Chances and challenges of personalized medicine: proposing the approval of therapeutic concepts

Kirsten Krollmann, M.Sc.

Doktorandentag AK Prof. Schweim

Drug Regulatory Affairs

01.02.2014

universitätbonn

Content

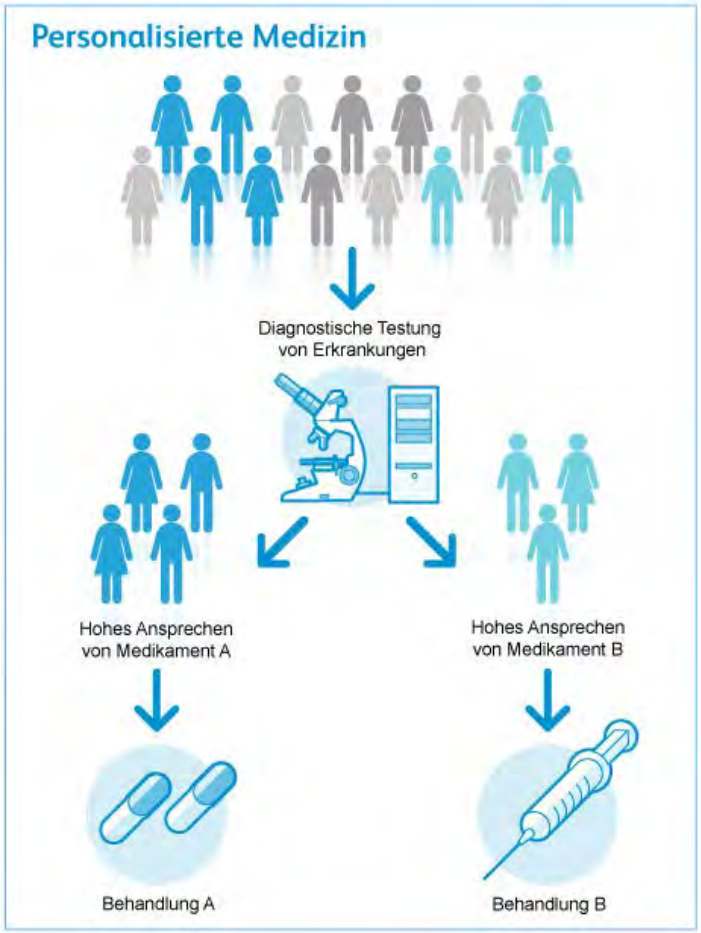
1. Personalized medicine
2. Regulatory challenges
   - Orphan drugs
   - Diagnostics
3. Medical guidelines
4. Drug combinations
5. A new approach: approval of “therapeutic concepts”

Personalized Medicine

Therapy based on genomic markers

- Metabolism (e.g. CYP- Enzymes)
- Mutations (e.g. KRAS)
- Biomarker

→ Patient **stratification**, not individualization



Quelle: Pfizer.de

Promises and questions of personalized medicine

Goals and Visions

- Prevention rather than reaction
- Less try-and-error, faster choice of best therapy
- Less ADRs
- Improving compliance
- Better cost effectiveness
- Improving Quality of life

Problems and Challenges

- Personalized treatment really superior to SOC? Appropriate validation is needed
- Proper biomarker identification must be available
- Possible genetic discrimination
- Disregarding social environment
- Shift of priorities: less conventional treatment and research?

