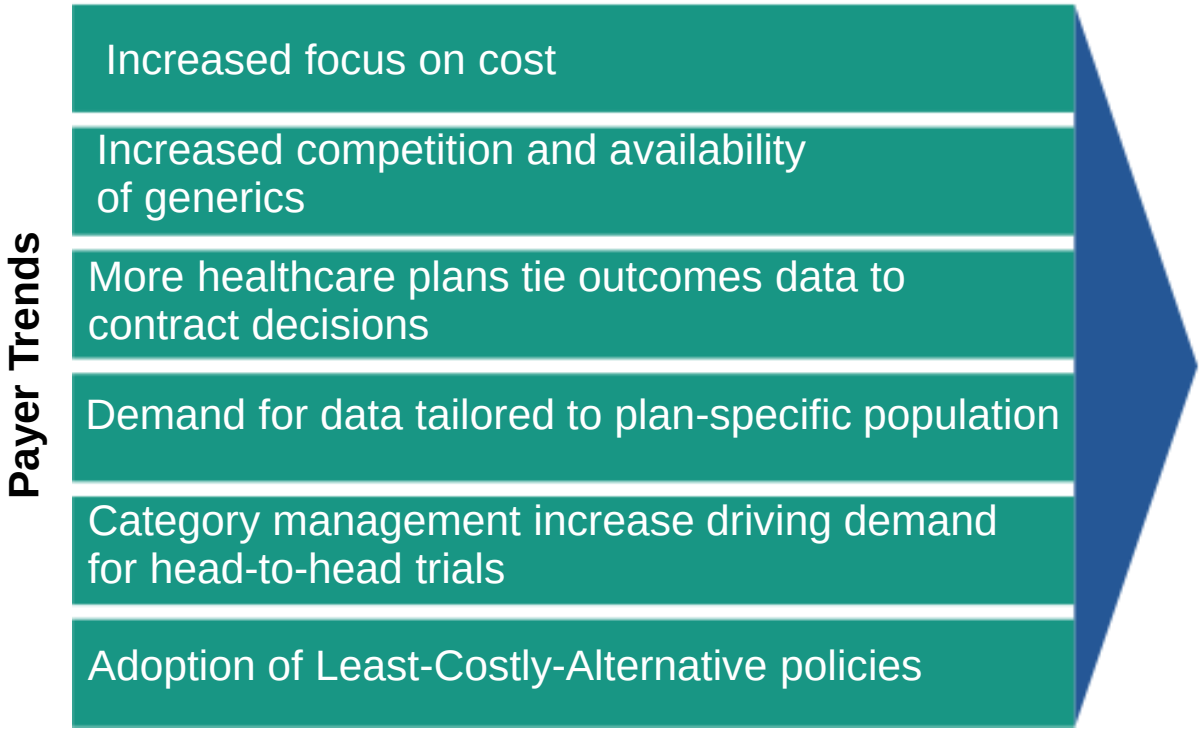
Currently focusing development of Santen's GMA capabilities in the U.S. and Europe

