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We make tomorrow's drugs possible.

A European perspective of global CMC innovation

FDA/PQRI – Rockville, MD – April 10, 2019

Univ.-Prof. Dr. *Sven Stegemann,* Technische Universität Graz

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- CMC considerations for patient-centric drug product design

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Introduction

- Burden of disease and disease prevalence over life span in developed countries.
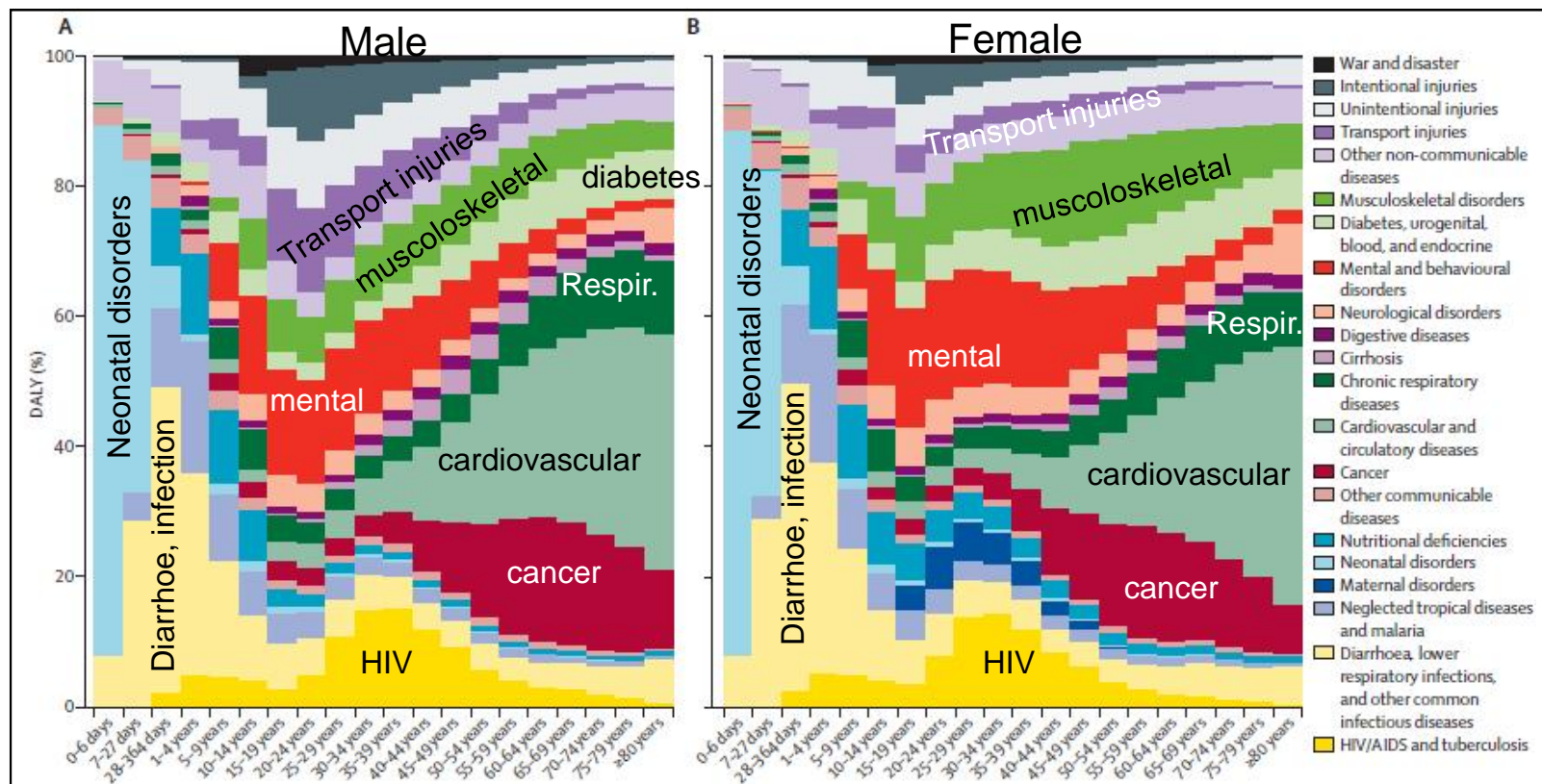
DALYs (disability-adjusted life years) across the life span

DALYs express the number of years lost due to ill-health, disability or early death.

DALY = YLL + YLD

Years of life lost (YLL) plus Years lost due to disability (YLD)

Murray et al Lancet 2012

Introduction

- Multimorbidity per age and socio-economic status and the relationship to prevalence of physical and mental disorders
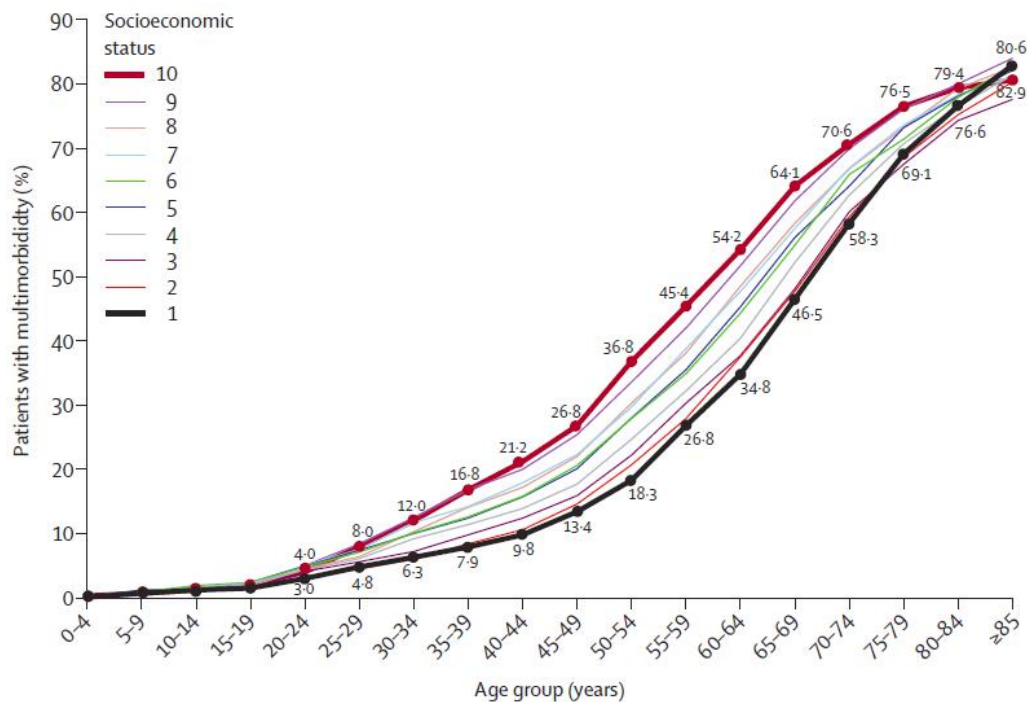
Multimorbidity and socio-economic status by age
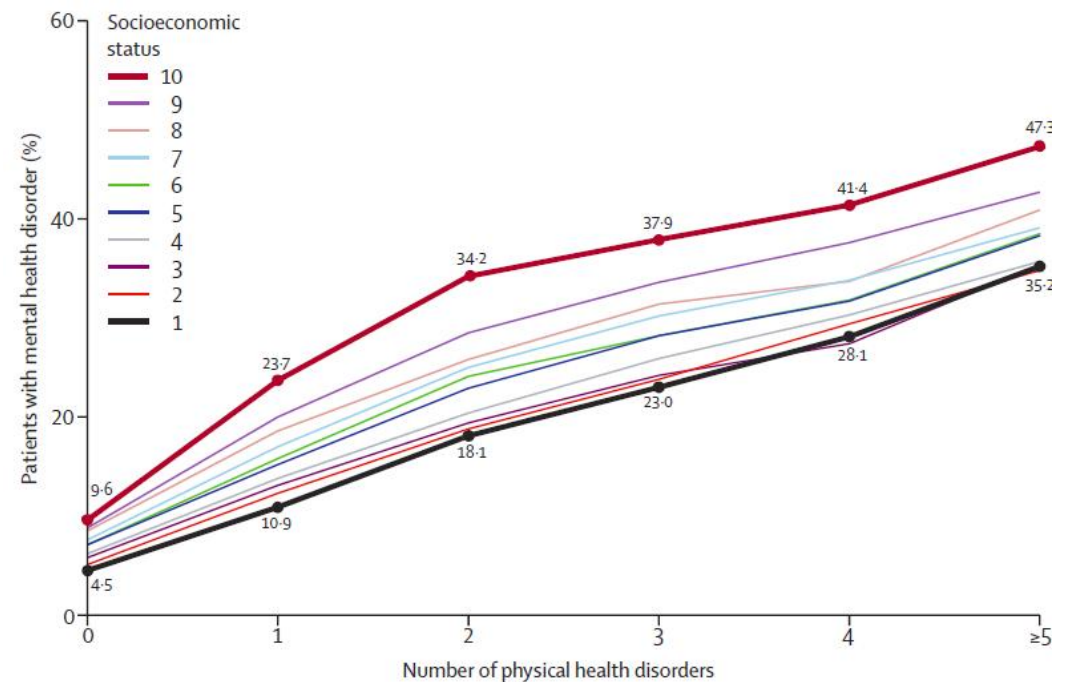
Multimorbidity related physical and mental disorders by socio-economic status