Regulatory challenges: Orphan drugs

Article 3 of Regulation (EC) No 141/2000 on orphan medicinal products:

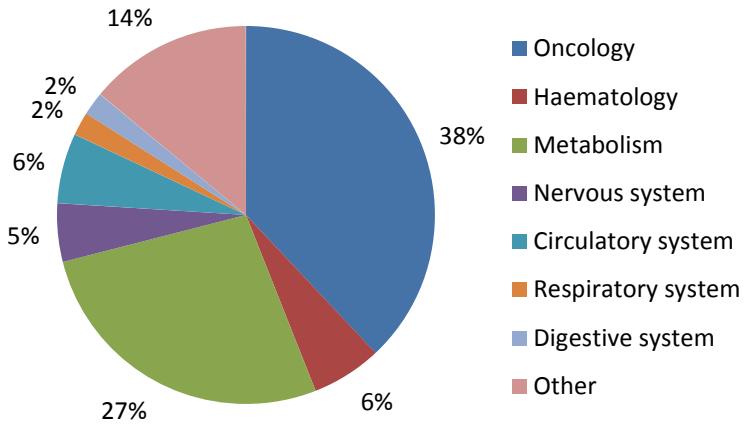
- ✓ Condition is life-threatening/ seriously debilitating/ serious and chronic and
- ✓ Affects no more than 5 in 10,000 persons in the Community or no sufficient return without incentives and
- ✓ No approved satisfactory method of treatment or of significant benefit for affected persons

Differences to US FDA:

- fewer than 200,000 patients in the US
- US designation criteria do not consider the unmet medical need
- US: 7 years market exclusivity

Rewards for orphan designation

- ✓ Market exclusivity (10 years)
- ✓ Reduction of agency fees



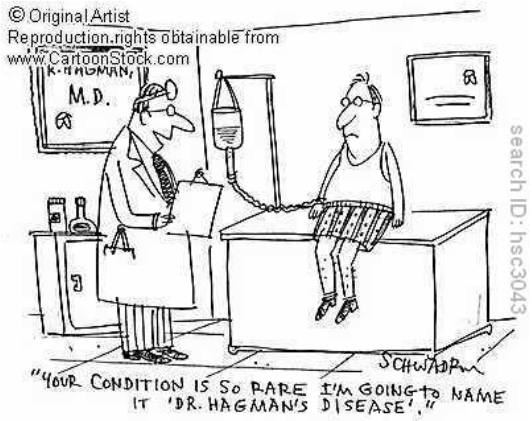
Orphan drugs – the future of personalized medicine?

Personalized medicine

- economically interesting
- sub-groups of well-studied conditions
- pathogenesis is usually well-understood

Orphan drugs

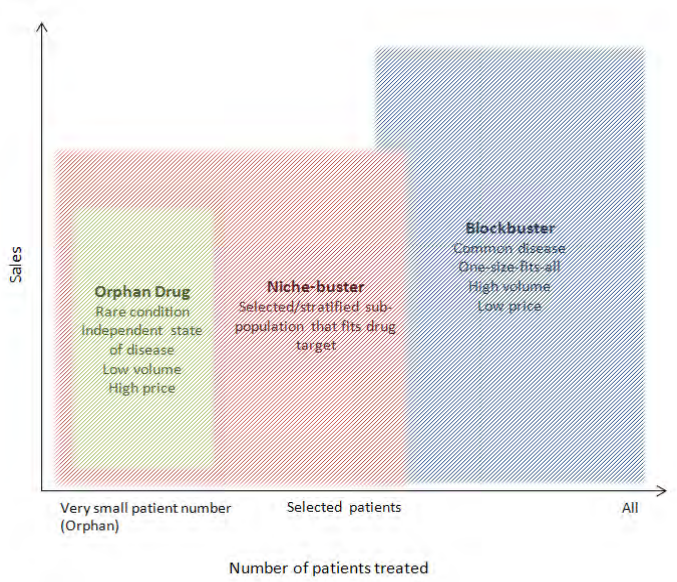
- little economic interest
- low level of expertise and medical knowledge
- high heterogeneity and great research effort needed



From blockbuster to niche-buster to orphan?

