Countering medical nihilism by reconnecting facts and values

by Ross Upshur, Maya Goldenberg: Studies in History and Philosophy of Science 2020, doi.org/10.1016/j.shpsa.2020.08.005

General argument (1): Medical nihilism is not the consequence

Ioannidis, Stegenga	Upshur/Goldenberg
Ioannidis (2005): Most scientific findings are probably false	U/G agree with Ioannidis
Stegenga (2018): We have little reason to have confidence in the vast output of medical research **= „Medicine is broken“ (Medical nihilism)**	U/G agree with Stegenga‘s analysis, but not with his conclusion: **Medical nihilism follows only if things could be otherwise.**

General argument (2): Medical nihilists have a false understanding of facts

EBM, Ioannidis, Stegenga	**Upshur/Goldenberg**
Evidence based medicine (EBM): Facts are measured quantities	
Ioannidis, Stegenga: Facts are static and stable	Facts are emergent, defeasible and socially situated
Ioannidis (2005), Stegenga (2018): Most scientific findings are probably false **= We are not able to meet our own requirements** → Collective despair (Medical nihilism)	Scientific account of the world is limited: It is at best suggestive, probably wrong, and difficult to find… **…but that‘s ok, because it‘s the best we can get**

General argument (3): Where values come into play

EBM, Ioannidis, Stegenga	**Upshur/Goldenberg**
EBM, Ioannidis and Stegenga adhere to a strict fact/value dichotomy	Facts and values are entangled
	Acknowledging the entanglement of facts and values explicitly will enable us to recognize the values in medical research
→ **Ioannidis, Stegenga & others:** **Stricter rules are the only way to improve medical evidence**	**Recognizing the values in medical research will enable us to discuss openly which values in medical research are good or bad**

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71 Postings

BIOSTATISTIK

US-Experte: Zwei Drittel der biowissenschaftlichen Studien nicht reproduzierbar

John Ioannidis fordert auf Kongress in Wien höheren Signifikanzwert als erste Gegenmaßnahme

29. August 2017, 19:03 71 Postings

Wien – Medizin, Biologie und viele andere "Life Sciences" umgeben sich gern mit dem Nimbus einer abgesicherten exakten Wissenschaft. Doch sehr oft sollte es besser heißen: "Nix is fix". Dies geht aus dem Keynote-Vortrag des in Fachkreisen bekannten US-Biostatistikers John Ioannidis (Stanford University) beim Internationalen Biometrie- und Biopharmazie-Statistik-Kongress (CEN ISBS) in Wien hervor.

https://www.derstandard.at/story/2000063330620/us-experte-zwei-drittel-der-wissenschaftlichen-studien-nicht-reproduzierbar

Dichotomies (1): Incontrovertible true evidence vs results that are suggestive at best

EBM, Ioannidis, Stegenga	Upshur/Goldenberg
Evidence has to be 100% true, otherwise it‘s worthless	Evidence is never 100% true; at best it is suggestive

Dichotomies (2): Facts and values

Facts	Values
World as it is	World as it ought to be
Realm of science	Realm of ethics (Wiener Kreis)
Keep values out of science = keep wishful thinking out	→ **Values are considered to be ethical values**
	Recent development in Analytic Philosophy (1990s): epistemic values and epistemic virtues
	→ **Truth, knowledge, plausibility, coherence, simplicity or the beauty of a hypothesis are values.**

- *1965
- MD, University of Athens School of Medicine, Athens, Greece, Medicine (1990)
- Citation index: h=199
- >4,500 new citations per month (among the 10 scientists worldwide who are currently the most commonly cited, perhaps also the currently most-cited physician) – *according to his Stanford profile*

Open access, freely available online

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

Summary

There is increasing concern that most current published research findings are false. The probability that a research claim is true may depend on study power and

factors that influence this problem and some corollaries thereof.