Introduction
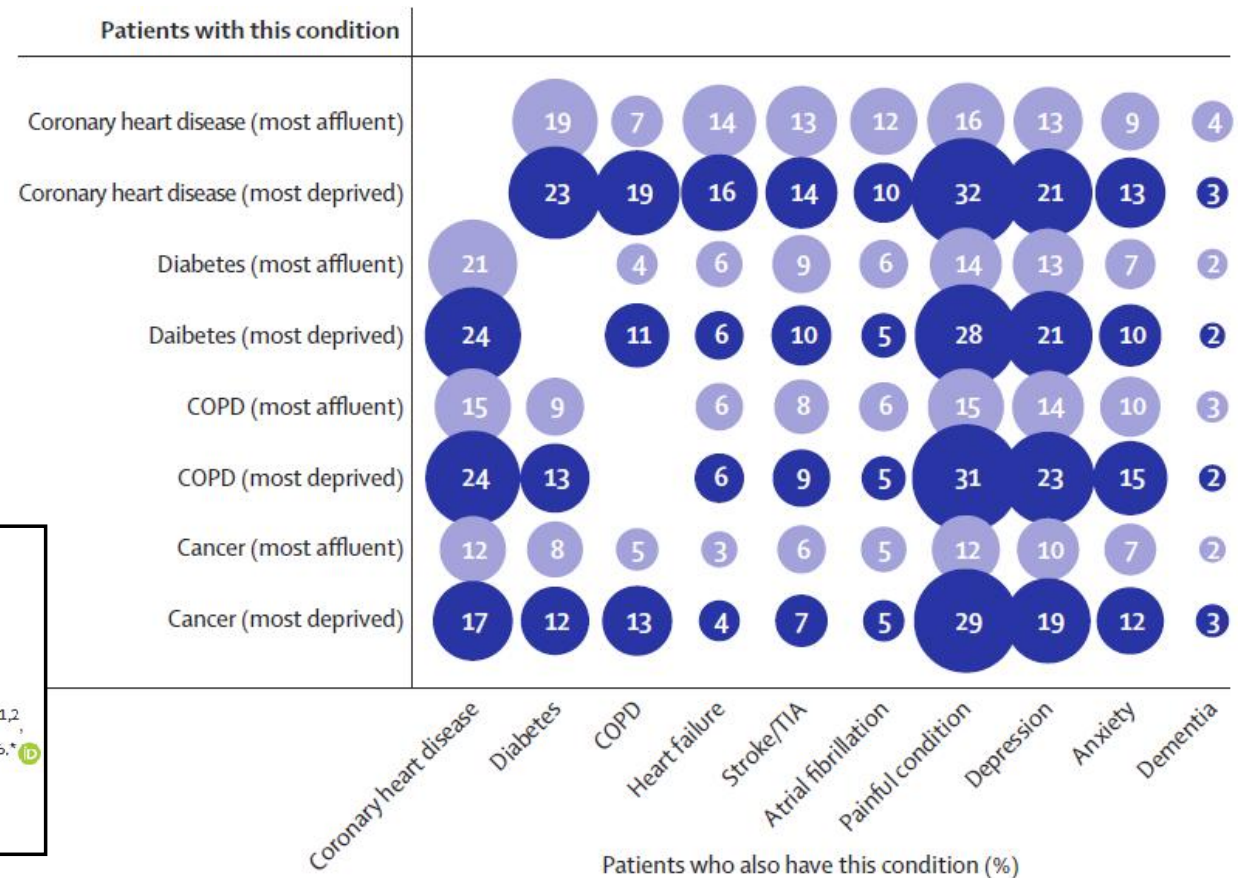
- Increasing evidence for typical disease and co-morbidity clusters forming distinct patient populations

- Pheno- and genotyping evolve through deep digital data analysis, iPSC and other emerging technologies

iPhemap: an atlas of phenotype to genotype relationships of human iPSC models of neurological diseases

Ethan W Hollingsworth[1,2], Jacob E Vaughn[1,2], Josh C Orack[1,2], Chelsea Skinner[1,2], Jamil Khouri[1,2], Sofia B Lizarraga[3], Mark E Hester[4], Fumihiro Watanabe[1], Kenneth S Kosik[5] & Jaime Imitola[1,2,6,*]

EMBO Mol Med (2017) 9: 1742–1762

Patients with this condition

	Coronary heart disease	Diabetes	COPD	Heart failure	Stroke/TIA	Atrial fibrillation	Painful condition	Depression	Anxiety	Dementia
Coronary heart disease (most affluent)	19	7	14	13	12	16	13	9	4	
Coronary heart disease (most deprived)	23	19	16	14	10	32	21	13	3	
Diabetes (most affluent)	21	4	6	9	6	14	13	7	2	
Daibetes (most deprived)	24	11	6	10	5	28	21	10	2	
COPD (most affluent)	15	9	6	8	6	15	14	10	3	
COPD (most deprived)	24	13	6	9	5	31	23	15	2	
Cancer (most affluent)	12	8	5	3	6	5	12	10	7	2
Cancer (most deprived)	17	12	13	4	7	5	29	19	12	3

Patients who also have this condition (%)

Barnett et al Lancet 2012

# A holistic view on drug therapy

Definition of health

- Medical: Absence of diagnosable deviations from the average population

- Personal: Absence of symptoms perceived as threatening or debiliating

- Society: Absence of behaviors outside the accepted norms

- WHO: „Health is a state of <u>complete physical, mental and social well-being</u> and not merely the absence of disease or infirmity."

Goals and objectives

- Medical: Prevent premature death and prolong life time

- Personal: Well-being, independence, functional capacity and quality of life

- Society: Organize and manage healthcare resources by ROI decisions

A holistic view on drug therapy

- In 2000, 44,000 to 98,000 deaths occur yearly due to 62 medical errors, making medical errors the eighth leading cause of death in the USA [1]

- Therapeutic Failures and adverse drug withdrawal events involving 54 drugs were associated 5.9% of hospitalizations; of these admissions, 90.0% were rated as potentially preventable mostly due to medication nonadherence and suboptimal prescribing.[2]

- Secondary non-adherence ranges from ~25 % in gastrointestinal disease to ~80 % oncology [3]

- Gap between efficacy and effectiveness or the randomized clinical setting and the real world [4]
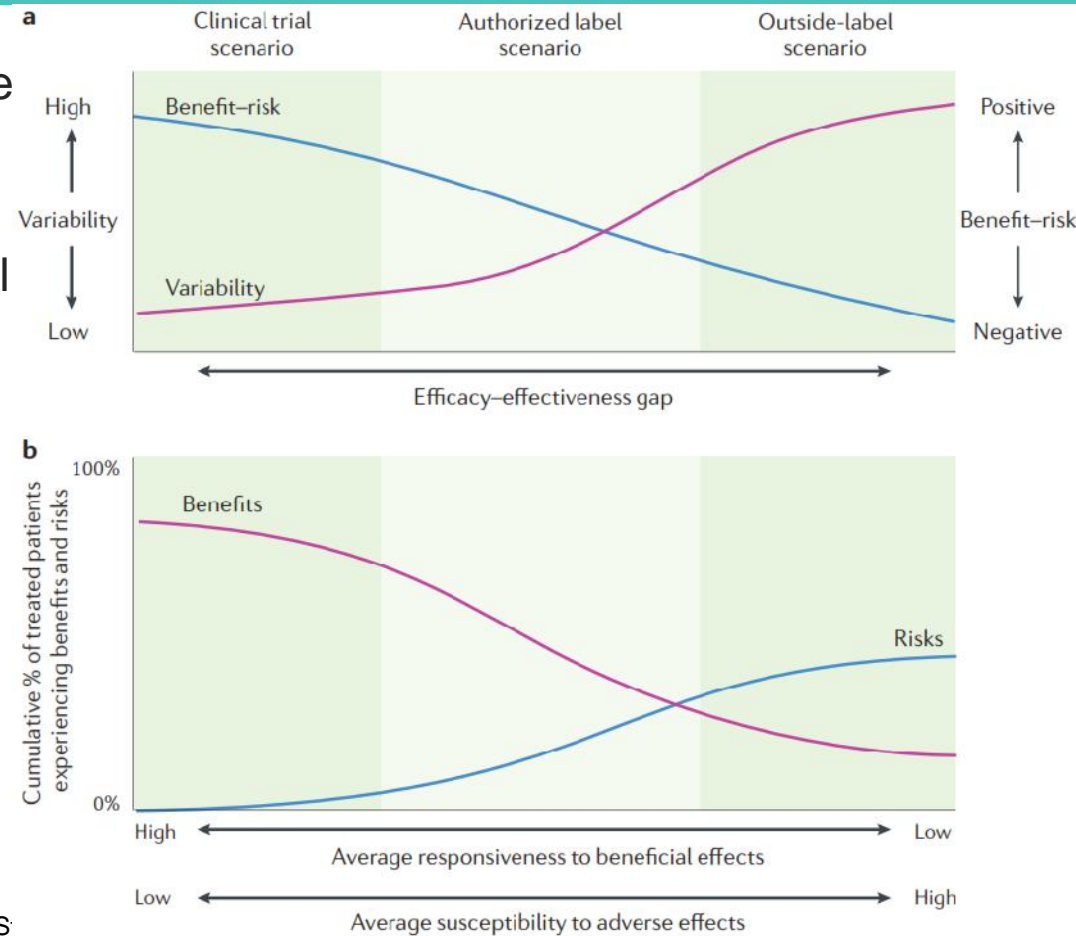
[1] American Hospital Association. Hospital S
[2] Marcum et al (2012) J Gerontol A Biol Sci Med Sci. 67(8):867–874
[3] Gapgemini Report: Estimated annual pharmaceutical revenue loss due to medication non-adherence (2012)
[4] Eichler et al Nature Rev Drug Discov 10:495 – 506 (2011)