Glivec® (Imatinib)

- Inhibitor of tyrosine kinase Bcr-Abl
- Initially approved as a therapy for chronic myelogenous leukemia (CML)
- 2006 revenue more than $2 billion (with only 55,000 patients)

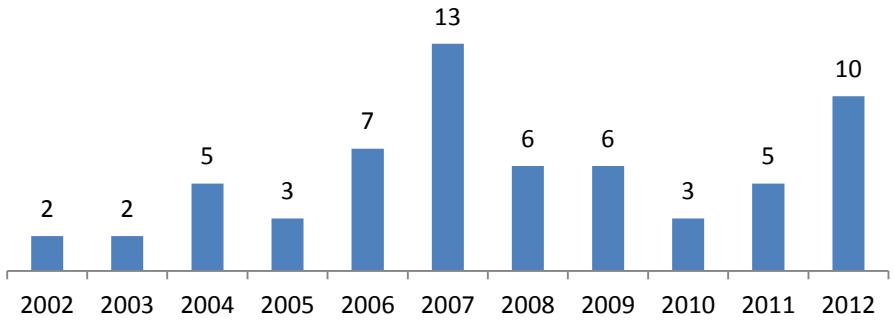


→ Targeted therapy for a small patient group with high efficacy justifies higher prices

Regulatory challenges: Orphan drugs

Shift towards more orphan drugs due to new findings and identification of new conditions possible?

- Advanced new technology and better understanding of diseases may lead to the discovery of new conditions
- “Condition” for which an orphan drug is intended to use must be a well-recognized disease and must clearly differ from other similar conditions and their treatment
- Down-slicing indications depending on the severity and course of a disease or its intensity variants is not sufficient to obtain orphan drug designation
- Recent developments do not show increase of approved orphan drugs



Number of approved orphan drugs in Europe by year of marketing authorization. Data for 2013 incomplete, by July 2013 two orphan drugs had been authorized in that year so far

Regulatory challenges: Diagnostics

Current legal framework

Three 20 year old Directives

- Directive 90/385/EEC on active implantable medical devices (AIMDD)
- Directive 93/42/EEC on medical devices (MDD)
- Directive 98/79/EC on in vitro diagnostic medical devices (IVDD)

Risk based conformity assessment (CE marking)

- Self-certification by manufacturer
- Assessment by notified body for high risk products

New proposed regulatory framework

Drivers for change

- Technical and healthcare developments (IVD, drug/device combinations)
- Globalization
- PIP scandal

Novelties

- Change of legal form: 3 Directive → 2 Regulation
- Scope (genetic tests, software) and **definitions (e.g. companion diagnostic)**
- Strengthened oversight of notified bodies
- Transparency and traceability (Unique Device Identification)
- Premarket authorization for high risk products
- **New IVD classification system**
- Introduction of qualified person on the manufacturer's side

→ New legislation aimed at enhancing safety, traceability, and transparency

Companion diagnostics (CDx)

- Directive 98/79/EC: no specific requirements for CDx, no definition
- Manufacturer's self certification unless IVD falls within higher risk list (annex II)
- IVD / CDx in regulatory documents currently poorly represented, usually no specific IVD identified on SmPC, only testing requirements

  "*To obtain accurate and reproducible results, the testing must be performed in specialized laboratories, which can ensure validation of the test methods.*" (Fachinfo Herceptin)

New

- Proposed definition

'companion diagnostic' means a device specifically intended **for and essential to the selection of** patients with a previously diagnosed condition or predisposition as **suitable or unsuitable** for a **specific** therapy **with a medicinal product or a range of medicinal products**

- New classification system: CDx class C, involvement of NB
- Enhanced conformity and quality assessment, clinical evidence, and post-market follow up

FDA companion diagnostic approach

Draft Guidance for Industry and FDA Staff - In Vitro Companion Diagnostic Devices (2011)

Definition companion diagnostic :

"an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product."

No approval of any novel therapeutic products without a cleared or approved IVD companion diagnostic device for the intended indication when safe and effective use depends on the test results.