Coordinated and timed MA activities will support successful product launch

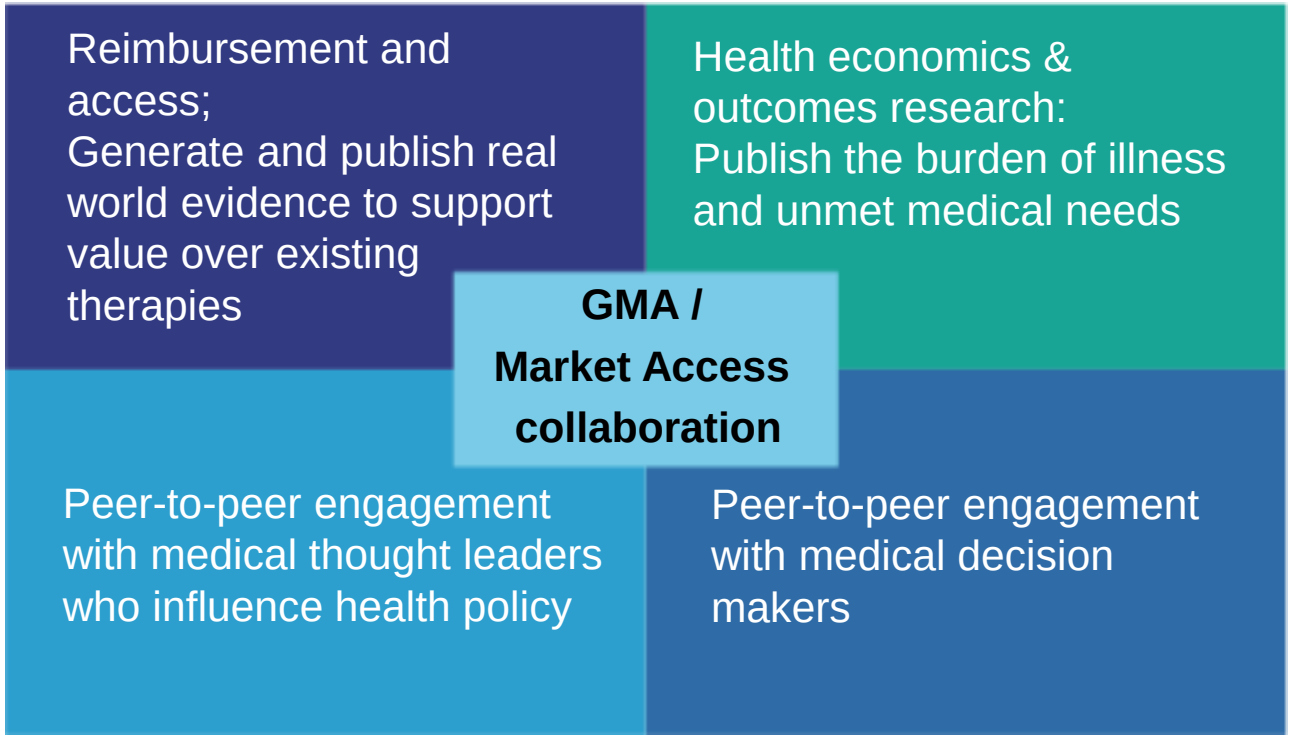
Launch(T-12 m)	Post-Launch
• Communicate value proposition • Educate and advocate for patients • Inform stakeholders of emerging therapies and competitive intelligence • Engage, educate and train TLs	• Communicate product safety and effectiveness • Provide training and education • Promote patient adherence • Pursue LCM • Generate real-world data • Expand HCP engagement

Currently focusing development of Santen's GMA capabilities in the U.S. and Europe

Payer trends demand communication of health outcomes data



Market Access and GMA collaboration ensures availability of drugs to patients in need



250 Medical Thought Leaders* identified globally

MTLs by Region

North America	105
South America	18
Europe	70
Asia	57

* MTLs relating to area of uveitis

GMA - Key accomplishments YTD (FY2015)

- Conducted 199 scientific interactions with U.S. MTLs (Advisors, symposium faculty, publications authors)
- Established 1.3m customer contact points (Congress, med ed, 1:1, publications)
- Supported 14 global congress medical affairs booths
- Hosted 7 global uveitis scientific symposia
- Grants in support of 8 CME monographs
- Held 10 scientific advisory board meetings
- Hosted 3 scientific open house events
- Published 8 manuscripts

Realizing Vision 2020 and beyond

Patients' Success → Success with Doctors → Success for Santen

- Advance **scientific knowledge** that affects disease awareness and health outcomes and empowers evidence-based decision making
- Deliver real-world **clinical insights** that inform and influence scientific objectives, product development, global registration, commercialization and value
- Translate clinical data into multi-faceted **scientific assets**

Creating value for Santen and stakeholders

Global Regulatory Affairs

Franz Buchholzer Ph.D.
Head of Global Regulatory Affairs

September 11, 2015

Santen's R&D Transformation

Global Regulatory Affairs (RA) leadership

Head, Global Regulatory Affairs

- Director, U.S.
- General Manager, Japan
- Asia Pacific Team Lead
- Director, Europe
- Manager Global RA Activities Coordination
- Director, China

About 70 regulatory experts worldwide

Accelerating market access to benefit patients and Santen in a new global regulatory era

Making a major contribution to Vision 2020

Global capability

Strong capability in key regions, optimal balance of global and local teams, respect for cultures, languages, people

Regulatory leadership and excellence

Knowledge, compliance and intelligence; at the forefront of regulatory trends and new standards

