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Scientific Evidence and the Law: An Objective Bayesian Formalization of the Precautionary Principle in Pharmaceutical Regulation

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Abstract The paper considers the legal tools that have been developed in German pharmaceutical regulation as a result of the precautionary attitude inaugurated by the Contergan decision (1970). These tools are (i) the notion of "well-founded suspicion", which attenuates the requirements for safety intervention by relaxing the requirement of a proved causal connection between danger and source, and the introduction of (ii) the reversal of proof burden in liability norms. The paper focuses on the first and proposes seeing the precautionary principle as an instance of the requirement that one should maximise expected utility. In order to maximise expected utility certain probabilities are required and it is argued that objective Bayesianism offers the most plausible means to determine the optimal decision in cases where evidence supports diverging choices.

1. **Precautionary attitudes in response to uncertain knowledge**

Historically, the precautionary principle arose in response to the lessons learnt from environmental disasters and injuries to human and animal health caused by chemical compounds (x-ray radioactivity, benzene, asbestos, PCB, halocarbons, DES sulphur dioxide, etc.). These tragedies could have been avoided if signals of alarm had been taken more seriously. This hindsight, together with the increasing awareness of the unpredictability of environmental and health effects created by the chemical industry, stimulated the development of juridical instruments for the management of lack of knowledge—see, for instance, the work done by the European Environmental Agency (2001). These instruments are meant to be able to enlarge the powers of intervention for authorities against sources of possible harm, even in the absence of scientific proof of a causal link. *Causal link* is the central notion in this context because it is the basis both for action on the one hand, and for responsibility attribution on the other hand.

The first programmatic documents advocating administrative intervention before a causal connection be scientifically established were developed in relation to

North Sea pollution. The first Conference for the Protection of the North Seas (Bremen, 1st November, 1984) asserts that the States "must not wait for proof of harmful effects before taking actions"; the second Conference (London, 24-25 November, 1987) makes reference to the precautionary attitude and insists that "[...] a precautionary approach is necessary which requires to control input of such substances even before a causal link has been established by absolutely clear scientific evidence" (art. VII). The Earth Summit in Rio de Janeiro, 1992, ratified the precautionary principle and extended it to the global environment. The key feature of the precautionary principle thereby ratified was the reversal of the burden of proof between intervening authority and potentially polluting agent. It is not the authority that must demonstrate that some human activities cause serious harm to the environment in order to be allowed to adopt adequate preventive measure; on the contrary, in order to postpone these measures, it must be proved that these activities *do not* cause any serious harm to the environment (principle 15).

In general, the precautionary principle responds to the needs of a complex society where *uncertainty* is endemic. Dupuy (2004: 80) even uses the term "radical uncertainty" (see also Tallacchini, 2005 and 2008 on this point). Science is called on to accomplish two interconnected tasks. The *first* is the traditional endeavour to increase knowledge about reality and its physical, chemical, biological principles; the *second* one is the prediction of the effects that the applications derived from this knowledge produce on the environment, as well as human and animal health (see for instance toxicological sciences). This second task is enormously more complex than the first; in fact, by studying the mechanisms of a phenomenon, the scientist focuses on a particular aspect of reality and on the potential consequences that technological interventions can produce (jointly or individually) on the environment. Such effects are by and large unpredictable for two reasons. *First*, nature is an integrated system where any "external" action can produce domino effects at any level; *second*, it is practically unfeasible to exhaustively detect all dependencies, independencies and interference relationships working in nature. Therefore, the greater the progress in science, the exponentially greater the uncertainty generated by lack of knowledge about the potential effects of its technological applications. Not only sociologists (Beck, 1986), but also ethicists (Jonas, 1979), and philosophers of science (Hacking, 1986) have emphasised a new epistemological era where the *unknown* and *lack of information* should turn into topics of research on their own.

In the pharmaceutical context, the multiplicity and sophistication of medical technologies has reached such a level that the term "medicalization of society" has been coined in order to describe the pervasiveness of health care at all societal levels (Zola, 1972; Domenighetti, 2005). After a first phase of unlimited confidence in medical progress, a cautious attitude followed the numerous pharmaceutical scandals that have marked the history of pharmacology. For instance, the tranquillizer Contergan© (thalidomide), marketed in Germany between 1957 and 1961, caused severe birth defects to more than 6000

children—mainly produced by drug inducted phocomelia—and fatally injured 2500 people. This and other tragedies (see the Cronassial© case in Germany, but also worldwide marketed products such as Lipobay©, Vioxx©, and Bextra©) have contributed to enhance efforts towards the development of strict pharmaceutical safety regulation grounded in the criterion of the precautionary principle, which has led to an extension of care duties[1] for dangerous entities, to an enlargement of intervention powers for the authority in charge, and to an amplification of the responsibility spheres for all concerned parties.[2]