510(k)/PMN	PMA/IDE
• Most commonly used for Class I and Class II devices	• Mainly for Class III device
• Clinical studies rarely required	• Clinical studies required
• "Substantial equivalence" to a device legally marketed (prior to May 28, 1976) must be demonstrated	• Safety and effectiveness for intended use must be demonstrated
• Device is cleared for commercial distribution by the FDA	• Device is approved by the FDA prior to marketing

New approach: Approval of therapeutic concepts

What is a „therapeutic concept“?

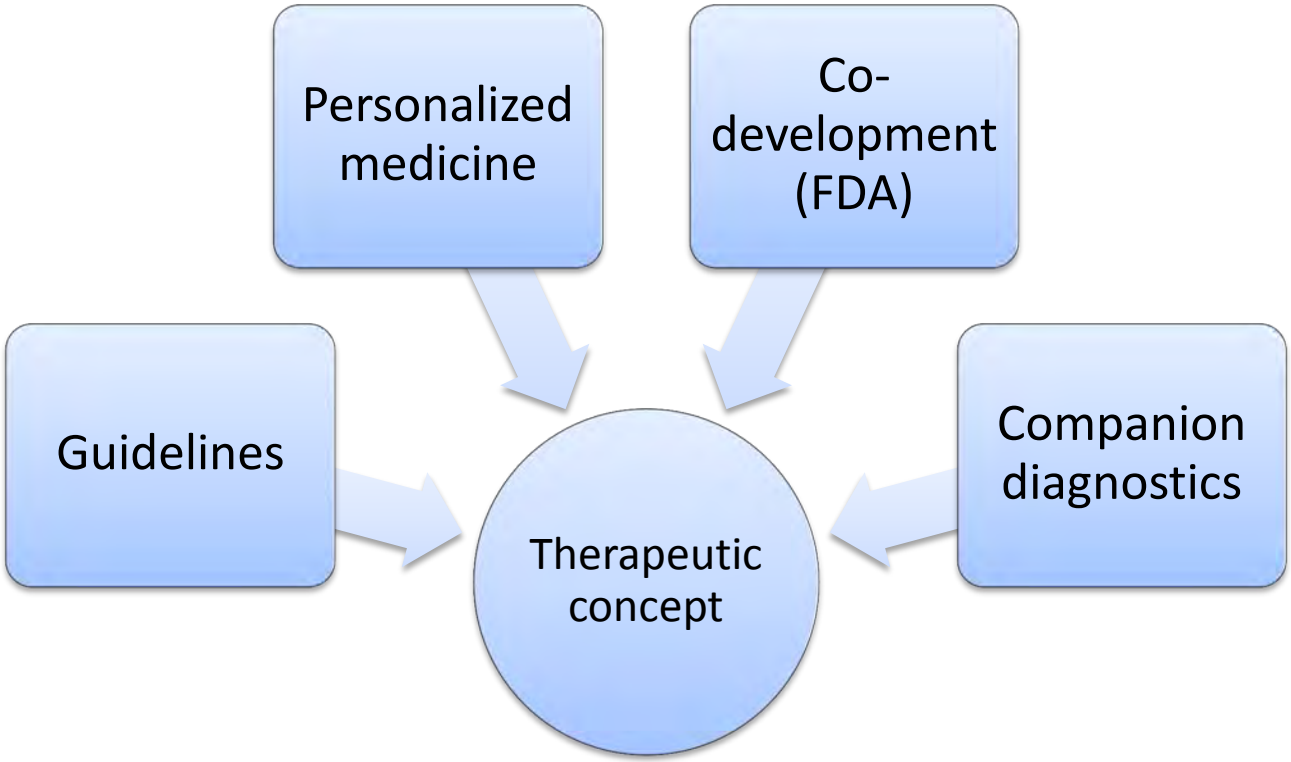
Approval of a treatment regimen, consisting of two or more, marketed or unmarketed, medicinal products for a specific condition and, if required for a safe and effective use of the regimen, approval of a companion diagnostic, that have been developed and studied together

Why approval of therapeutic concepts?