Modeling the Framework for False Positive Findings

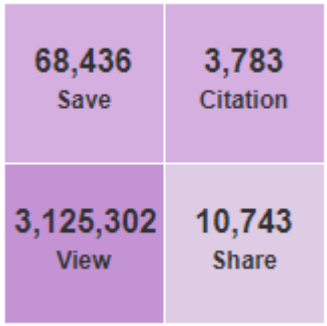
Several methodologists have

is characteristic of the field and can vary a lot depending on whether the field targets highly likely relationships or searches for only one or a few true relationships among thousands and millions of hypotheses that may

Table 2. Research Findings and True Relationships in the Presence of Bias

Research Finding	True Relationship		
	Yes	No	Total
Yes	$(c[1-\beta]R + uc\beta R)/(R+1)$	$c\alpha + uc(1-\alpha)/(R+1)$	$c(R+\alpha-\beta R+u-u\alpha+u\beta R)/(R+1)$
No	$(1-u)c\beta R/(R+1)$	$(1-u)c(1-\alpha)/(R+1)$	$c(1-u)(1-\alpha+\beta R)/(R+1)$
Total	$cR/(R+1)$	$c/(R+1)$	c

DOI: 10.1371/journal.pmed.0020124.t002



Wikipedia.de: Most requested publication of Public Library of Science

- PLoS Med. 2005 Aug; 2(8): e124. Doi: 10.1371/journal.pmed.0020124

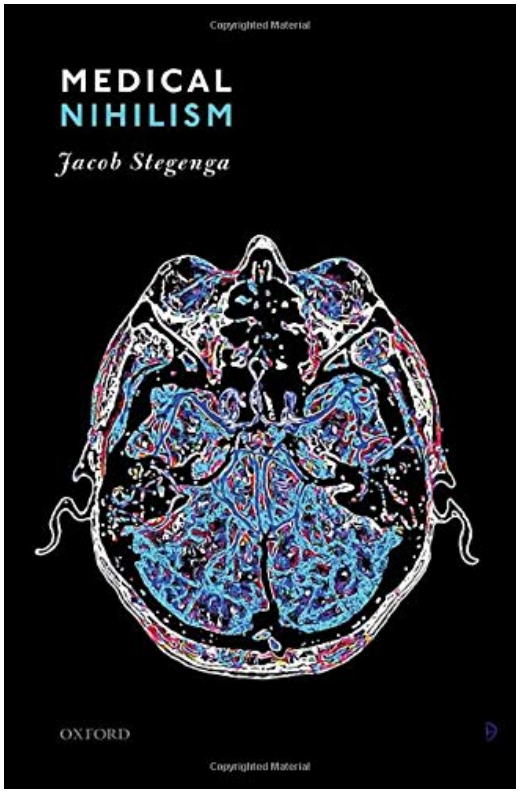
Jacob Stegenga

Reader in Philosophy of Science

Jacob Stegenga is a Reader in the Department of History and Philosophy of Science at the University of Cambridge. He has published widely on fundamental topics in reasoning and rationality and philosophical problems in medicine and biology. Prior to joining Cambridge he taught in the United States and Canada, and he received his PhD from the University of California San Diego. He is the author of *Medical Nihilism* and *Care and Cure: An Introduction to Philosophy of Medicine*, and he is currently writing a book on the sciences of sexual desire.

- Currently Reader at UNIVERSITY OF CAMBRIDGE
- 1999 BA, Biology & Philosophy, University of Victoria
- 2003 MSc, Physiology/Neuroscience, University of Toronto
- 2005 MA, History & Philosophy of Science, Univ. of Toronto
- 2011 PhD, Philosophy, University of California, San Diego

https://cambridge.academia.edu/JacobStegenga/CurriculumVitae



Jacob Stegenga: *Medical Nihilism*. Oxford University Press 2018.

This book defends **medical nihilism**, which is the view that we should have little confidence in the effectiveness of medical interventions.