Notwithstanding these efforts directed at making cautious decisions to license drugs, cases of product retirement are more common than it may be thought, and proposals for improved monitoring systems are regularly advanced in the literature (see for instance Olivier and Montastruc 2006; Gassner and Reich-Malter 2006; Laupacis et al. 2003; Waller and Evans 2006; Talbot and Nilsson, 1998). As a matter of fact, it is not rare that pharmaceuticals are withdrawn from the market only too late, i.e. when extensive damage on the population of users has already been produced, which happened, for instance, with the above-mentioned products.

Various factors are at the origin of the discontent about how pharmaceutical decisions are taken both by responsible authorities and by the pharmaceutical industry (see for instance Reiss and Kitcher, 2008; Abraham and Davis, 2005; Abraham and Reed, 2001; Demortain, 2008): the complexity and inconsistency of data documenting drug efficacy and risks, the conflict of interest affecting the principal investigators of chemical entities and information deliverers (pharmaceutical sponsors), as well as time pressure in the approval procedure. Besides incentives and deterring instruments aimed at more transparent and safer pharmaceutical marketing (for instance through fiscal and financial regulation), formal instruments are needed in order to provide clear guidelines for the application of the legal norms developed in the area of safety protection and liability attribution.[3]

2. **The Contergan decision: origin of the precautionary attitude in pharmaceutical regulation**

Drugs have a Janus character as healing promise and poison at the same time. Debates about pharmaceutical products focus on one and the same principle: health as an individual and societal good, which drugs contribute both to promote and to endanger. Pharmaceutical regulation is the consequence of a growing awareness about the uncertainties surrounding the short, medium and long-term effects of chemical entities on the human organism.

In the Sixties and Seventies, the trial and decision about Contergan set the basis for thorough reflection on the specific epistemic status of pharmaceutical knowledge in relation to the health risks posed by pharmaceutical products. The Contergan trial has been one of the longest in the history of German

jurisprudence. The Contergan sentence was rather inconclusive with regard to imputing responsibilities and torts to the defendants: it ended up with a suspension of the trial by invoking § 153, abs 3 of the Strafprozessordnung – code of criminal procedure.[4] Yet, it settled the future standard of conduct for pharmaceutical firms and their employees, thereby deeply changing the framework of responsibilities concerning the management, disclosure and possible prevention of pharmaceutical risks (see below). More recently, the IInd amendment law for compensation and the 2002 amendment to the German Medicines Act have further developed these sorts of considerations — more on this later on.

The Contergan sentence (18 December 1970) contributed to the development of a precautionary attitude in pharmaceutical regulation by (i) increasing the responsibility scope for pharmaceutical sponsors through the introduction of strict liability for pharmaceutical products (until then, only tort liability required the assessment of negligence for responsibility attribution), and (ii) the principle of well-founded suspicion. The Contergan sentence establishes that, because positive proof of damage causality requires time, a large epidemiological basis, and can never be definitively assessed, a scientific proof of causality *cannot* be a valid criterion for determining the threshold of safety countermeasures:[5]

> Before a risk suspicion can be founded scientifically, enough time may pass as to produce damage in some consumer. During this vacillation time, the risk has to be undertaken by the pharmaceutical firm. Moreover, for the principle of inverse proportionality inherited from danger prevention regulation, even very low probable suspicions ask for timely countermeasures.

In fact, the principle of inverse proportionality says that the higher the value assigned to the endangered good, the lower the probability of damage for approving intervention in its defence. General criteria for determining the opportunity and entity of safety actions are therefore:

1. *Severity* of the suspected health damages: the more dangerous the drug is supposed to be, the earlier and prompter must the firm react to risk news concerning the product;
2. The nature of the damage: *irreversible* damage requires quicker reactions than transitory disturbances;
3. Side effects' *frequency*: the higher the observed frequency, the lower the suspicion needs to be in order to require safety countermeasures from the firm and/or the responsible authority;
4. *Therapeutic importance*: the higher the interests of patient in the availability of the drug, the higher the permissible risk in allowing the drug to stay on the market. Therapeutic importance is determined by the lack of alternatives and the severity of the illness.