- Today, one agent at a time is reviewed and approved
- Yet, combination therapy is advised or absolutely necessary for many diseases

→ Gap between treatment reality, research and approval practice

New approach: Approval of therapeutic concepts



Medical guidelines - Leitlinien

Objectives

- Improvement of quality in health care
- Application of evidence based and economically appropriate medicines
- Present the current state of scientific knowledge
- Help avoid unnecessary and obsolete methods
- Source of information for public and professionals
- Helps to find (drug) combinations suitable for a specific treatment

*"Guidelines are **systematically developed statements** reflecting the **current state** of knowledge and meant to support **doctors and patients** in making decisions concerning appropriate care for specific health problems. Guidelines are important and effective instruments for quality development in health care. Their primary objective is to **improve medical care** by disseminating current knowledge. Guidelines […] formulate **clear recommendations** for treatment backed up by a **clinical weighting of the power and applicability** of the study results. Guidelines can be understood as **"treatment and decision corridors"** which can or should be **deviated** from in justified cases."* -AWMF

Medical guidelines – legal considerations

- Not legally binding for health care professionals and therefore neither liability nor liability claim liberating effect
- Guidelines are to be understood as guidance, they cannot adequately determine an error in treatment
  - Error in treatment is characterized by the deviation from the standard of care at the particular time of the patient's treatment
- Uncertain legal status of guidelines leads to a lower acceptance in the medical profession
- Guidelines can influence social law by initiating reimbursement

Despite some legal uncertainties, guidelines are a useful, important and indispensable tool in healthcare!

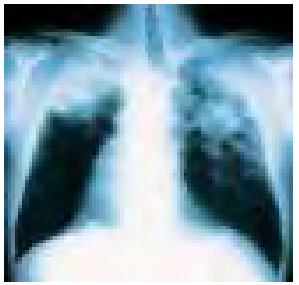
Reasons to use drug combinations

- Biological rational/Prevention of resistance
- Differentiation in the cause of disease
- Subgroup analysis/Stratification

Reasons to use drug combinations

- **Biological rational/Prevention of resistance: Tuberculosis**
  - Bacterium is resistant against most known anti-infective medications due to specific cell wall structure
  - Therapy aims to minimize risk of resistance
  - Drugs used in the regimen have different modes of action to target all *M. tuberculosis* populations
  - Success rate (Germany) ~ 85%

	Medication	Dosing regimen
Intensive phase	Isoniazid + Rifampicin + Pyrazinamide + Ethambutol	2 months 1-0-0
Continuation phase	Isoniazid + Rifampicin	4 months 1-0-0



- Differentiation in the cause of disease
- Subgroup analysis/Stratification

Reasons to use drug combinations

- Biological rational/Prevention of resistance
- **Differentiation in the cause of disease: *Helicobacter pylori***
  - Stomach ulcers and gastritis were generally treated with antacids until the end of the 1980s
  - In 1983 *Helicobacter pylori* was identified
  - Identification of this particular bacterium suggested that ulcers and gastritis may underlie different mechanisms of pathogenesis other than gastric hyperacidity or stress
  - First-line therapy for eradication is a triple therapy consisting of a proton pump inhibitor (PPI) and two antibiotics
- Subgroup analysis/Stratification

Reasons to use drug combinations

- Biological rational/Prevention of resistance
- Differentiation in the cause of disease
- **Subgroup analysis/Stratification: BiDil**
  - Two vasodilators: hydralazine hydrochloride + isosorbide dinitrate
  - Rejected by the FDA in 1997, no convincing efficacy in the overall population
  - Post hoc subset analysis indicated that the drug works better in black patients
  - Approved by the FDA in 2005 for treatment of heart failure for patients that “self-identify as black”

FDA codevelopment guidance

Guidance for Industry Codevelopment of Two or More New Investigational Drugs for Use in Combination (June 2013)