A holistic view on drug therapy

- Understand the patient journey

Location	Task	Concerned domain	Physical/cognitive capability
Home	Recognition of symptoms	Sensory Cognition memory	Sensation of the symptoms, differentiation from normal aging, identification as disease and save this in memory
	Decision to visit physician	Cognition Routine/structure	Recognition of medical problem, planning to visit physician
Physician	Visiting the physician	Mobility Routine/structure	Preparing and planning a visit, driving-walking to the physician
	Recalling/describing symptoms	Cognition Memory Hearing/ comprehension	Remember reason for visit, recall and explain symptoms, answering questions
	Receipt of disease and prescription information	Hearing/ comprehension Cognition Memory Literacy	Physicians verbal communication, clarifying questions, comprehension of therapy
Pharmacy	Visiting pharmacy	Mobility Routine/structure	Decision to purchase drug, driving-walking to pharmacy
	Receipt of drug products and additional information	Visual Cognition Hearing/ comprehension	Exchange of prescription by drug products, receipt of additional information, clarifying questions

Stegemann Int J Pharm 2016

A holistic view on drug therapy

- Understand the patient journey

Home	Recall of drug products & recall or reading of drug information	Memory Cognition Literacy	Recognition of the drug products, recall of the reason for prescription and use information, read and understand leaflet information
	Set a medication schedule	Cognition Memory Visual Literacy	Understand drug product use and administration, develop a medication plan or incorporate new prescriptions or modifications into a medication plan, store plan in memory or respective written note
	Set an implementation plan	Cognition Memory Visual	Incorporate the medication schedule into daily life, set time or cues, use assistance tools
	Recall or read product information and administration time	Memory Cognition Literacy Routine/structure	Execute the medication plan, recall time, identify right products, recall administration requirements
	Release products from packaging	Hand function/ force Dexterity Sensory Visual	Opening packaging, release the drug products, keep or place them on a table, prepare the administration e.g. glass of water
	Pick up the drug product for administration	Hand sensitivity Dexterity	Identify the drug products, pick up them up and keep them in the hand
	Administration of the drug product	Arm/hand function Dexterity Administration ability	Take the drug product to the mouth, swallow and drink or administer the drug product as requested (e.g. inhalation, patches etc)
	Experience drug effects	Cognition Sensory	Perceiving and accepting drug effects, recognize adverse drug reactions that would require physicians contact

Stegemann Int J Pharm 2016

A holistic view on drug therapy

What is progressing in healthcare and its provision

- Physicians progress into shared decision making
- Wearable diagnostics and digital health
- Organisation of lay persons in the internet (information access)
- Patient involvement in technology design

CyberPsychology & Behavior, Vol. 7, No. 5 | Reviews

How Internet Users Find, Evaluate, and Use Online Health Information: A Cross-Cultural Review

Dr. Janet M. Morahan-Martin

Health Information, The Internet, And The Digital Divide

Despite recent improvements, Americans' access to the Internet—and to the growing body of health information there—remains uneven.

by Mollyann Brodie, Rebecca E. Flournoy, Drew E. Altman, Robert J.

Expert and patient consensus on a dynamic model for shared decision-making in frail older patients

Marjolein H.J. van de Pol[a,*], Cornelia R.M.G. Fluit[b], Joep Lagro[c], Yvonne H.P. Slaats[d], Marcel G.M. Olde Rikkert[e], Antoine L.M. Lagro-Janssen[f]

[a] Departm
[b] Academ
[c] Departm
[d] Departm
[e] Departm
[f] Departm

VIEWPOINT

The Evolution of Patient Diagnosis From Art to Digital Data-Driven Science

Kenneth D. Mandl, MD, MPH
Computational Health Informatics Program, Boston Children's Hospital, Boston, Massachusetts.

Physicians are still taught to diagnose patients according to the 19th-century Oslerian blueprint. A physician takes a history, performs an examination, and matches each patient to the traditional taxonomy of medical conditions. Symptoms, signs, family history, and laboratory reports are interpreted in light of clinical experience and scholarly interpretation of the medical literature. However, diagnosis the National Human Genome Research Institute's Genome-Wide Association Study [GWAS] Catalog). Second are databases, such as the Genome Aggregation Database (gnomAD),[4] the next iteration of the Exome Aggregation Consortium (ExAC) database,[5] and the 1000 Genomes Project,[6] that aggregate sequences collected from other studies for secondary use.

Participatory Design in Gerontechnology: A Systematic Literature Review

Sebastian Merkel, PhD[*] and Alexander Kucharski, BA

Institute for Work and Technology, Westphalian University of Applied Sciences, Gelsenkirchen, Germany.

New Perspectives on User Participation in Technology Design Processes: An Interdisciplinary Approach

Miriam G. Grates, MSc,[1,*] Ann-Christin Heming, MA,[1] Marina Vukoman, MA,[1] Peter Schabsky, BSc,[2] and Jonas Sorgalla, MSc[2]

A holistic view on drug therapy

What is progressing in healthcare and its provision

- Physicians progre...
- Wearable diagnos...
- Organisation of lay... access)
- Patient involveme...

Patients are increasingly recognized as one of the most important factors in achieving the therapeutic outcomes as they are „in control" of the last step

and

getting more and more empowered by education and information accessability.

CyberPsychology & Behavior, Vol. 7, No. 5 | Reviews

How Internet Users Find, Evaluate, and Use ...rmation: A Cross-Cultural

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Expert and patient conse... decision-making in frail ...

Marjolein H.J. van de Pol[a,*], Cor... Marcel G.M. Olde Rikkert[e], Anto...

[a] Departm... [b] Academ... [c] Departm... [d] Departm... [e] Departm... [f] Departm...

VIEWPOINT

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the National Human Genome Research Institute's Genome-Wide Association Study [GWAS] Catalog). Second are databases, such as the Genome Aggregation Database (gnomAD),[4] the next iteration of the Exome Aggregation Consortium (ExAC) database,[5] and the 1000 Genomes Project,[6] that aggregate sequences collected from other studies for secondary use.

A holistic view on drug therapy – *Expectation to treatment model*
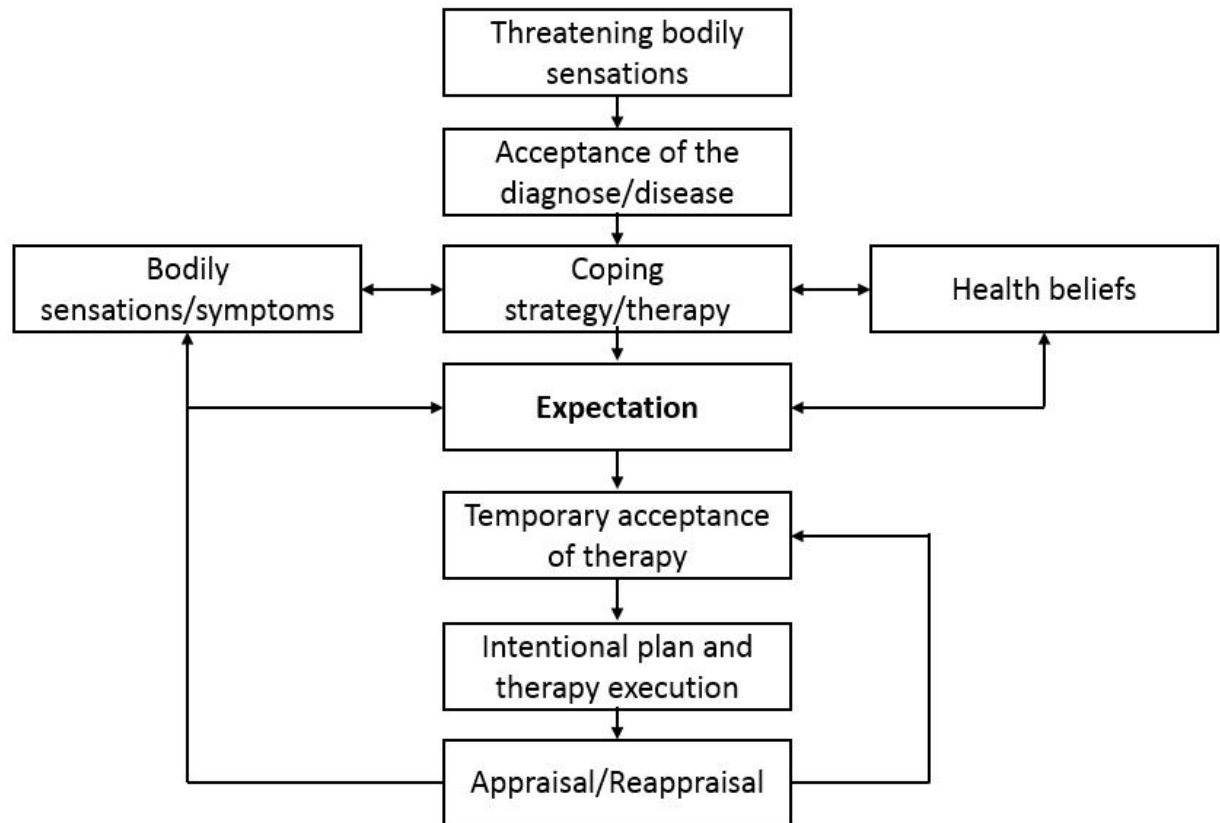
1. Acceptance of the disease