General safety measures include the adoption of warning actions towards the health professional and the end-user, the introduction of stricter prescription requirement, up to product retirement from the market.[6]

3. **Legal instruments of safety protection in the German Medicines Act**

The German Medicines Act (AMG) was the first law in western countries to translate the precautionary principle into concrete and legally binding norms. It was enacted in 1976 and is the result of the political debate that followed the Contergan tragedy and of the implementation of the European directives 75/318/EEC and 75/319/EEC that also followed this pharmaceutical catastrophe.[7]

Since 1976, AMG has undergone 14 amendments (the first one being ratified in 2005, while a fifteenth amendment has been drafted in 2008-2009 and is still under approval). The explicit purpose of AMG is the safety of drugs administered to the public through the establishment of criteria for the efficacy, quality and safety ("Unbedenklichkeit") evaluation of candidate drugs.[8] The term "Unbedenklichkeit" refers to a safety judgment based on a risk/benefit assessment and is explicitly translated with the English term "safety" in the European regulation (Scheu, 2003). It warrants for safety through drug approval, surveillance and liability norms. Risk prevention is managed through two control systems: drug approval and post-marketing control. It is worth noting that drug approval status is, by default, prohibition, with reserve of permission ("Verbot mit Erlaubnisvorbehalt"). Liability norms also constitute an indirect incentive to safety beyond their principal compensatory aim.

The precautionary principle is embodied in the AMG through two articles that received much attention in the legal literature: article 5 (prohibition of unsafe medicines: "Verbot bedenklicher Arzneimittel") and article 84 (strict liability: "Gefährdungshaftung"). In the following, we shall focus on article 5.

Article 5 of AMG establishes safety criteria of drug circulation and withdrawal.[9] This norm stipulates prohibition of circulation for "unsafe drugs" and provides a definition thereof: unsafe drugs are those for which there is *well-founded suspicion* that, by adequate use, will have damaging effects exceeding a tolerable *threshold*, according to the knowledge of the medical science (§ 5 II) on the basis of available scientific data.[10]

This norm has three main components:

1. The degree of causal association between risk and danger source required for intervention need not be certain ("well-founded suspicion");
2. The level of causal association required for intervention is linked to the tolerance threshold, i.e. to the (un)balance between drug risk and benefit (and the related notion of "residual risk");

3. The tolerance threshold is established through reference to the state of the art of relevant medical knowledge.

In sections 3.1 and 3.2 we will analyse the first two criteria. For the sake of argument, we will take the third component as unproblematic in this context. In sections 4 and 5 we will outline the general features of Bayesian epistemology and propose an objective Bayesian formalisation of the principle of well-founded suspicion. It is worth noting that although the legal setting considered here is the German one, risk management strategies are indeed very similar across different geographic areas such as Europe, U.S. and Japan. Indeed, responsible authorities and pharmacovigilance agencies are engaged in a continuous effort towards the harmonization of procedures and policy and of related legal tools (see the International Harmonization Conference[11]). Therefore, our arguments, although based on the German setting, are not strictly limited to it and can indeed contribute to these harmonization efforts.

3.1 **The principle of well founded suspicion**

Because drug reactions are idiosyncratic and depend on several environmental, biological, and genetic factors, knowledge about the effects of any drug grows with the number of its users. This means that even many years after approval, any pharmaceutical is still an "experimental product", the information about which is neither exhaustive nor conclusive. As the Health Minister Dr. Focke declared in the ministerial statement for the provision of the German Medicines Act, drugs are products under constant testing ("Arzneimittel sind Produkte in Dauererprobung")[12]. The general recognition of the limited and fragmentary knowledge related to chemical and pharmaceutical technologies has contributed to the awareness that criteria for the management of *partial and uncertain* knowledge are needed.[13]

The concept of "well-founded suspicion" has been introduced into risk-management regulation, in order to decrease the threshold level for signal detection and alerting measures. This instrument represents an answer to the opacity associated with the pharmaceutical product: given that knowledge of possible unintended effects is limited and that the causal nexus can seldom be proven, waiting for the causal connection to be established before intervening would most times lead to late intervention and irreparable damage. The historical importance of the principle of well-founded suspicion is related to its fundamental role in moving pharmaceutical regulation from a "danger avoidance" system into a "risk prevention" (precautionary) system.

