ERC Starting Grant 2014
Research proposal [Part B1]

Philosophy of Pharmacology: Safety, Statistical standards and Evidence Amalgamation

PhilPharm

Cover Page:
- Name of the Principal Invesitgator (PI): **Barbara Osimani**
- Name of the PI's Institution for the project: **Ludwig-Maximilians-Universität, München (MCMP)**
- Proposal full title: **Philosophy of Pharmacology: Safety, Statistical standards and Evidence Amalgamation**
- Proposal short name: **PhilPharm**
- Proposal duration in months: **60**

Proposal summary
The PhilPharm project intends to address the issue of safety assessment in pharmacology with a view on philosophical work on causality and causal inference from statistical data (Hartmann & Sprenger, 2011; Pearl 2000; Spirtes, Glymour, Scheines 2000, Woodward 2003, Cartwright, 2007b). This interest is motivated by the fact that current evidence standards emphasize internal validity of studies and hence randomization, disregarding alternative routes to causal assessment, such as the joint support of different sorts of evidence to a given hypothesis. This may be particularly detrimental to safety assessment in that, much of the evidence for harms comes from anecdotal reports, case series, or survey data, which standard guidelines of evidence evaluation regard as being of poorer quality with respect to controlled (randomized) experiments. Although the role of this "lower level" evidence is increasingly acknowledged to be a valid source of information that contributes to assessing the risk profile of medications (Howick et al. 2009, Hauben and Aronson, 2007, Benson and Hartz, 2000; Golder et al. 2011), current practices have difficulty in assigning a precise epistemic status to this kind of evidence and integrating it with more standard methods of hypothesis testing. The philosophical debate has already addressed similar questions in relation to the assessment of treatment efficacy (Worrall 2010, Papineau, 1993; Cartwright, 2007a). However, none of these contributions expressly addresses the specific issues arising in causal assessment for harms. Epidemiologists such as Vandenbrouke (2008) as well as Ioannidis and colleagues (Papanikolaou et al. 2006) have recognized the distinctive virtues and drawbacks of randomization in efficacy vs. safety assessment, but their analyses fall short of providing a solid explanation for this asymmetry. Rudén & Hansson (2008) point out that the focus of research in risk detection is on false negatives, rather than on false positives; hence scholarly work developed to refine methods for assessing efficacy/effectiveness may miss relevant issues when dealing with causal claims concerning adverse drug reactions (ADRs). I also contributed to this topic (Osimani 2013 a,b) by emphasizing that evidence about adverse events accumulates over time and there comes a point where the signal strongly suggests causation without demonstrating it, hence an epistemology grounded on hypothesis rejection, such as the one underpinning standards of efficacy assessment is of no help in this situation. The project intends to change the evidence standards for safety assessment by providing a unified framework for the amalgamation of diverse evidence aimed at justifying causal claims in safety assessment. In particular, the project intends to:
1. Present a foundational analysis on statistical/causal inference with a focus on the critical assessment of current practices in drug approval and pharmacosurveillance;
2. Build a unified epistemic framework within which different kinds of evidence for pharmaceutical harm can be combined and used for decision: evidence amalgamation;

Provide the theoretical framework for the development of new standards of drug evaluation.
These issues will be addressed by drawing on current philosophical accounts of causality and causal inference on one side and current methodological proposals for causal modelling in the sciences on the other.

Section a. Extended Synopsys of the project proposal (max 5 pages)

State of the Art and objectives

Adverse drug reactions (ADRs) are responsible for a heavy economic and social burden (Lundkvist and Jönsson, 2004), constitute a concern for the industry in that the attrition rate is continuously increasing (Hay et al. 2014) and represent a key ethical issue in decisions concerning pharmaceutical products. Also in view of this, the European Parliament and the European Council have recently emanated Directive 2010/84/EU and Regulation (EU) No 1235/2010 in order to encourage the integration of information coming from different sources of safety signals (case reports, literature, data-mining, pharmacoepidemiological studies, post-marketing trials, non-clinical studies, late-breaking information, see also Herxheimer 2012) in drug monitoring. Yet, the methodological bases for implementing such a policy are shaky in that causal assessment of ADRs is still parasitic on the (statistical) methods developed to test drug efficacy (see also Senn, 2007).