2. Patient expectation
- Effect bodily sensation/symptomes
- Compatibility with health believes
- Product perception and experience

3. Implementation plan

4. Reappraisal

5. Illusion of control

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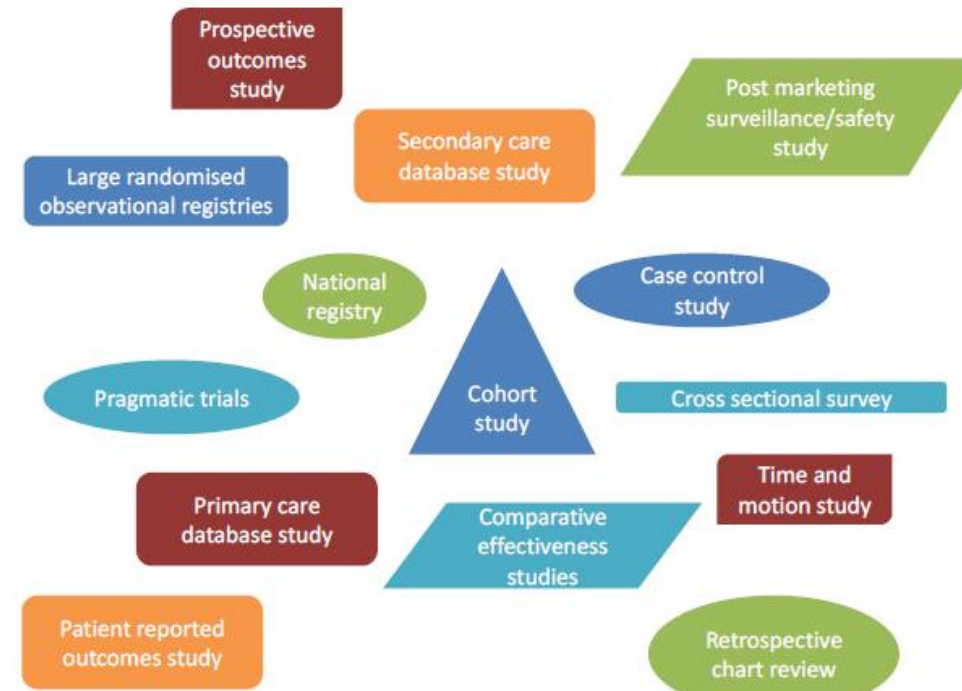
We make tomorrow's drugs possible.

A holistic view on drug therapy

- The patient is the „owner" of the disease and therapy and carries all the burden and outcomes

- The experience and perception of the disease and the treatment is a sum of many factors of which the experience and expectations are key

- Patient centricity starts with the patient and patient research
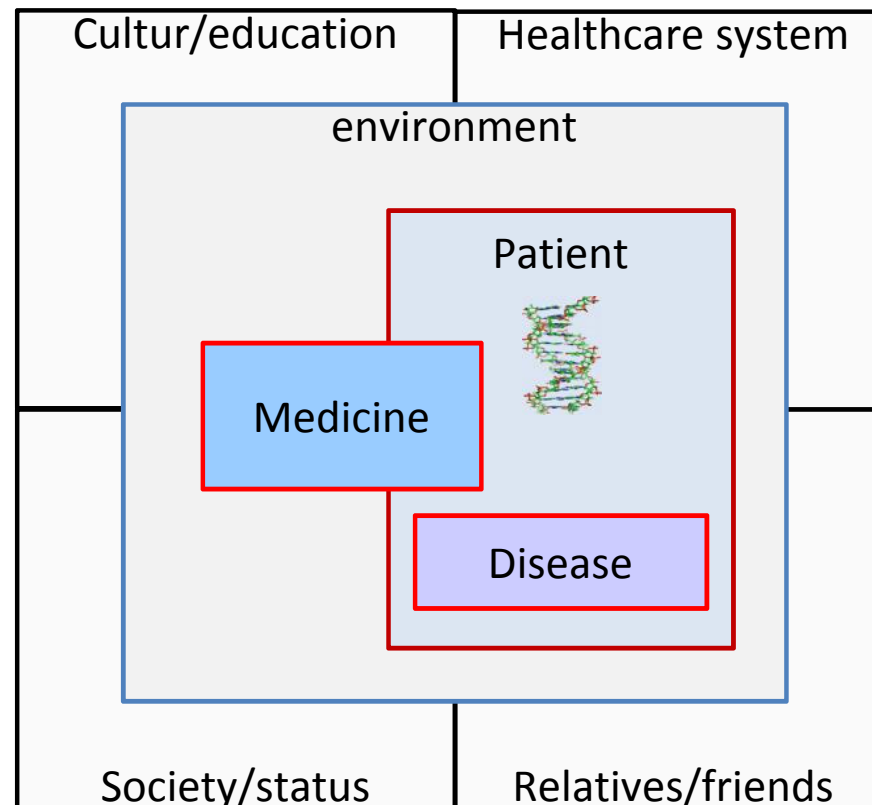
Regulatory framework

- Increasing focus on

  - Real World Evidence (RWE) and Real World Data (RWD)

  - Patient involvement in drug development and the regulatory decision process

  - Broader definition of „Quality" beyond the technical and chemical

  - „intended use" as one endpoint

  - „special populations" with regard to their needs

  - Consideration of the aging process and potential undiagnosed physiological changes

Prospective outcomes study

Secondary care database study

Post marketing surveillance/safety study

Large randomised observational registries

National registry

Case control study

Pragmatic trials

Cohort study

Cross sectional survey

Primary care database study

Comparative effectiveness studies

Time and motion study

Patient reported outcomes study

Retrospective chart review

ABPI Guidance 2011: Demonstrating Value with Real World Data

Regulatory framework

Undiagnosed physiological changes: e.g. kidney function between older individuals

- Chronic Kidney Disease (CKD) is defined as $eGFR_{FAS}$ <60 mLmin/ 1.73 m^2 and/or an albumin/creatinine ratio >30 mg/g

- In the BASE II Study 25 % had CKD of which only 1 % was aware of

Kidney function dependend the age. Different diagnostic methods
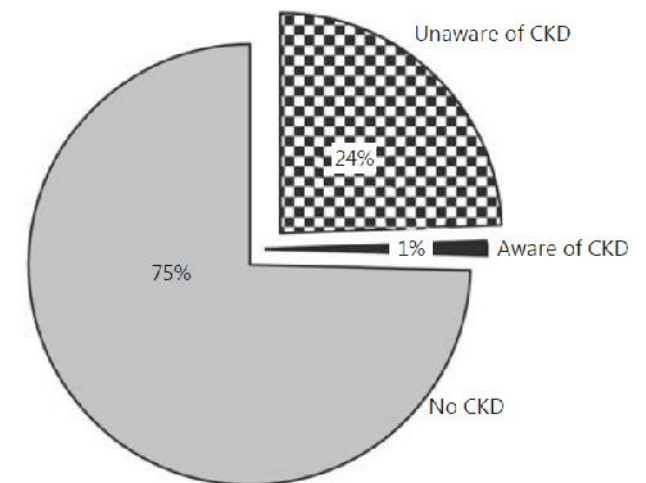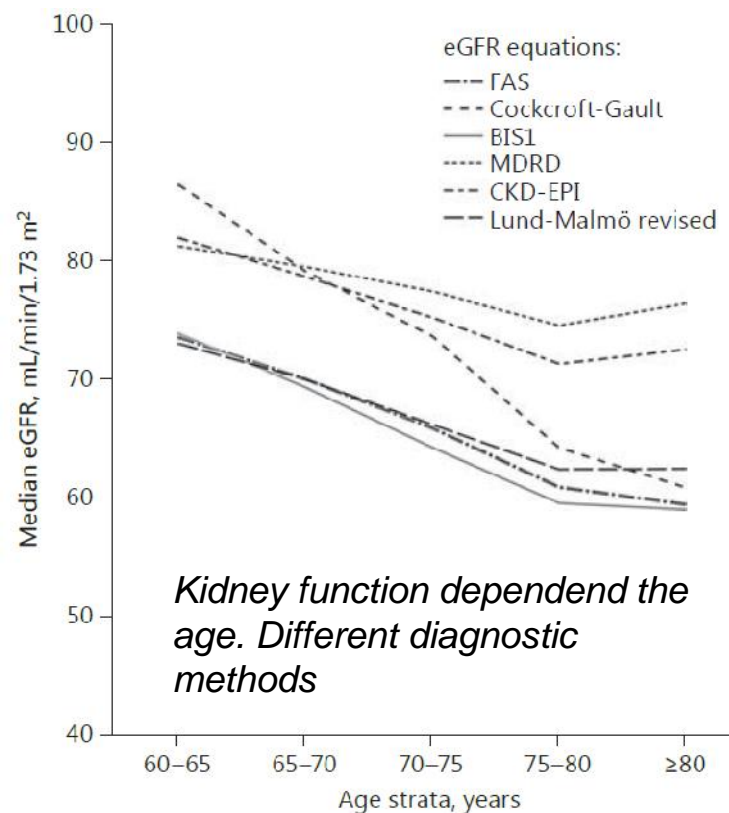
CKD in the BASE II population. 25 % CKD, of which 1 % was aware of.

