BfArM
Bundesinstitut für Arzneimittel
und Medizinprodukte

Warum fordern Zulassungsbehörden in der Regel eine Replikation von Studienergebnissen?

Armin Koch
Bundesinstitut für Arzneimittel
und Medizinprodukte
Kurt-Georg-Kiesinger Allee 3
D-53175 Bonn

The views expressed in this paper are those of the author and not necessarily those of the BfArM

Warum fordern Zulassungsbehörden in der Regel eine Replikation von Studienergebnissen?

Ja warum denn eigenlich?

- die FDA verlangt es,
- die *emea* verlangt es,
- Karl Popper hat es schon viel früher gesagt,
- es gibt empirische Evidenz, daß Replikation wichtig ist,
- unter welchen Bedingungen ist Replikation verzichtbar?
- Diskussion.

… FDA asks for replication:

"... it has been FDA's position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness."

"Congress amended ... to make clear that the agency may consider data from one adequate...."

"In making this clarification, Congress confirmed FDA's interpretation of the statutory requirements for approval and acknowledged the Agency's position that there has been substantial progress in the science of drug development"

FDA: Guidance for Industry:
Providing Clinical Evidence of Effectiveness for
Human Drug and Biological Products

… *emea* asks for replication:

EWP, brave position:

"The minimum requirement (for confirmatory phase III data) is generally one controlled study with statistically compelling and clinically relevant results."

…

"To summarise, there is no formal requirement to include two or more pivotal studies in the phase III program."

CPMP/EWP: PtC on Validity and Interpretation of Meta-Analyses, and One Pivotal Study

… *emea* asks for replication:

EWP: conservative position:

However, in most cases a program with *several studies* is the most, or perhaps *only feasible way* to provide the variety of data needed to confirm the usefulness of a product in the intended population.

In the *exceptional event* of a submission with *only one pivotal study*, this has to be particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency.

CPMP/EWP: PtC on applications with
(1) Meta-Analyses, and (2) One Pivotal Study

… Karl Popper has said it years ago:

"... we do not, as a rule, further question eyewitness of an experiment, but, if we doubt the result, we may repeat the experiment, or ask somebody else to repeat it."

K. Popper, zitiert nach Högel & Gaus (CCT 20, 511-518)

- Es ist der gesetzliche Auftrag der Zulassungsbehörden, an den Resultaten einer klinischen Studie zu zweifeln.
- Ist es nicht interessant, wie weit wir uns bereits von den Vorstellungen von Karl Popper entfernt haben?

… there is empirical evidence

Example: Bond & Opera studies

Two three-arm studies comparing Omeprazole (10mg, 20mg) vs. Placebo for the treatment of functional dyspepsia. Combined because "they were completely identical in design, except that different countries recruited the patients".

(Talley et al, Alliment. Pharmacol. Ther. (12) 1998: 1055-1065)

Individual studies:

Study	***Omeprazole 20mg relief / treated***	***Placebo relief / treated***
Bond	93/219	57/219
Opera	68/202	62/203

… there is empirical evidence

Example: Bond & Opera studies

Study	***Oprazole relief/treat***	***Placebo relief/treat***	***risk diff 95%CI P-Value***	***weight contr. to χ^2 P-Value(het)***
Bond	93/219 42.5%	57/219 26.0%	0.16 (0.077;0.252) 0.0002	51.9% 2.05 .
Opera	68/202 33.7%	62/203 30.5%	0.03 (–0.060;0.122) 0.5009	48.1% 2,22 .
Meta-Analysis (FEM)	*161/221* *72.8%*	*119/222* *53.6%*	*0.10* *(0.037;0.164)* *0,0018*	*100%* . *0.0386*

… there is empirical evidence

Example: OASIS 1 & OASIS 2:

2 studies comparing Hirudin and Heparin for anticoagulation in patients with unstabel angina or AMI without ST elevation.

OASIS1 is a 3-arm study (N=909) with two dosage regimens of Hirudin.

OASIS2 (N=10141) replicates the comparison of the low dose group with Heparin.

… there is empirical evidence

Consistent findings?

As no difference between the two dosage groups was observed in OASIS 1, groups are pooled for the MA.

ID	*Lepirudin*	*Hirudin*	*OR*	*weight*	*P-Value*	*Q(i)*
OASIS1	14/538	18/371	0.52	7.3942	0.0706	1.4916
OASIS2	178/5045	211/5033	0.84	92.6058	0.0836	0.1191

day 7 triple endpoint

(OASIS-2 investigators, Lancet (353) 1999, p.429 f.)