Much of the evidence for harms comes from anecdotal reports, case series, or survey data. However, standard guidelines of evidence evaluation regard this sort of evidential source as being of poorer quality with respect to controlled (randomized) experiments. Although the role of this "lower level" evidence is increasingly acknowledged to be a valid source of information that contributes to assessing the risk profile of medications (Howick et al. 2009, Hauben and Aronson, 2007, Benson and Hartz, 2000; Golder et al. 2011), current practices have difficulty in assigning a precise epistemic status to this kind of evidence and integrating it with more standard methods of hypothesis testing. The philosophical debate has already addressed similar questions in relation to the assessment of treatment efficacy (Worrall 2010, Papineau, 1993; Cartwright, 2007a). However, none of these contributions expressly addresses the specific issues arising in causal assessment for harm. Epidemiologists such as Vandenbrouke as well as Ioannidis and colleagues have recognized the distinctive virtues and drawbacks of randomization in efficacy vs. safety assessment, but their analyses fall short of providing a solid explanation for this asymmetry. Rudén & Hansson (2008) point out that the focus of research in risk detection is on false negatives, rather than on false positives; hence scholarly work developed to refine methods for assessing efficacy/effectiveness may miss relevant issues when dealing with causal claims concerning ADRs. Furthermore, evidence about adverse events accumulates over time and there comes a point where the signal strongly suggests causation without demonstrating it. An epistemology grounded on hypothesis rejection, such as the one underpinning standards of efficacy assessment is of no help in this situation. The project intends to address these issues by providing a unified framework for the amalgamation of diverse evidence aimed at justifying causal claims in safety assessment. In particular, the project intends to:

1. Present a foundational analysis on statistical/causal inference with a focus on the critical assessment of current practices in drug approval and pharmacosurveillance;
2. Build a unified epistemic framework within which different kinds of evidence for pharmaceutical harm can be combined and used for decision: evidence amalgamation;
3. Provide the theoretical framework for the development of new standards of drug evaluation.

In order to realize these three objectives I intend to work with three research fellows: one post-doc expert in statistics/epidemiology, another one in pharmacology, and a PhD candidate in philosophy of science with a degree in computational biology or related fields. As a team, we will be supported by four focus groups of experts in related fields: a focus group on philosophy of science formed by MCMP researchers, particularly, Prof. Stephan Hartmann (expert in formal epistemology), director of the Center; Gregory Wheeler, expert in computational logic and probability theory; Alexander Reutlinger, Post-doc (expert in causality and explanation); Aidan Lyon, Post-doc (Philosophy of Probability, Philosophy of Mathematics); and Seamus Bradley (Post-doc) with research interests in uncertainty and decision theories; another focus group in statistics/epidemiology and public health, formed by Dr. Eva Grill from LMU, Public Health Department, and other experts in the field (Prof. Stephen Senn, Director of the Competences Center for Methodology and Statistics, Luxembourg, as well as other two participants coming from the public sector, such as National and Federal Authorities for Drug Approval); a third focus group in pharmacology/toxicology (with Prof. Ralph Edwards - Uppsala Monitoring Center among others); and a fourth focus group formed by experts of bioinformatics. The focus groups members will have regular contacts, and meet once a year in Munich at MCMP. A workshop and a final conference in addition to participation to conferences and publication by the Team members will provide extensive dissemination of the research results.

Project proposal and structure. The project is structured in three phases: one for each objective. The first one will be addressed in the first two years of the project, the second on year 3 and 4; the last year will be devoted to the third objective as well as to refine previous achievements, and finalize deliverables.