Regulatory framework

Reflection Paper & Practice Guides

- Reflection paper: Formulations of choice for the **paediatric population** (2006)

- EMA **Geriatric Medicines** Strategy (2011)

- Outcome report on pilot phase for participation of **patient representatives** in Scientific Advisory Group (SAG) meetings (2011)

- Position paper on potential **medication errors** in the context of benefit-risk balance and risk minimisation measures (2013)

- Points to consider for baseline characterisation of **frailty status** (2015)

- Good practice guide on risk minimisation and prevention of medication errors (2015)

- Reflection paper on the use of extrapolation in the development of medicines for paediatrics (2017)

- Reflection paper on the pharmaceutical development of medicines for use in the **older population** (2017)

- Reflection paper on physical frailty: instruments for baseline characterisation of older populations in clinical trials (2018)

Regulatory framework

Guidelines

- ICH Q8 (R2) guideline on pharmaceutical development (2009)
    - quality defined as the suitability drug substance/product for **intended use**
    - *"in all cases, the product should be designed to meet* **patients' needs** *and intended product performance"*

- ICH Topic E7 Studies in Support of **Special Populations**: Geriatrics (2009)

- EMA The role of **patients** as members of the EMA Human Scientific Committees (2011)

- **Pharmacovigilance** Module VI (2012)
    - This includes adverse reactions which arise from:
        - *"the use outside the terms of the marketing authorisation, including overdose, off-label use, misuse, abuse and* **medication errors"**

- EMA Guideline on pharmaceutical development of medicines for **paediatric** use (2013)

- Addendum to ICH 11: Clinical investigation of medicinal products in the paediatric population (2017)

- EMA Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations IV: Paediatric population (2018)

CMC considerations for patient-centric drug products

Pharmaceutical drug product

- The comprehensive presentation of the therapeutic entity to the end user (patient/caregiver/ health care provider) including the type of dosage form; formulation; dose; dosing frequency; primary, secondary, and tertiary packaging; medical device; dosing devices; instructions for use (as in the SmPC/PIL/ product label); and other authority-approved patient support tools and programs.

Patient centric pharmaceutical drug product design

- The process of identifying the comprehensive needs of individuals or the target patient population and utilizing the identified needs to design pharmaceutical drug products that provide the best overall benefit to risk profile for that target patient population over the intended duration of treatment.

CMC considerations for patient-centric drug products

(Quality) Target Product Profil ((Q)TPP)

- Forms the basis for product development considering **product related characteristics**:
  - Intended use in clinical setting, route of administration, dosage form, delivery systems, dosage strength(s), container closure system etc
  - Therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance) appropriate to the drug product dosage form being developed
  - Drug product quality criteria (e.g., sterility, purity, stability and drug release) appropriate for the intended marketed product.

- ..and considering **patient related characteristics**:
  - Individual physiology related factors (e.g. ADME, disease, drug-disease, drug-drug & age related changes)
  - Personality related (e.g. psychological situation, cognitive capacity, health literacy)
  - physical functioning related (e.g. dexterity, sensory, motoric changes)

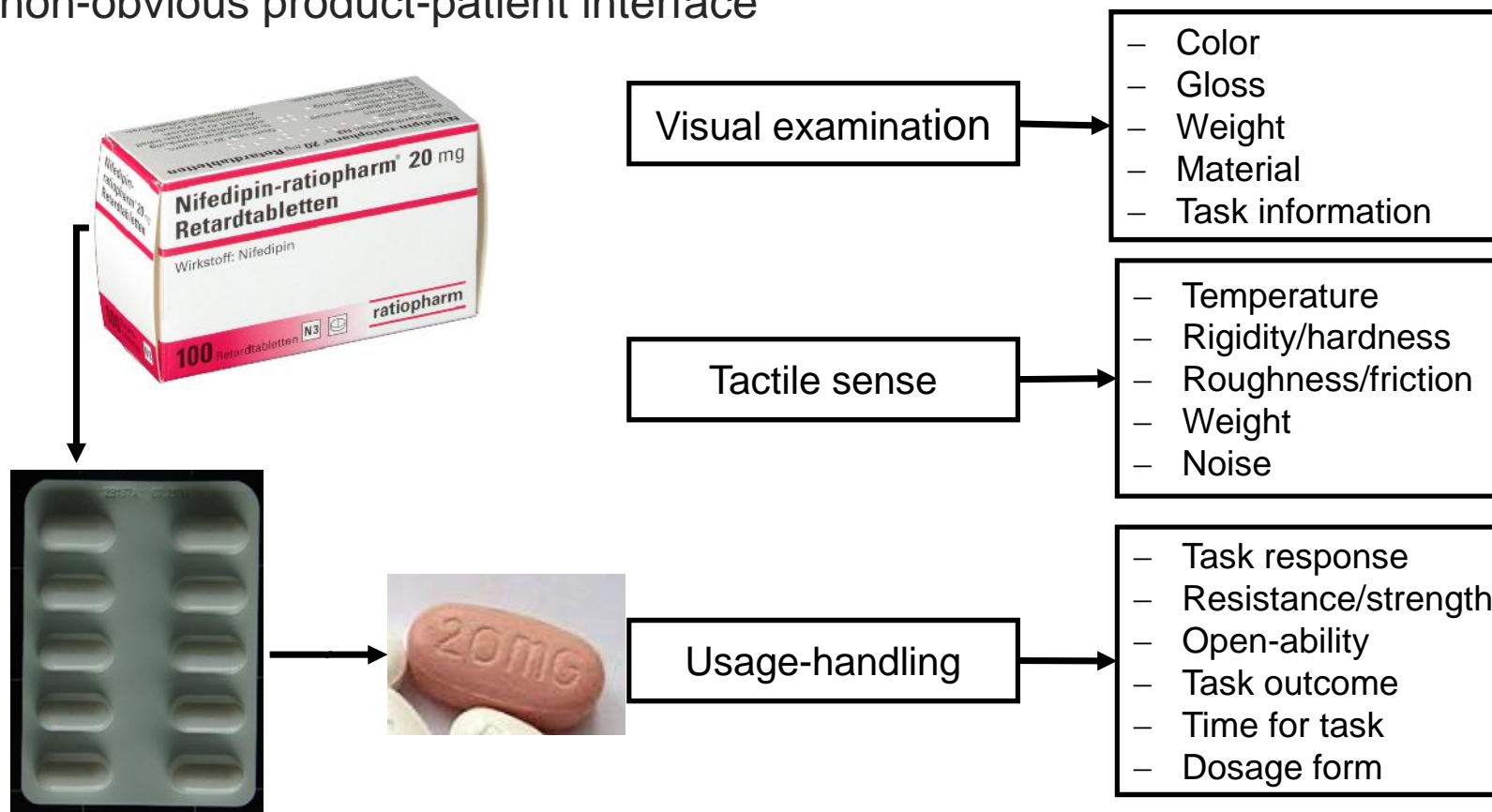# CMC considerations for patient-centric drug products

Patient-centric pharmaceutical drug product design elements

- Divided into:
  - Design Drivers (Characteristics disease/condition, Characteristics drug substance/ physiology, characteritistics drug therapy, characteristics drug product, patient characteritics, medication management (adherence and administration), Usability (handling, storage and disposal)
  - Design inputs (e.g. specific needs tobe considered)
  - Design outputs (e.g. design option to address such needs)

Design Drivers	Design Inputs	Design Outputs
Characteristics disease/condition	• Disease-specific expression • Multi- and co-morbidity • Frailty • Disease severity/burden • Disease stage	• Individual drug/drug combination • Individual drug dose accuracy • Dose range • Disease-specific disabilities
Characteristics drug substance/ physiology	• Developmental stage (maturation, declining body functions) • Oro-esophageal and GI transit • Permeability • Fat/water ratio • Drug metabolism and clearance • Homeostasis	• Flexible dose adjustment • Appropriate dosage form • Excipient safety/total amount of excipients • Low adverse drug reactions • Low intake/administration frequency