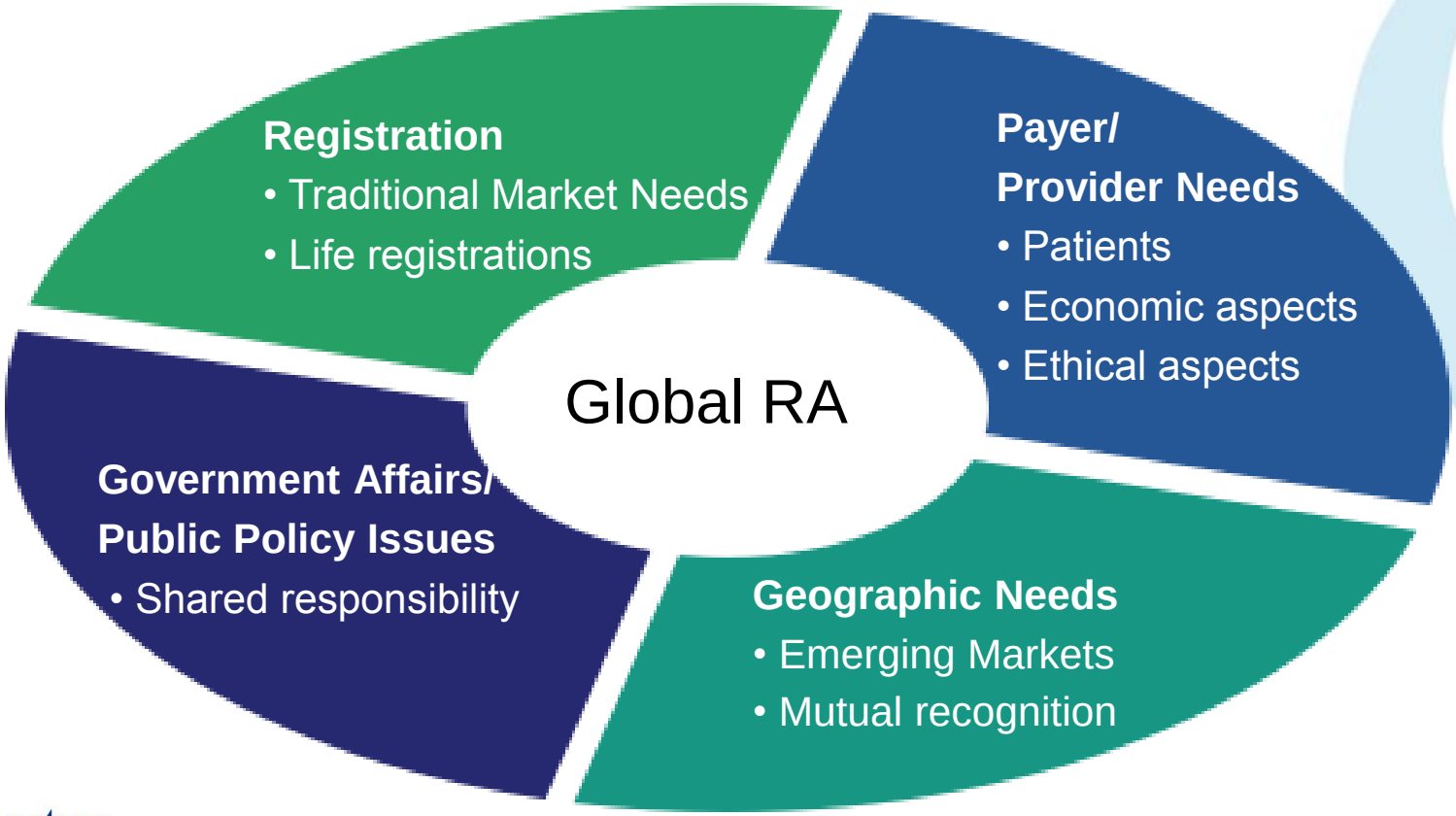
Business mindset

Dynamic and innovative approach; accelerating time to market; Make the impossible possible