If we consider the frequency of failed medical interventions, the extent of misleading evidence in medical research, the thin theoretical basis of many interventions, and the malleability of empirical methods in medicine, and if we employ our best inductive framework, then our confidence in the effectiveness of medical interventions ought to be low.

https://oxford.universitypressscholarship.com/view/10.1093/oso/9780198747048.001.0001/oso-9780198747048

Ross Upshur MD, MSc, MA

- *1958
- Professor at: UNIVERSITY OF TORONTO DALLA LANA SCHOOL OF PUBLIC HEALTH
- 1983 MA Queen's University Philosophy Thesis: *Prejudice and Understanding: A Study of Hans-Georg Gadamer's Philosophical Hermeneutics*
- 1986 MD McMaster University
- 1997 MSc University of Toronto Epidemiology Thesis: *Measuring the Impact of Influenza on Hospitalizations of the Elderly in Ontario*

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"My research addresses the fundamental epistemic question, "How do we know what to believe?" (or when are knowledge claims justified) in health care."

Further discussion points (1)

- **Kelly, Heath, Howick & Greenhalgh (2015):** Failure to address values in a systematic way has hindered the development of EBM
- **Benjamin et al (2018):** "Redefine statistical significance": change the default p-value threshold for statistical significance for claims of new discoveries from 0.05 to 0.005.
- **Ioannidis (2005):** Studies are less likely to be true:
  - When the studies conducted in a field are smaller
  - When effect sizes are smaller
  - When there is a greater number and lesser preselection of tested relationships
  - Where there is greater flexibility in designs, definitions, outcomes, and analytical modes
  - When there is greater financial interest and other interest and prejudice
  - When more teams are involved in a scientific field in chase for statistical significance

www.ebmplus.org

"EBM+ is a network of people seeking to improve the ways in which evidence-based medicine handles evidence of mechanisms."

Further discussion points (2)

- **Stegenga (2018):** Master argument for medical nihilism uses a Bayesian theory of scientific inference: one's confidence in the effectiveness of a medical intervention is a conditional probability: P(H/E) – H=hypothesis regarding the effectiveness of the intervention; E=available evidence regarding the effectiveness of the intervention
- **Peirce (1955):** The scientific spirit requires a man to be at all times ready to dump his whole cartload of beliefs, the moment experience is against them. The desire to learn forbids him to be perfectly cocksure that he knows already.

Theorem of Reverend Thomas Bayes

Bayes' theorem

From Wikipedia, the free encyclopedia

"Bayes rule" redirects here. For the concept in decision theory, see Bayes estimator.

In probability theory and statistics, **Bayes's theorem** (alternatively **Bayes's law** or **Bayes's rule**), named after Reverend Thomas Bayes, describes the probability of an event, based on prior knowledge of conditions that might be related to the event.[1] For example, if the risk of developing health problems is known to increase with age, Bayes's theorem allows the risk to an individual of a known age to be assessed more accurately (by conditioning it on his age) than simply assuming that the individual is typical of the population as a whole.

One of the many applications of Bayes's theorem is Bayesian inference, a particular approach to statistical inference. When applied, the probabilities involved in Bayes's theorem may have different probability interpretations. With Bayesian probability interpretation, the theorem expresses how a degree of belief, expressed as a probability, should rationally change to account for the availability of related evidence. Bayesian inference is fundamental to Bayesian statistics.

Contents [hide]

https://en.wikipedia.org/wiki/Bayes%27_theorem

Further discussion points (3)

- **Putnam (2002)** argues from a perspectice informed by pragmatism that the fact-value dichotomy has collapsed
- **Helen Longino (1990):** Social criticism is key to science's epistemic success. Objectivity in science is interactive. Scientific inquiry is objective to the degree that it permits transformative criticism.
- **Heather Douglas (2009):** Determinations of evidentiary justification are qualified by determinations of inductive risk: what is the consequence of wrongly accepting or rejecting a hypothesis (inductive risk = how social values enter medical science)

Structure of "Countering medical nihilism"

- Upshur/Goldenberg claim: **science is socially embedded; organization of science has impact on results**

Their paper is socially embedded in philosophy departments:

Introduction → Michael P Kelly et al. 2015 (philosopher) →

→ Daniel J Benjamin et al. 2018 (behavioural economist) →

→ John P.A. Ioannidis 2015 (statistician) →

→ Jacob Stegenga 2018 (philosopher) →

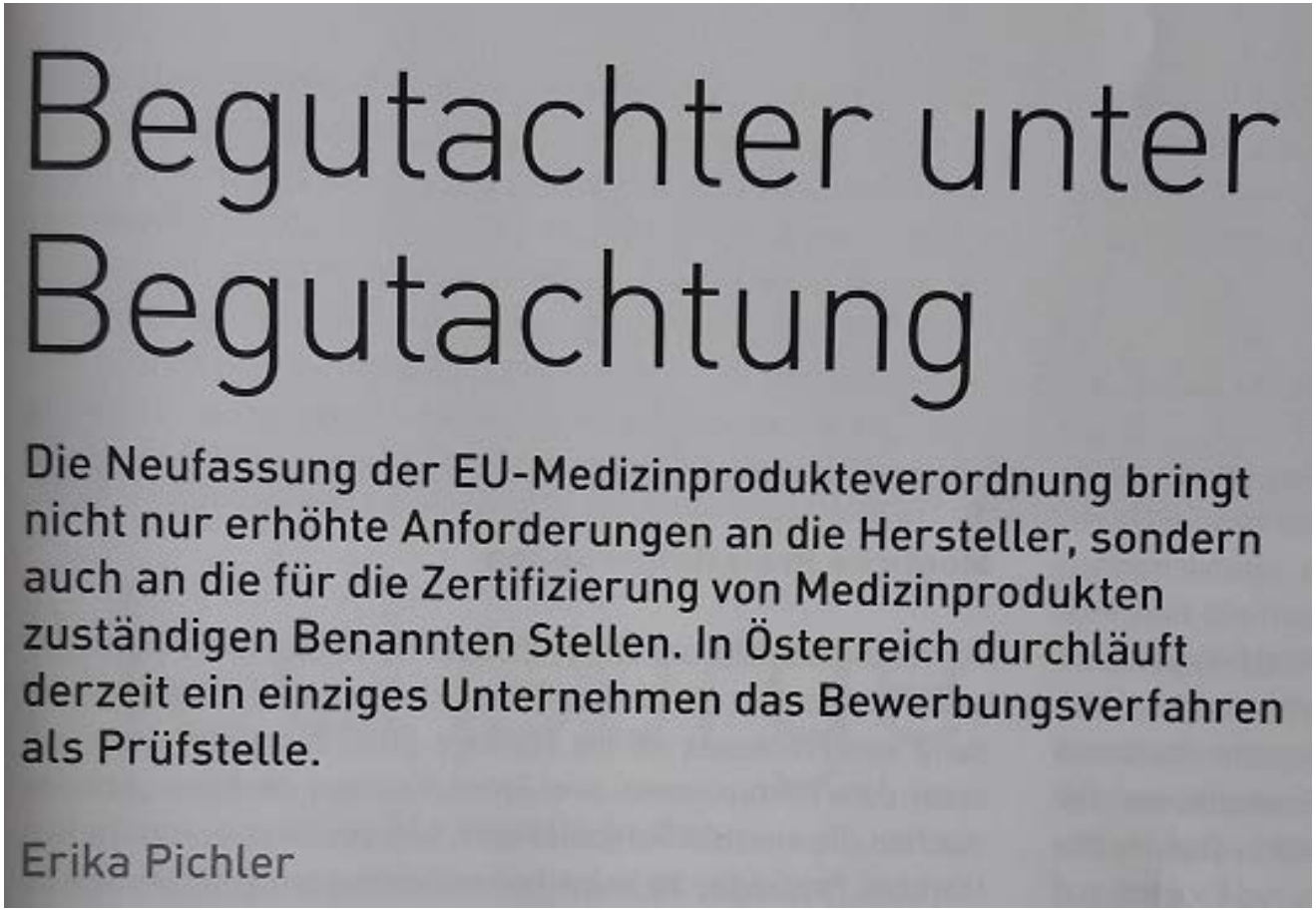
→ Charles Sanders Peirce (philosopher) →

→ Hillary Putnam 2002 (philosopher) →

→ Helen Longino (philosopher) →

→ Heather Douglas 2009 (philosopher) → *conclusion*

Topic: tightening the rules



Begutachter unter Begutachtung

Die Neufassung der EU-Medizinprodukteverordnung bringt nicht nur erhöhte Anforderungen an die Hersteller, sondern auch an die für die Zertifizierung von Medizinprodukten zuständigen Benannten Stellen. In Österreich durchläuft derzeit ein einziges Unternehmen das Bewerbungsverfahren als Prüfstelle.