CMC considerations for patient-centric drug products

- The non-obvious product-patient interface

Visual examination →
- Color
- Gloss
- Weight
- Material
- Task information

Tactile sense →
- Temperature
- Rigidity/hardness
- Roughness/friction
- Weight
- Noise

Usage-handling →
- Task response
- Resistance/strength
- Open-ability
- Task outcome
- Time for task
- Dosage form

CMC considerations for patient-centric drug products

- The non-obvious product-patient interface

Sensation	→	− Activate cells, receive signals
Perception	→	− Interpret signals and stimuli
Cognition	→	− Translate, elaborate into information
Memory	→	− Recall, compare information
Movement	→	− Physical response

- The non-obvious product-patient interface

Sensation*

e.g. product identification error

Perception*

e.g. product scheduling error

Cognition*

e.g. product manipulation error

Memory*

e.g. product handling/use error

Movement*
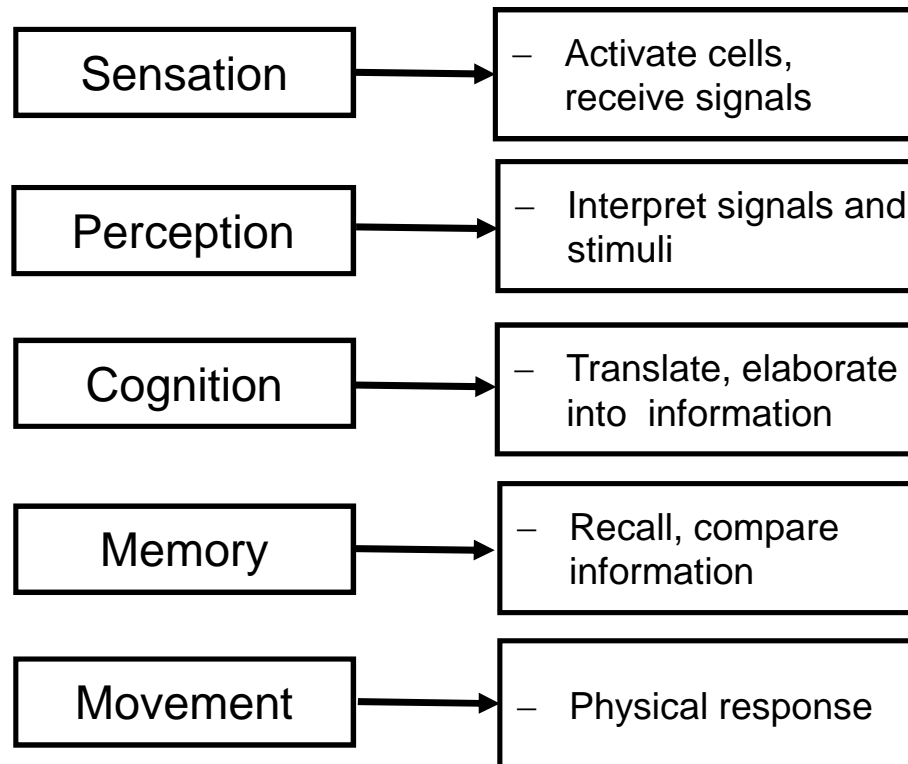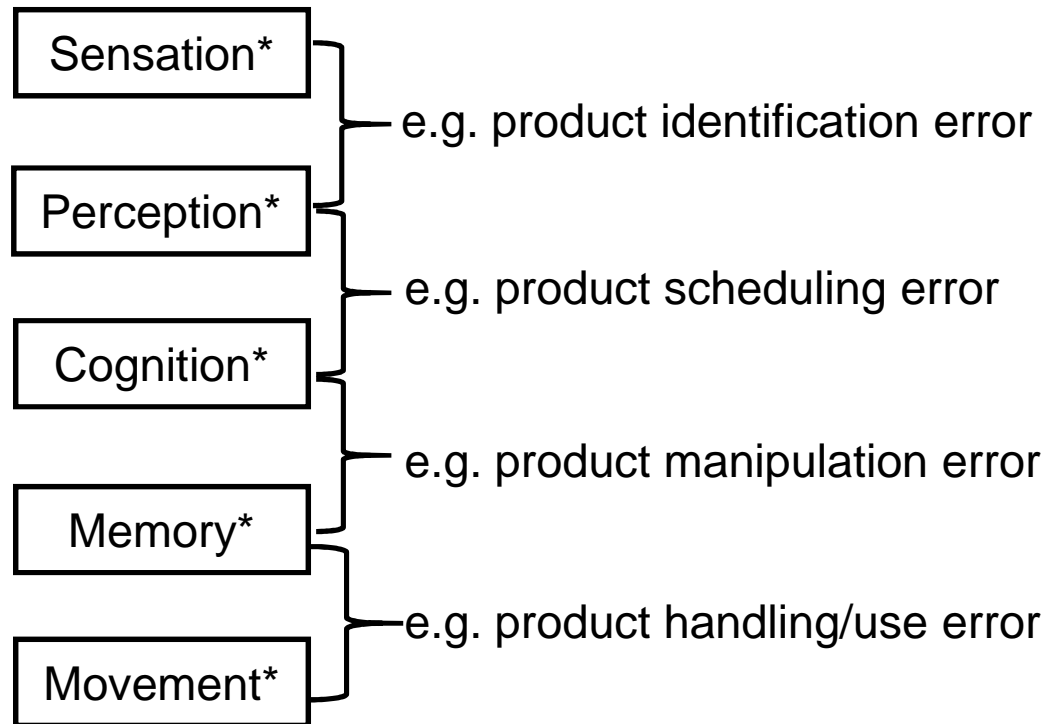
CMC considerations for patient-centric drug products

- „In general, older people are the **majority users of many medicines** and **at highest risk** of encountering practical medication (useability) problems, which may increase the risk for poor adherence, medication errors and/or reduced patient or care givers quality of life."

- „The Reflection Paper **applies to any new application** for a marketing authorization (MA) or variation to en existing MA , and for all application types including full and abridged MAs (i.e. new medicinal products, generics, well established use)."

- „They may also be of **relevance for other age groups** suffering from similar impairments and/or needs (e.g. An easy to open packaging is relevant for rheumatic patients of eny age). They need to be considered in a **patient centric approach to pharmaceutucal dervelopment**."

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 February 2011
EMA/CHMP/137793/2011

EMA geriatric medicines strategy

18 May 2017,
EMA/CHMP/QWP/292439/2017 Rev.: 4.0

Reflection paper on the pharmaceutical development of medicines for use in the older population

Draft

Draft reflection paper agreed by QWP	February 2017
Adopted by CHMP for release for consultation	18 May 2017
Start of public consultation	01 August 2017
End of consultation (deadline for comments)	31 January 2018

CMC considerations for patient-centric drug products

- Patient *acceptability* defined as ability and willingness of the patient to self administer (or lay or professional care giver)

- The different route of administration, the pro's and con's of preparations

  - ✓ For oral use (swallowing, not to swallow)
  - ✓ Different preparation for ear and eye
  - ✓ Nasal and pulmonary delivery
  - ✓ Cutaneous and transdermal
  - ✓ Rectal, vaginal and urethral dosage forms
  - ✓ Parenteral administration froms

- Administration through enteral feeding tubes

- Modifications of dosage forms

  - ✓ Co-administration or mixing with food or beverages
  - ✓ Tablet splitting

CMC considerations for patient-centric drug products

- Dosing frequence

- Excipients in the formulation

- Container and closure systems
  - ✓ Ease of opening
  - ✓ Multi-compartment compliance aids, Multi Dose Dispening systems

- Devices and technologies

- Medicinal and product information

- Medication management
  - ✓ Multiple medication use & polypharmacy
  - ✓ Medication recognition
  - ✓ Switching between medicines

A paradox situation of multimorbidity

- Increasing therapeutic complexity
- Declining management capabilities

7 „dosing moments"
30 min before breakfast
1 - ½ - 1 tablet schedules

	Morning	Noon	Evening	Night	Drug Form	Instructions to use
Moxonidin (0.3 mg)	1				Tablet	
Tyronajod (125µg)	1				Tablet	30 ' before breakfast, glas of water
Tamsulosin 0.4 mg)	1				HGC	
Furosemid (40 mg)	1	1			Tablet	30' before breakfast
Nifedipine 5 mg)	1	1	1		SGC	With meal
Enalapril (20 mg)	1		½	1	Tablet	
Propiverin 15 mg)	1		1	1	Tablet	With meal
Lithiumcarbonate 450 mg)	½		½		MR Tab	
Vitamin D 20000IE		1 week			SGC	Once a week with fat meal
Allopurinol 300 mg)		⅓		1	Tablet	
Omeprazole (20 mg)	1				MR Tab	30' before breakfast
Vertigogeel	2	2	2		Subling	Dissolving sublingual

75 year old patient Asthma, diabetes type 2, coronary heart disease, RLS, leg edema, lumbosciatica

CMC considerations for patient-centric drug products

- „As **knowledge** on testing a product's patient acceptability in the older population **is fragmented**, the selection of the method and acceptance criteria **is left to the company**. However, **companies will need to justify their approach** with respect to the product benefit to risk considerations in the older population, including the risk of poor adherernce and/or alternative administration strategies."