1. Year 1-2: Foundational analysis of statistical/causal inference. Evidence of pharmaceutical harm is gathered at different stages through different methods. However, the epistemic rationale underpinning the decision making practice is fundamentally shaped by the standards developed by hypothesis testing methodologies used for efficacy assessment. Hence, randomized studies are often recommended in order to definitively prove causation. However, the requirement of randomization needs to be evaluated by considering its epistemic, ethical, and economic costs and benefits in relation to alternative options. Philosophy of science might come to rescue here for three fundamental reasons 1) it helps clarify the *raison d'être* behind the requirement of randomization in causal inference from statistical data (Worrall, 2010, Papineau 2001, 1993); 2) it puts hypothesis testing into context by analysing its epistemological underpinnings and offering alternative epistemological paradigms (Gelman, 2009; Senn, 2007; Williamson, 2011/2013); 3) it offers a plurality of definitions of causality and alternative pathways to causal inference grounded on alternative epistemologies (Spirtes et al. 2000, Pearl 2000, Woodward 2003, Williamson, 2005, Cartwright 2007b). PhilPharm will focus on point 3 while taking into account the discussion developed in relation to points 1 and 2. Drugs may have paradoxical or bidirectional effects, i.e. effects which are opposite to the intended drug effect or produce both the desired effect and its opposite (Aronson and Hauben 2006); as well as effects which are indistinguishable from the disease symptoms and thus may be confused with them. More generally, the harmful effect of drugs is highly variable among individuals and is characterized by cumulative and interactive mechanisms. Hence, a reflection on causal mechanisms is an essential pre-requisite of (statistical) causal modeling. However, their role is strongly debated in relation to evidence standards. Philosophers closer to the Evidence Based Medicine approach doubt that mechanisms can bridge the gap of statistical black-box evidence because of the limited and fragmentary knowledge of the "causal web" in which they are embedded (Howick, 2011); other philosophers instead generally recognize that knowledge about mechanisms plays a plurality of roles. In particular, from a methodological point of view, mechanisms are important for supporting the reliability of model assumptions and for interpreting experiment results; also, they are held to have an epistemological/theoretical relevance, in that they can provide the hypothesis which puts together disparate data (through so called abduction; see also Craver, 2005). My focus on the relationship between mechanisms and statistical knowledge regards how the former might constrain the assumptions on which the latter is grounded. In particular, three distinctive dimensions of causal structures in pharmacology will be taken into account: 1) the drug intervenes on a state of malfunctioning (generally by reinstating an equilibrium state in the organ system, disrupted by the disease); 2) equilibrium and disequilibrium states are characterized by causal cycles (positive/negative feedback): 3) system-level reactions to the drug.
The Project will elaborate on these points by reviewing current methods of causal assessment and causal modelling in the sciences (potential outcome approach, structural equation modeling, (recursive) Bayesian nets, dynamic causal models, systems dynamics, agent based modeling) and appraise them on the basis of their ability to meet the challenges posed by unintended/unexpected effects of interventions with a particular focus on the pharmacological domain.
2. Year 3-4: Evidence amalgamation. The privilege accorded to RCTs as gold standard for justifying causal claims, thwarts any attempt to warrant causality through alternative routes, such as amalgamation of different kinds of evidence. Parallel to the foundational-methodological research, PhilPharm will therefore insist on the distinction between *grading evidence*, such as proposed by the Oxford CEBM levels of evidence, or Guyatt's and colleagues GRADE system, vs. *evidence amalgamation*, particularly with respect to the purpose of evaluating side effects of interventions. In particular, the project will attempt to provide instruments for *grading causal claims*, on the basis of the amount, scope and reciprocal support of evidence with respect to the target context, rather than grading evidence tout court. Current standards of evidence offer two fundamental methods: meta-analyses and qualitative systematic reviews. However, regarding the former, this method does not allow to amalgamate evidence at different levels; quite the contrary, in order for results to be at all meaningful, studies in the meta-analysis need to be as homogeneous as possible. Concerning Systematic Reviews, also here, the increasing emphasis on internal validity (Waddington et al. 2012) obscures the importance of other issues in evidence amalgamation, such as the combination of heterogenous evidence for the purpose of "connecting the dots" between different constituents of a phenomenon. With the PhilPharm project I intend to develop a method of evidence amalgamation for the justification of causal claims which combines statistical and non-statistical evidence of relevant mechanisms at different levels (in silico, in vitro, in vivo, clinical, epidemiological) and allows to probabilistically update causal hypotheses as evidence accumulates. This part of the project is mostly exposed to high-risk/high-gain outcomes. On one side, no explicit attempt in this sense has been made until now regarding safety assessment. However there is a tradition on Bayesian causal modelling on which to build on, where heterogenous evidence may be combined, and causal assessment may be made in probabilistic terms. Furthermore, from an empirical point of view, *in silico* studies of off-target binding by the drug constitute an additional basis for risk prediction and causal modelling of ADRs (Xie et al. 2009). In particular the PhilPharm