Erika Pichler

Source: Das österreichische Gesundheitswesen – ÖKZ / ÖKZ EXTRA: MedTech & Medica, 61. Jg. (2020), p. 5-6.

“Begutachter unter Begutachtung”

- Something happened: PIP scandal 2015 (deficient breast implants)

  → New EU Medical Devices Regulation 2017

  → Austria’s two Notified Bodies (Benannte Stellen) for the conformity of Medical Devices (TÜV Austria in Vienna and PMG at the TU in Graz) discontinued their activities because of the elevated requirements of the new MDR Regulation.

  → Status quo: No Notified Body in Austria for MDR. (15 in the whole EU.)

  → QMD Services (founded 2018), subsidiary of Quality Austria – Trainings, Zertifizierungs und Begutachtungs GmbH applies for appointment as Notified Body

  - Certification process requires a number of years; not certain that QMP will pass.
  - Greatest challenge: to provide an expert panel consisting 3 experts with documented expertise for nearly every medical device (1 for medical use, 1 with technical expertise, 1 with quality management expertise)

  → Prices of medical devices (contain already 30% for certification and market admission) will probably increase

What is missing in Upshur's & Goldenberg's paper

- GxP (GMP, GLP, GCP, GDP, etc.), cGMP
- Guidelines, directives (EU, USA, ICH)
- Scientific advices by competent authorities
- Pharmacopoeias (EU, US, GB, International)
- Regulations for clinical trials (randomizing, blinding)
- Regulations for toxicology studies
- Role of the Qualified Person (QP)
- Pharmacovigilance

Good Clinical Practice NETWORK

ICH GCP REGULATIONS CRO LIST CLIN

2. THE PRINCIPLES OF ICH GCP

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

https://ichgcp.net/2-the-principles-of-ich-gcp-2

- Principles 2.1 – 2.3: values are involved in medical research
- Principle 2.2: risk-benefit assessments are involved, too

Good Laboratory Practice (GLP): principles

2. **Quality assurance programme**

2.1. *General*

1. The test facility should have a documented quality assurance programme to assure that studies performed are in compliance with these principles of good laboratory practice.

2. The quality assurance programme should be carried out by an individual or by individuals designated by and directly responsible to management and who are familiar with the test procedures.

3. This individual(s) should not be involved in the conduct of the study being assured.

- **DIRECTIVE 2004/10/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 11 February 2004**
- **In German: Deutschland: Chemiekaliengesetz (ChemG), Anhang 1: https://www.gesetze-im-internet.de/chemg/BJNR017180980.html**