Win-win relationships

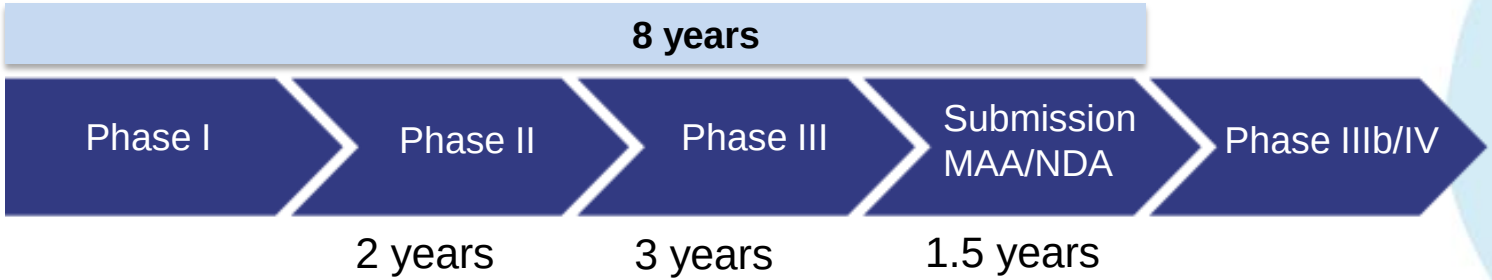
Partner with government bodies and regulators; lobby as appropriate

New RA agenda for success in the 21st century

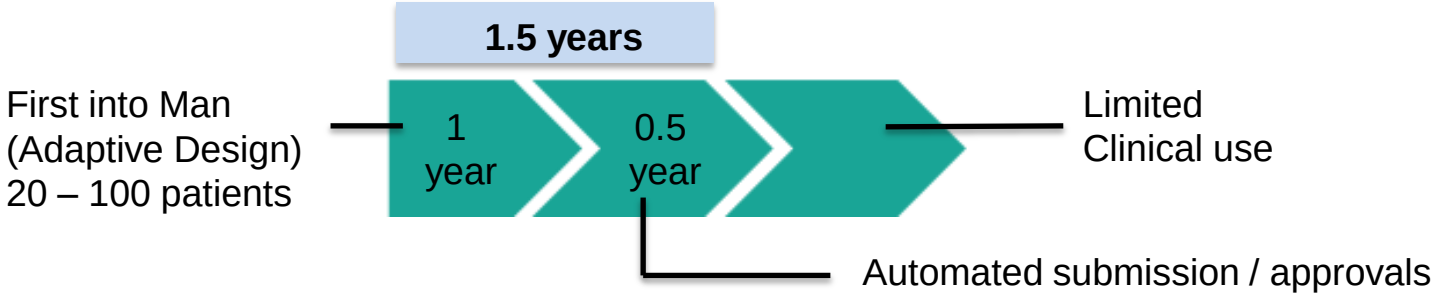


Global regulatory affairs – new era

Current development process



What the development process might look like in 2020



Pharma 2020: The vision, PricewaterhouseCoopers

Summary

Global RA – new era

- Shorten developmental programs: Adaptive design, conditional approval
- Share responsibility and risk: Early collaboration and communication with regulators, payers, and government bodies
- Prioritize mutual recognition of data throughout agencies
- Accelerate patient access to new medicines: Time to market, registrations on limited data

A Clear Vision For Life

DISCLOSURE NOTICE

- Information given in this announcement and accompanying documentation contains certain forward-looking statements concerning forecasts, projections and plans whose realization is subject to risk and uncertainty from a variety of sources. Actual results may differ significantly from forecasts.
- Business performance and financial condition are subject to the effects of medical regulatory changes made by the governments of Japan and other nations concerning medical insurance, drug pricing and other systems, and to fluctuations in market variables such as interest rates and foreign exchange rates.
- The process of drug research and development from discovery to final approval and sales is long, complex and uncertain. Individual compounds are subject to a multitude of uncertainties, including the termination of clinical development at various stages and the non-approval of products after a regulatory filing has been submitted. Forecasts and projections concerning new products take into account assumptions concerning the development pipelines of other companies and any co-promotion agreements, existing or planned. The success or failure of such agreements could affect business performance and financial condition significantly.
- Business performance and financial conditions could be affected significantly by a substantial drop in sales of a major drug, either currently marketed or expected to be launched, due to termination of sales as a result of factors such as patent expiry and complications, product defects or unforeseen side effects. Santen Pharmaceutical also sells numerous products under sales and/or manufacturing license from other companies. Business performance could be affected significantly by changes in the terms and conditions of agreements and/or the non-renewal of agreements.
- Santen Pharmaceutical is reliant on specific companies for supplies of certain raw materials used in production. Business performance could be affected significantly by the suspension or termination of supplies of such raw materials if such and event were to adversely affect supply capabilities for related final products.
- This presentation includes discussions of certain Santen products marketed in certain markets and compounds in clinical trials, as well as competitors' products and compounds in clinical trials which are given for illustrative purposes only. Such discussions may include views subject to data interpretation that may or may not be views shared by regulatory authorities in the various regions in which the Company operates.