approach will try to adopt and develop Recursive Bayesian Nets with nested cycles (Clarke et al. forthcoming) in order to provide a representational and inferential tool for causal justification through evidence amalgamation in safety assessment. Gaining new insights with a strong focus on the development of evidence amalgamation methods, especially for the purpose of safety assessment in pharmacology would constitute a high payoff in many respects: epistemological, scientific and also practical (in terms of patient safety and health expenditures).

3. Year 5: New standards of evidence evaluation for safety assessment. Current evidence standards obscure the distinctive challenges posed by efficacy vs. safety assessment. CEBM levels of evidence (Howick et al. 2011) distinguish between therapy, prognosis, diagnosis, and economic analysis but fail to discriminate efficacy and harm assessment. Similarly, Guyatt et al. (2011) admit the specific difficulties inherent in the evaluation of evidence for harm, but propose a framework (the GRADE System) where evidence quality for safety assessment follows the same criteria proposed for efficacy evaluation. On the other side, guidelines on pharmacosurveillance and signal detection promote a flexible strategy to safety monitoring. Furthermore, most drug withdrawals are based on individual case studies or case series reporting dramatic/fatal effects (Olivier and Montastruc, 2006; Arnaiz et al. 2001); but for less dramatic outcomes, no clear guidance is available. By taking into account the points developed in the two previous objectives, the PhilPharm project intends to propose alternative methods of evidence evaluation based on a plurality of sources and epistemological warrants. This objective will be mainly achieved by critically reviewing current standards of evidence, especially the GRADE system, and by collecting and analysing past cases of drug withdrawals (Croniassal, Vioxx, Lipobay, Bextra) and cases where the development process has been interrupted before the drug has reached the market (see for instance the Torcetrapib case: Tall et al. 2007). A selection of cases will be chosen and simulation studies will be carried out by using the evidence amalgamation method developed in the previous phase of the project. Simulations will constitute the basis for developing an alternative method of evidence evaluation which takes into account all available evidence and integrate it on rational grounds.

Methodology

The research will be carried out jointly by the team members (full time each for 60 months): the PI will coordinate the other members' research. In turn, each researcher will coordinate the work of their focus groups and liaise with them on a regular basis. For ease of exposition, I will denote the researcher expert in statistics/epidemiology with the acronym "SR", the researcher expert in pharmacology with "PR", and the researcher expert in computational biology with "CR". Safety assessment will be denoted by "SA".

Work plan for objective 1: Analysis of statistical/causal inference with reference to pharmaceutical safety assessment (year 1-2). The first two years will be devoted to a complete review and critical analysis of: 1. Current statistical standards for safety assessment at all stages of product development, approval and postmarketing (source: authority guidelines, in particular European Medicines Agency): PI, SR and PR; 2. Relevant cases of drug withdrawals and early interruption of product development (subdivided by macro-categories: chemical entity, biological product, biotechnological product; and subcategories: drug classes): PI and PR; 3. Philosophical theories of causality with a special focus on SA: PI and SR. Purposes: 1) analysis of their limits and virtues with reference to the biological phenomena underlying ADRs; 2) benchmark with conception of causality underpinning current standard methodology (see point 1 and 2) 4. Current methods of computational biology developed for safety assessment (CR under PI supervision): classification of the different methods, kinds of evidence produced, and potentials for combining such evidence with laboratory/clinical/epidemiological data; 5. Causal modeling techniques in the health and social sciences with a focus on their possible virtues and drawbacks with reference to SA. A special attention will be given to Recursive Bayesian Nets and other kinds of influence diagrams (such as DAGs) on one side; and structural equation modeling on the other: PI, SR, PR, CR.