… there is empirical evidence

Example: Thrombolysis in stroke

success	***rt-PA***	***Placebo***	***risk differ-ence***	***weight***
NINDS-B	65/168	43/165	12,6%	37%
NINDS-A	68/144	40/147	20,0%	31%
ECASS 1	19/49	10/38	12,4%	9%
ECASS 2	34/81	29/77	4,0%	16%
Atlantis A	2/10	5/12	-21,6%	3%
Atlantis B	9/13	9/26	34,6%	4%
Total	197/465	136/465		

(Saver, J.L. et al. BMJ (324), p. 727 f.)

… there is empirical evidence

Example: Thrombolysis in stroke

Base for decision making:

- Estimated 400 000 strokes per year (NEJM,333,1581)

	rt-PA	Placebo
treated in above mentioned trials	1162	1122
included in meta-analysis	465	465

Under which conditions is replication not required?

EWP: Indications and contraindications for OPT:

may be prudent to plan for more than one Phase III trial	***prerequisites for reliance on OPT***
•Lack of pharmacological rationale •New pharmacological principle •Phase I / II limited or unconvincing •history of failed studies or contradictory results •no effective treatment exists •demonstrate efficacy in different sub-populations / co-medications / interventions / comparators •need to address additional questions in phase III	•internal validity: no indication for bias •external validity: suitable for extrapolation •clinical relevance: clinically valuable treatment effect •degree of significance: 5% not sufficient •data quality •Internal consistency: similar effects in pre-specified subgroups, w. r. to all important endpoints •no centre dominates results •plausibility of hypotheses tested

Under which conditions is replication not required?

FDA: Situations to distinguish

1	complete extrapolation	(a) paediatric use (b) bioequivalence (c) modified release forms (d) different doses, regimens or dosage forms
2	single adequate study + information from other related studies	(a) different doses with no well understood relation between blood concentration and response (b) studies in other phases of disease available (c) studies in other populations (d) studies in combination and as mono-therapy
3	one single multi-centre study	Prerequisites: (a) clinically meaningful effect on mortality, irrev. morbidity or prev. of disease with serious outcome (b) large multi-centre trial, no centre dominating, consistency across centres (c) consistency across pre-specified subsets of the patient population (d) multiple studies in one study (ISIS IV: factorial design) (e) multiple pre-specified endpoints covering different aspects of disease (f) balance of important prognostic factors (g) statistically very persuasive findings (h) related investigations come up with similar results

Discussion:

Where to set the hurdle?

situation with two pivotal trials	***Only OPT***
$P < 0.025 \times 0.025 = 0.000625$	$P < 0.01$?
Replication of findings (?)	Similar effects demonstrated in different pre-specified sub-populations
Significant effect w. r. to a primary end-point	All important endpoints showing similar findings

"In some instances the two trials use exactly the same protocol but are assigned different numbers; in this case it is somewhat artificial to distinguish between one large, multi-center study and the two identical trials that result from dividing the enrollees into two studies depending on which clinic enrolls the participants.

(L. Fisher, DIJ (33), p. 265-271)

Discussion:

Even P < 0.000625 in an application with one pivotal trial is not sufficient:

"Success is being demanded in two different tests ... so that to be a graduate in economics and statistics, for example, you have to have proved yourself as an economist and a statistician".

(Senn: Statistical Issues in Drug Development)

Precise replication of a trial is only one of a number of possible means of obtaining independent substantiation of a clinical finding and, at times, can be less than optimal as it could leave the conclusions vulnerable to any systematic biases inherent to the particular study design

(FDA, Providing evidence…)

References:

Food and Drug Administration U.S.Department of Health and Human Services. Guidance for industry: *Providing clinical evidence of effectiveness for human drug and biological products*. 1998.

http://www.fda.gov/cder/guidance/index.htm

CPMP/EWP/2330/99: Points to Consider on Validity and Interpretation of Meta- Analyses, and one Pivotal study (2001).

http://www.eudra.org/humandocs/humans/ewp.htm

J. Högel and W. Gaus. The procedure of new drug application and the philosophy of critical rationalism or the limits of quality assurance with good clinical practice. *Contr.Clin.Trial.* 20:511-518, 1999.