"Combination therapy is an important treatment modality in many disease settings, including cancer, cardiovascular disease, and infectious diseases"

- co-development of novel unmarketed drugs for use in combination
- only to be developed for serious diseases
- strong biological rationale for use of the combination

New approach: Approval of therapeutic concepts

Benefits

- Patients
  - gain earlier access to new treatments that have been thoroughly tested in clinical trials
  - Stratification may lead to less side effect and higher treatment efficacy
  - Higher acceptance
  - Reimbursement
- Physicians
  - Therapy can be easily adjusted to patient
  - Higher legal security
- Industry
  - more efficient clinical trials in terms of time and costs
- Authorities
  - More control about used combinations

New approach: Approval of therapeutic concepts

Risks

- Smaller knowledge about the single agents in the combinations
- Cooperation of several pharmaceutical companies:
  - What if a drug is found to be better or more toxic than the other?
  - Abuse potential of individual combination compounds
  - Vigilance

Vigilance and Labeling

Risk based vigilance system

- Are one or more substances of the combination already in use? If so, can these substances be considered as high risk or low risk?
- Is it likely to administer other drugs with the combination?
- Are drugs from the combination likely to be used individually?

Labeling

1. Drugs are only to be used within the therapeutic concept
2. Drugs of the combination are also used for treating other indications

Labeling shall include the statement that it is a combination regimen. Criteria for patient stratification should be included, as well as a suitable diagnostic.

→ Dual conception for leaflet

Conclusion

- Personalized medicine provides both opportunities and risks
- Knowledge and patient stratification can lead to improved patient care
- Drug combinations are already in use in clinical practice, yet it is insufficiently represented in the legal framework
- Better care could be provided by the authorization of novel “therapeutic concepts”
- “Therapeutic concepts” combine different active ingredients to ensure optimal care
- This can strengthen the importance and safety of CDx

Thank you for your attention

Medical guidelines - Benefits and Harms

	Benefits	Harms
Health care professionals	• Clear guidance for clinical decision-making • Improved quality of care • Attention for harmful or ineffective treatments • Legal protection in some respects	• Flawed or outdated guidelines with incorrect information • Time consuming use • Difficult to implement when guideline does not meet clinical demands • Reimbursement questionable when intervention is not recommended
Patients	• Improved health care outcome • Standardized care • Information	• Inflexibility • Treatment with incorrect or outdated recommendations • Disturb patient-doctor relationship
Heath care system	• Cost reduction • Standardized care	• Waste of resources

Medical guidelines – legal considerations

- Who initiated the clinical practice guideline process and selects those involved in the discussion and creation?
- Which criteria determine content and evidence?
- How is the development financed?
- Are (employees of) pharmaceutical companies allowed to participate financially or through collaboration?
- Who is liable for the accuracy, e.g. in the event of a faulty dosage?
- Can companies sue guideline developers should their drug or therapy not be included despite existing evidence?

BiDil

- Huge political controversy
- Missing knowledge why the drug works better in black patients
- FDA stated approval reasonable conclusion based on data from clinical studies
- Drug's patent was extended by 15 years through the approval as race-specific drug
- In the end, BiDil was no commercial success

Companion diagnostics (CDx)

- Directive 98/79/EC: no specific requirements for CDx, no definition
- Manufacturer's self certification unless IVD falls within higher risk list (annex II)
- IVD / CDx in regulatory documents currently poorly represented, usually no specific IVD identified on SmPC, only testing requirements

  "…, muss die Testung in spezialisierten Laboratorien durchgeführt werden, die eine Validierung der Testmethoden sicherstellen können." (Fachinfo Herceptin)

New

- Proposed definition

*'Companion diagnostic' means a device specifically intended to **select** patients with a previously diagnosed condition or predisposition as **eligible** for a **targeted therapy***

- New classification system (IMDRF): CDx class C, involvement of NB
- Enhanced conformity and quality assessment, clinical evidence, and post-market follow up