Separation of roles between researchers and quality assurance

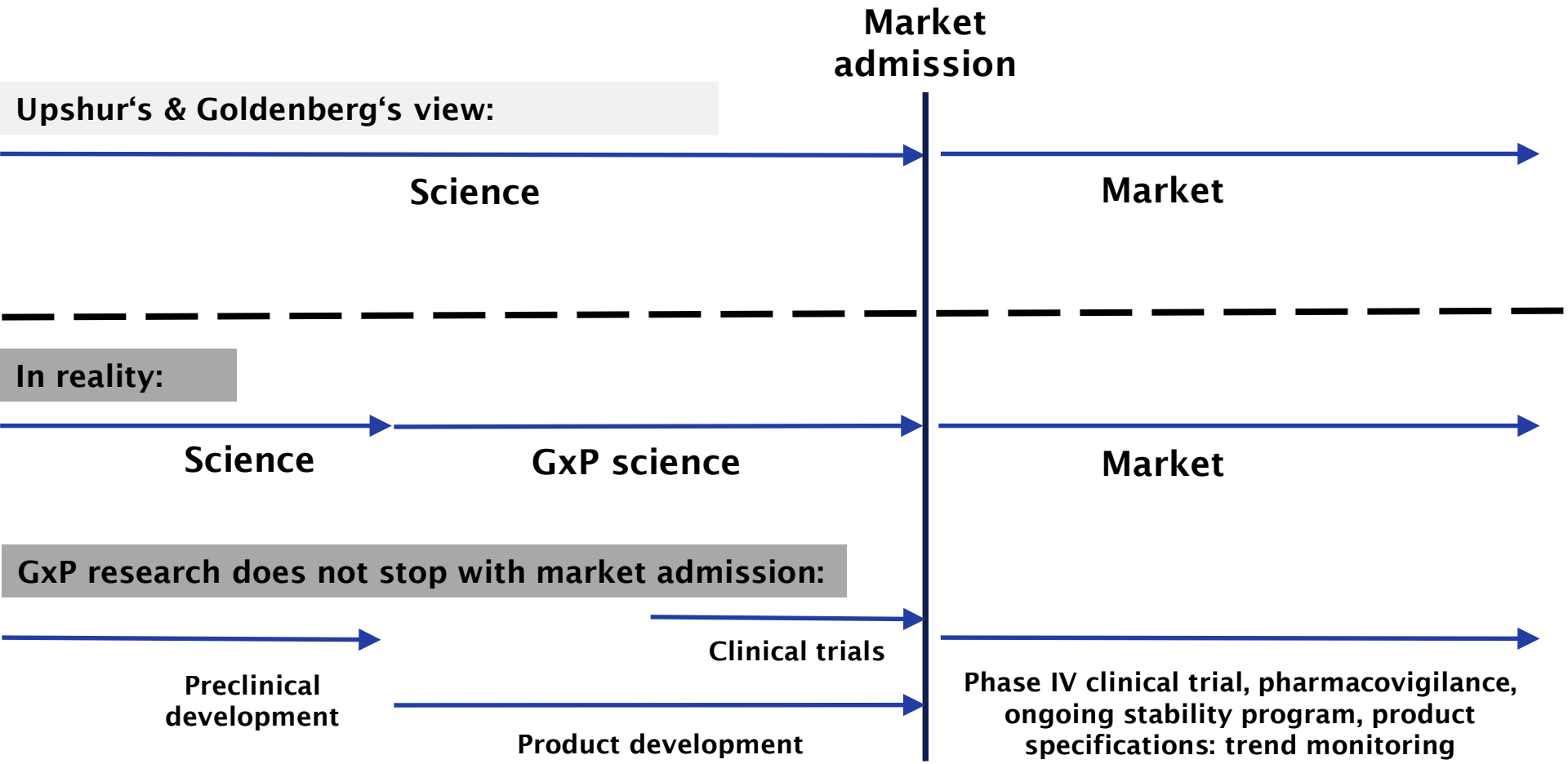
GLP = Science + Quality Management System

- Some (selected) principles of GLP
  - Adequate premises (buildings, labs)
  - Qualified staff (documented)
  - Written procedures for all work steps (SOPs – Standard Operational Procedures)
  - Study director and person responsible for quality assurance (QA)
  - All analytical tests have to be validated
  - Analytical devices and EDV system have to be qualified
  - Study plan approved by study director
  - QA should store copies of all SOPs and approved study plans
  - Conduct of a Master Schedule by QA (register of the current status of all studies)
  - Study report signed by Study Director and QA

GxP is not considered to be science; neither science+

- 2019 Aposcience grant application to Wirtschaftsagentur Wien – WA: a stability study does not have any novelty value (Neuheitswert) = **It is no science.**
- GxP product development research is not undertaken out of curiosity for outcomes, but because you have to (guidelines, directives, laws) = **an important characteristic of science is missing**
- On the other hand: Guidelines, directives & laws also state only that GxP research has to be scientifically sound = **GxP is not considered to be more than science (science+)**