Work plan for objective 2: evidence amalgamation (year 3-4). First of all, the case studies selected in the first phase (Point 2) will be analyzed in depth, with the joint help of the statistics, pharmacology and philosophy focus groups (PI, SR, PR): the decision making process which determined drug withdrawal (or development interruption) and, particularly, the evidence supporting such decisions will be scrutinized in order to draw a list of implicit and explicit criteria of causal assessment concerning ADRs. A particular attention will be devoted to how heterogeneous evidence is combined for the purpose of causal assessment. This descriptive work will be then complemented by a normative counterpart. This will be carried out in two strands: one formal and the other substantial. The formal one will regard, on one side the evaluation of available (statistical) methods for the purpose of evidence amalgamation (PI and SR), on the other the examination of the epistemological rationales for their justification on philosophical grounds (through reference to relevant literature) (PI). The substantial one will regard the classification of safety evidence in terms of scope and patterns of possible combination with each other (PI, SR, PR, CR). In particular, it will be important to analyze information gaps and see how they can be bridged by alternative inferential routes. As a final step, a framework for causal justification through evidence

amalgamation should be developed and tested through simulation of the selected case studies (point 2) (PI, SR, PR, CR). In parallel, current analogous methods of evidence amalgamation, such as systematic reviews and meta-analyses will also be analytically examined as to their limitations/virtues for the purpose of SA. This will be also functional to the third project objective.

Work plan for objective 3: new standards of evidence evaluation for safety assessment. The fifth year will be devoted to the refinement of the achievements obtained in phase 1 and 2, to finalize the edited volume and the book, as well as to produce a series of guidelines for safety assessment in pharmacology. These will be developed by building on the previous work on one side and on the analysis of available guidelines on the other. The final conference should bring together the major experts both in the scientific as well as in the public sector and produce the expected paradigm change in safety assessment.

Detailed Project Schedule

Year	***Activities***	Events
1	*Research Team and Website set-up. Constitution of four focus groups and organization of first meeting. Start working on points 1-5 for objective 1.* *2 papers in high profile journals for each researcher*	Focus groups meeting: focus on comparative analysis of methods of evidence evaluation. PI and Team separately attend conferences in respective expertise. PI presents research at Evidence and Causality Conference
2	*Carry out points 1-5 for objective 1. Organization of second focus groups meetings* *2 papers in high profile journals for each researcher*	Focus groups meeting: focus on comparative analysis of methods for causal modeling. PI and Team separately attend conferences in respective expertise. PI presents research at Philosophy of Science Association
3	*Start working on project objective 2: evidence amalgamation: review of relevant philosophical and scientific literature: organizing third focus groups meeting also in view of edited volume. 2 papers in high profile journals for each researcher + one/two co-authored*	Focus groups meeting: focus on evidence amalgamation and on prospective publication of edited volume. PI and Team attend conferences both separately and jointly. PI presents research at European Philosophy of Science Association.
4	*Complete objective 2; Organization of workshop on evidence amalgamation and preparation of edited volume* *2 papers in high profile journals for each researcher + one/two co-authored*	Workshop on evidence amalgamation with focus groups members and external participants
5	*Complete objective 3: guidelines for new standards of evidence in safety assessment* *Book by PI.*	Final conference with invited speakers and institutional/private stakeholders (presentation of edited volume)

Significance and ground-breaking potentials

The PhilPharm project comes at a point where both the philosophical debate on scientific evidence and the methodological developments in epidemiology and medical evidence can meet and deliver a new interpretative framework for safety assessment. In fact, regarding risk assessment, both proponents of evidence hierarchies and epidemiologists are increasingly acknowledging the importance of what until now has been generally considered "lower level" evidence, but lack the theoretical instruments for justifying this change of persepctive. On the other hand, philosophy of science have long debate on experimental vs. observational evidence but have failed to distinguish between efficacy and safety assessment. The PhilPharm project bridges this gap with the intention to provide new standards for safety assessment. In turn, philosophy of science would greatly benefit by being confronted with the complex challenges related to (statistical) causal inference in pharmacology. The project aims also to have a practical (and economic) impact in terms of reduced health expenditures through increased risk prevention.

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