- „The aspects associated with older age may **also be of relevance to adults of middle or younger age as well as children** (e.g. juvenile idiopathic arthritis). Therefore, a **patient centric approach** to the medicine's pharmaceutical development is encouraged."

CMC considerations for patient-centric drug products

Patient characteristics

- Motoric
- Sensoric
- Cognition
- Visual
- Hearing
- Saliva
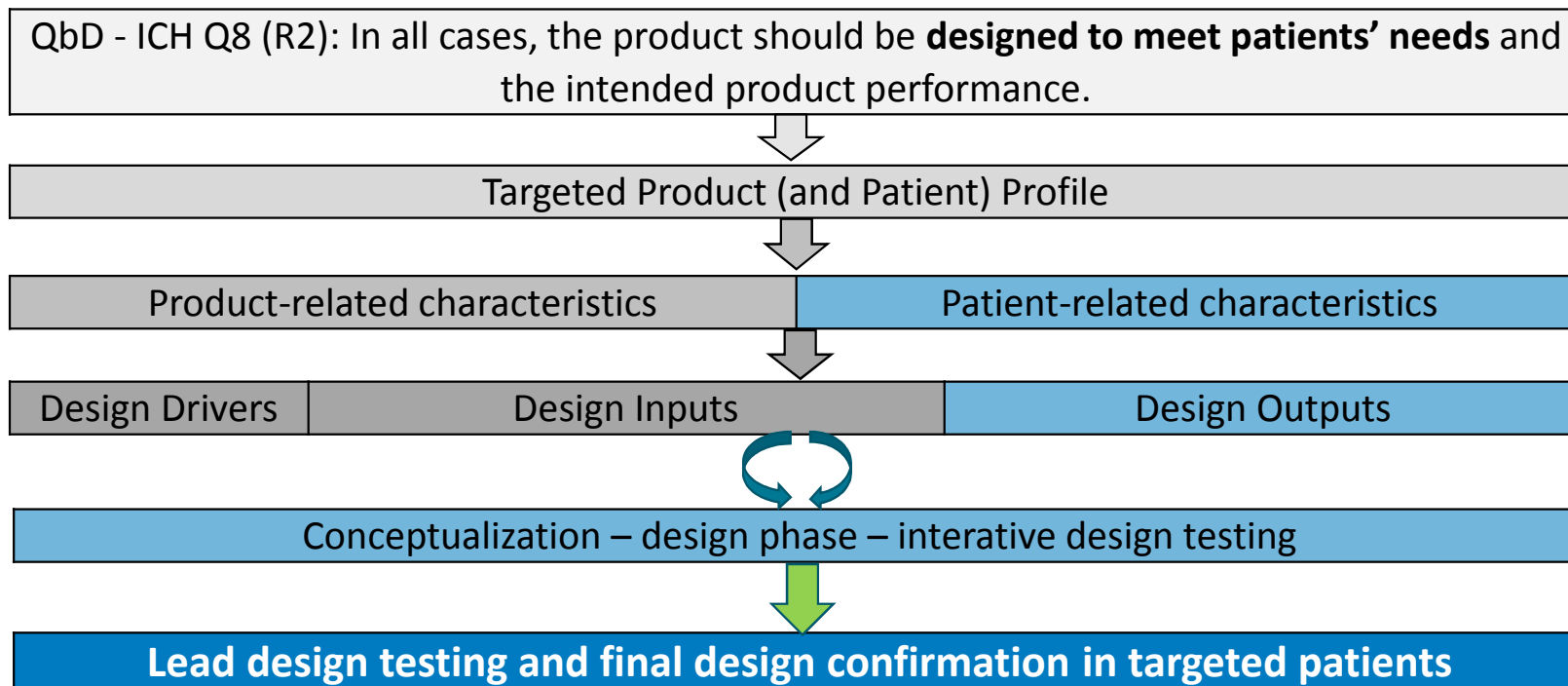- Taste
- Psychological

Targeted patient profile

- Pharmacokinetic & Pharmacodynamic changes
- Multimorbidity
- Vulnerability
- Polypharmacy
- Frailty-Syndrom
- Homeostasis

Patient perception

- The critical personality
  „Each pill is one too much"
- The organized personality
  „I take my tablets regularely, independent from the circumstances."
- The helpless personality
  „This should be decided by the doctor, I don't have a clue on it."
- The routine personality
  „I am used to it. The idea to not take anything – I would be concerned."

CMC considerations for patient-centric drug products

- Patient-centric pharmaceutical drug product design

QbD - ICH Q8 (R2): In all cases, the product should be **designed to meet patients' needs** and the intended product performance.

↓

Targeted Product (and Patient) Profile

↓

Product-related characteristics	Patient-related characteristics

↓

Design Drivers	Design Inputs	Design Outputs

Conceptualization – design phase – interative design testing

| **Lead design testing and final design confirmation in targeted patients** |
|---|

Case studies

For the rheumatoid arthritis (RA) compound certolizumab pegol, UCB developed an ergonomically design self-injection syringe and performed comparative testing with 22 RA patients and several endpoints

- User perception

- Grip strength and force exertion profile during injection

Simulated skin pad placed on their thigh to mimic the injection

thumb pad

plunger

finger flange

barrel

cap

Sheikhzadeh A, *Appl Ergon*. 2012;43:368-375
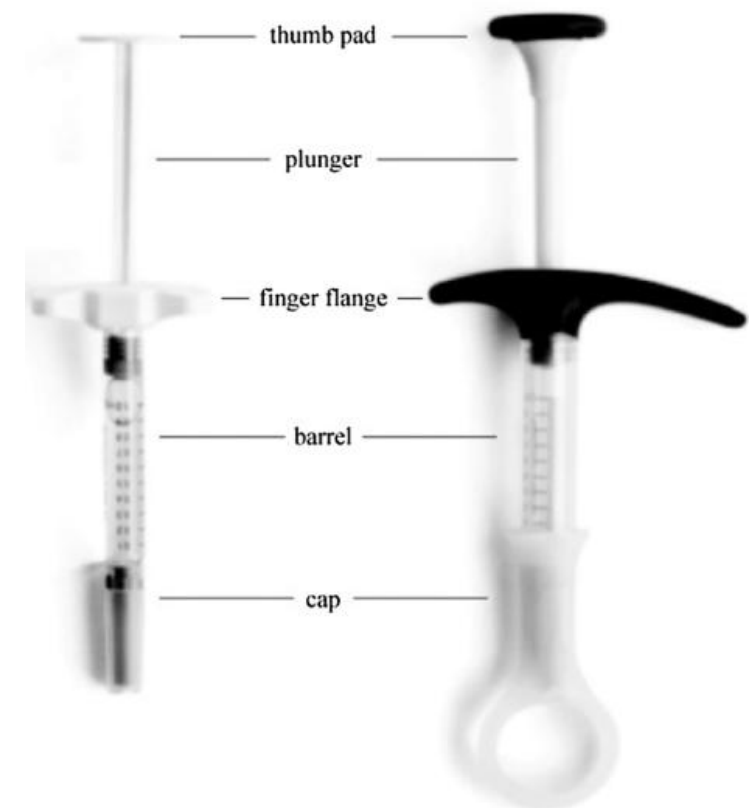
Case studies

Comparative study in RA patients with the existing syringe ® and ergonomic design syringe (N)