GxP: Science is not enough for pharmaceutical product development



FDA concept: cGMP – current GMP

The CGMP requirements were established to be flexible in order to allow each manufacturer to decide individually how to best implement the necessary controls by using scientifically sound design, processing methods, and testing procedures. The flexibility in these regulations allows companies to use modern technologies and innovative approaches to achieve higher quality through continual improvement. Accordingly, the "C" in CGMP stands for "current," requiring companies to use technologies and systems that are up-to-date in order to comply with the regulations. Systems and equipment that may have been "top-of-the-line" to prevent contamination, mix-ups, and errors 10 or 20 years ago may be less than adequate by today's standards.

https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practices-cgmps

- Responsibility is always with the manufacturer
- cGMP – manufacturer has always be up-to-date

Safety of a pharmaceutical product

Toxicology studies:

- Acute toxicity studies (single dose)
- (Sub-)chronic toxicity studies (repeated dose)
- Genoxicity studies
- Cancerogeneity studies
- Reproduction and Developmental Toxicity
- Local Tolerance

Clinical Trials

- Ethics committee vote
- National competent authority decision
- Adverse events reporting
- DSMB (Data Safety Monitoring Board)

After Market Admission

- Clinical Phase IV trial
- Pharmacovigilance
- PSUR (Periodic Safety Update Report)

Therapeutic efficacy vs therapeutic effectiveness in clinical trials

• In clinical phase II trials

- *"**Efficacy** can be defined as the performance of an intervention under ideal and controlled circumstances,…*
- Defined patient group under **optimal treatment conditions**
- **IMP vs Placebo**
- Measures whether a treatment influences **positively the outcome of interest** (e.g. wound size reduction)

• In clinical phase III trials

- *…whereas **effectiveness** refers to its performance under 'real-world' conditions."*
- With **inhomogenous** patient groups and **insufficient** medical resources.
- **IMP vs Standard of Care**
- Measures whether a treatment **influences positively the (whole) disease**
- **Measures to increase patient compliance** are not allowed

Singal AG et al. A primer on effectiveness and efficacy trials. Clin Transl Gastroenterol. 2014 Jan 2;5(1):e45. doi: 10.1038/ctg.2013.13.

The role of the Qualified Person (QP)

General principles

The ultimate responsibility for the performance of a medicinal product over its lifetime, its safety, quality and efficacy, lies with the marketing authorisation holder (MAH).

However, the QP is responsible for ensuring that each individual batch has been manufactured and checked in compliance with laws in force in the Member State where certification takes place, in accordance with the requirements of the marketing authorisation (MA) and with Good Manufacturing Practice (GMP).

EU GMP Guide: EudraLex Volume 4, Annex 16: Certification by a Qualified Person and Batch Release, https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/v4_an16_201510_en.pdf

- Every site manufacturing pharmaceutical drugs is required to have available at least one Qualified Person (Austrian Arzneimittelbetriebsordnung (AMBO) 2009, §7)
- Role separation between QP, Head of production and Head of quality assurance
- A QP may share responsibility only with another QP

The Pharmacopoeias


EUROPEAN PHARMACOPOEIA 10.0 Contents of the 10th Edition

IV. CONTENTS OF THE 10th EDITION

- Analytical methods
- Reference standards
- Reagents
- Dosage forms
- Container materials
- Monographs on specific drug compounds

Market approval ≠ clinical adoption

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Academia and industry: allocating credit for discovery and development of new therapies

Jeffrey S. Flier

First published May 20, 2019 - More info

JCI – The Journal of Clinical Investigation

- "**Importantly, FDA approval does not ensure clinical adoption.** Physicians may or may not prescribe an approved drug, and health insurers and formularies may or may not cover the cost of therapies, further increasing the financial risks of drug development."

Formulary: A list of prescription drugs covered by a prescription drug plan or another insurance plan offering prescription drug benefits. Also called a drug list.
https://www.healthcare.gov/glossary/formulary/

Conclusion: staircase of confidence levels in science