- Higher acceptability of the new syringe

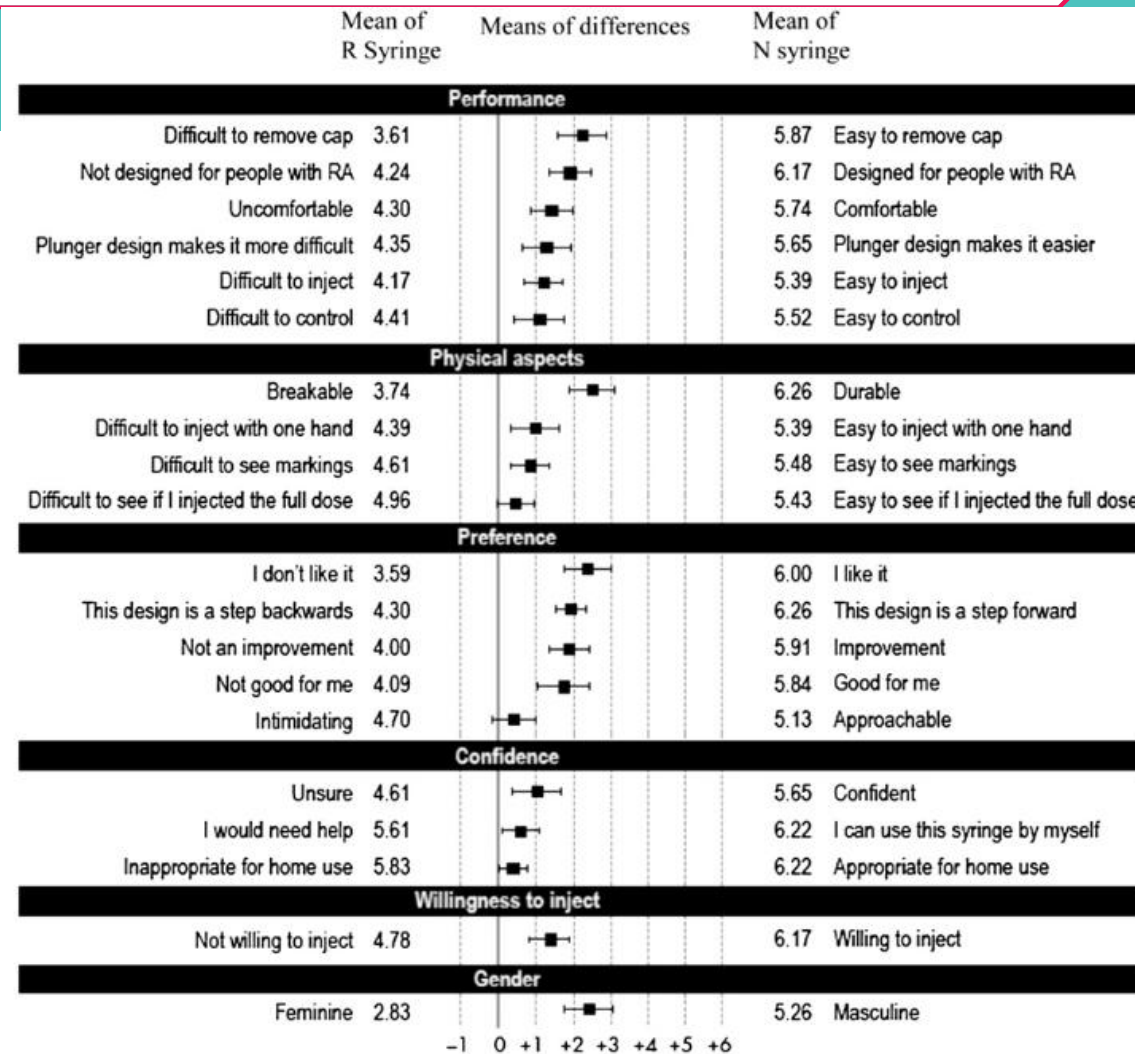- Patients were able to exert higher forces on the plunger during administration
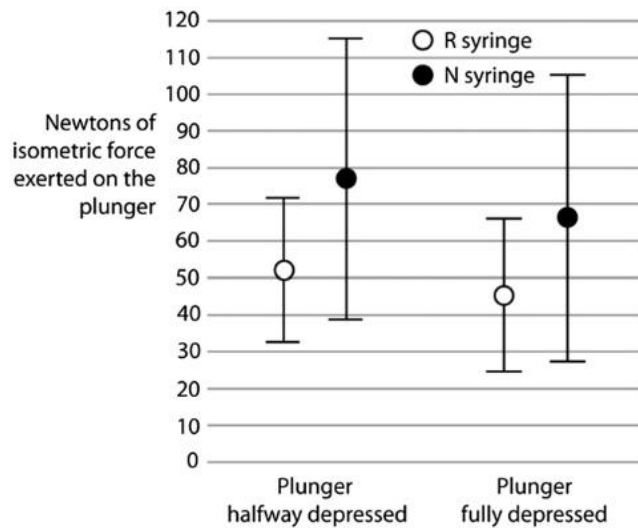
Fig. 4. Mean scores rated on a 7-point likert-like scale for two syringes based on twenty attributes.

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Case studies

The features of the ergonomically designed self-injection syringe for the treatment of rheumatoid arthritis

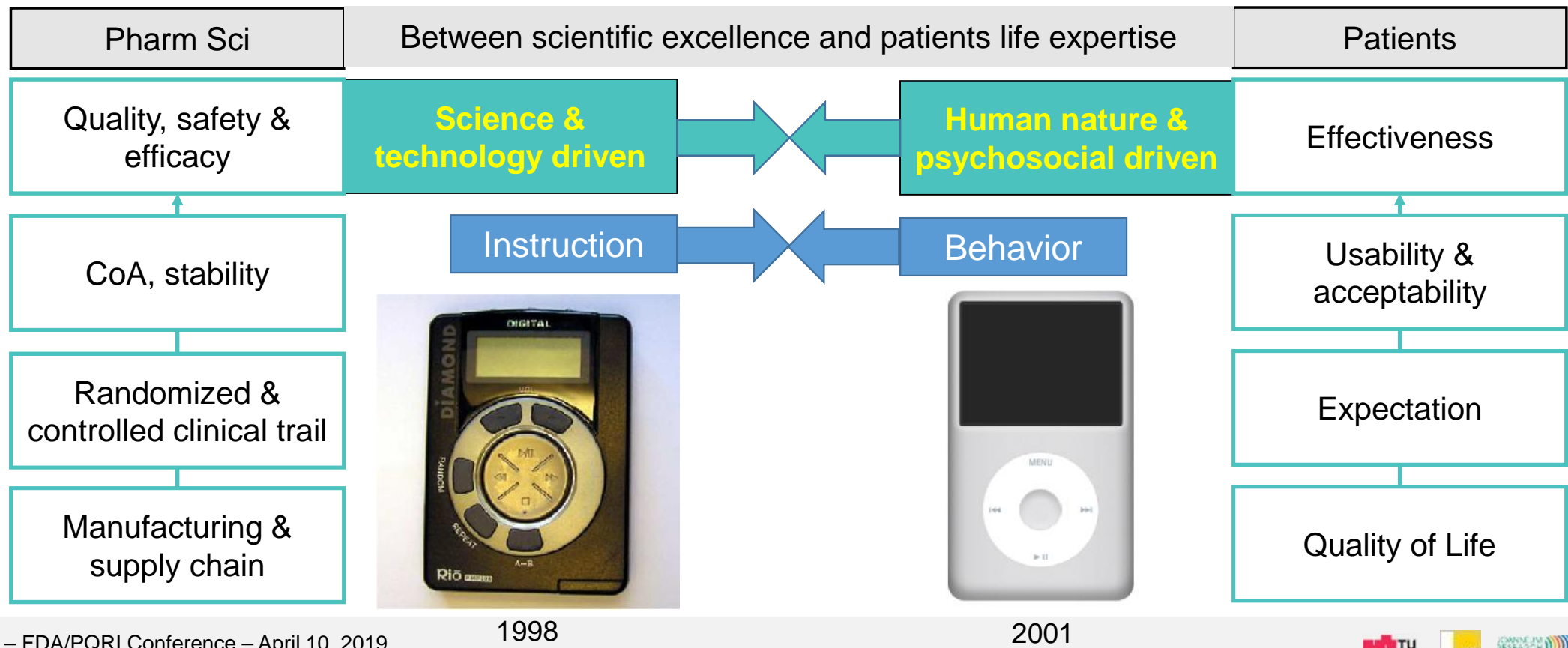**Prefilled Syringe Designed With Patients in Mind[4]**

- **Oversized plunger rod** provides stability
- **Oval syringe barrel** helps prevent spinning between fingers and magnifies graduation, allowing patients to see medication
- **Rounded finger loop** for easy removal of pull cap
- **Large thumb pad** makes it easy for patients to push the plunger
- **Nonslip finger grip** allows patients to hold the syringe steady using various grip positions

cimzia
(certolizumab pegol)
200 mg/mL

Case studies

- **The BAGSO Working Group on Patient Information leaflet**
  - Together with the various stakeholders, the BAGSO working group developed guidance for the design of patient information leaflets

- **The 7 points that are consider important:**
  - Readable scripture and letter size
  - Patient appropriate language
  - Information about the disease and the effect of the drug product
  - Structured, well arranged document presentation
  - Use of pictures and pictograms
  - Use of information and advice boxes
  - Quoting additional support offers e.g. Self-help groups

- **It will remain most difficult to provide sufficient knowledge on health-disease**

The patient centric product development dilemma

The mismatch with the existing business model and mind set

Pharm Sci	Between scientific excellence and patients life expertise	Patients
Quality, safety & efficacy	**Science & technology driven** ⟷ **Human nature & psychosocial driven**	Effectiveness
CoA, stability	Instruction ⟷ Behavior	Usability & acceptability
Randomized & controlled clinical trail	1998	Expectation
Manufacturing & supply chain	2001	Quality of Life

Conclusion

- Patients are being recognized as a major factor in achieving therapeutic outcomes in the real world settings (effectiveness)

- Patients are getting more involved in their health and healthcare decision by ease of information access and lay-person organization in the internet (eroding the white coat authority)

- The pharmaceutical product is beyond simple "health repair", it is the patient experience with the disease (disease burden), the treatment (therapeutic burden) and the expectation in the personal outcomes

- Multimorbidity is associated with cumulative complexity (polypharmacy) and declining patient capability (functional impairment and disability)

- The benefit to risk might change with age (life expectancy, severity of ADR) and multimorbidity (drug – drug, drug – disease interactions)

- Multidisciplinary collaborations are required to understand patient behavior and intuitive use of medicines including learnings from the consumer industry

Conclusion

- Building on intuition – dealing with transport damage

VanMoof reduced transport damages from Europe to the USA by 80 %
using a simple visual trick: The perception of a sensitive TV screen inside!

Conclusion

- Fashion & its tissue is very sensitive to the washing conditions

- Yet, we manage many different types of clothes without issues, because…

… we agreed globally on pictograms

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