Both systems function according to the principle of inverse proportionality: the more severe the expected damage, the lower the probability of its occurrence need be in order to intervene. The difference between the danger avoidance and the risk system lies in the kind of causal link between danger source and damage required for action. Whilst in the danger avoidance system a causal connection

between danger source and damage needs to be established with certainty before the authority can intervene, in a risk prevention system it suffices to have a *suspected* causal connection between danger source and damage. Notice, moreover, that the principle of well-founded suspicion integrates the principle of inverse proportionality too: the higher the expected damage, the lower the *probability of causal connection* in order to require for intervention measures.[14] In fact "well-founded suspicion" is defined as "*hypothesis* of causal connection" (Scheu, 2003: 113) and, as such, it is quantified in probabilistic terms, i.e. the probability *P* that the drug (*D*) causes harm (*H*) can be less than 1 ($P(D \rightarrow H) < 1$), that is less than certain. In other words, the more severe the harm, the lower $P(D \rightarrow H)$ need be.

This means that the authority and industry are not justified in not intervening because a causal connection between damage and source has not been conclusively established, i.e. $P(D \rightarrow H) = 1$. Instead, they are supposed to act as soon as the probability of a causal connection is sufficiently high with respect to the potential harm in relation to the potential benefit.

A major problem with the principle of well founded suspicion, however, is that neither a practical nor a formal rule has been defined in order to provide standards of conduct and accountability criteria for pharmaceutical marketing and policy. Differently put, no formal guidance is given as to how and where to set the relevant *P*-threshold.

Indicators of suspicion are rather vague and prone to a biased interpretation, as the facts supporting the suspicion need not necessarily be concrete cases of damage. Also, the acquisition of new substantial theoretical knowledge can be a ground for risk suspicion, especially when there is little or no experience with the drug that could refute the theory (Di Fabio, 1993: 126-127). New theoretical insights might contribute to deeper pharmacological understanding and favour or contradict established knowledge about the effects of a specific substance (Di Fabio, 1993: 126-127; Räpple, 1991: 90-91); also, suspicion about potential damage begins as soon as a doctor assesses an association between a side effect and a drug (Di Fabio 1993: 125).

Indeed, the above-mentioned cases of unjustifiably late product withdrawals testify that more detailed yardsticks should be provided to the responsible authority and industry so as to decrease arbitrariness in decision making and establish stronger accountability constraints.[15]

Furthermore, it is advocated that in such a complex field as pharmacology, decisions be taken on the basis of *all* available evidence. A useful statistical paradigm for the integration of data coming from heterogeneous sources is constituted by the objective Bayesian methodology, to be discussed later in the paper (Williamson 2010b). This paradigm can also be used for integrating

knowledge of different experts, i.e. as a knowledge-integration platform (see Hughes et al., 2007, Cowell, 2007).

3.2 **Risk-benefit assessment**

Given the ambiguous character of pharmaceuticals and the consequent impossibility of absolute safety, the evaluation of drugs cannot result in a distinction between riskless and harmful products, but rather between an acceptable ("zumutbar") and an unacceptable ("unzumutbar") risk.[16] A risk *tolerance threshold* is established such that, below the threshold, the drug is considered "safe".

This threshold is relative to the benefit expected from the drug through a risk-benefit evaluation: this decides how much risk is to be accepted in the face of how much benefit. The risk-benefit assessment is made on the basis of *known* risks and benefits, therefore the proportion of ignorance surrounding the drug (epistemic uncertainty) is only indirectly relevant here. The risk-benefit evaluation is affected by "ecological" uncertainty[17] in the sense that pros and cons should be weighed against each other, and sometimes they are both equally strong. The main implication of this procedure is that, if the drug is approved, then the related risk is considered part of the bargain: this is called "acceptable", "tolerable", "unavoidable" or "residual".

The necessary condition for market approval is a positive result of risk-benefit assessment in "absolute" terms—that is when no other drugs in the market compete with the candidate drug—as well as "relative to" the pharmaceutical environment—that is in relation to the treatments already present in the market for the same indication.[18]

This evaluation is based on a comparative weighting of therapeutic importance and efficacy on one side, and of risk severity and frequency on the other. The definition of risk traditionally adopted by safety regulations has been inherited from natural sciences and engineering and consists in the product of the two dimensions of damage—*severity* and *probability*—where the damage is any injury caused to goods protected by the law (Räpple, 1991: 49).

In decision-theoretic terms, drug approval can be formalized as follows:

$$EU(D) > EU(\neg D).$$

The expected utility (*EU*) of drug approval (*D*) should be higher than that of drug refusal (¬*D*), where both utilities are computed out of the formulae below.

$$EU(D) = \sum_{i} [P_D(i) \cdot U_D(i)]$$

The expected utility of drug approval is the sum of the utility times probability products for all relevant attributes $\{i_1, \ldots i_n\}$ associated with the drug (benefits,

ADRs). Attribute utilities have a positive sign for the drug benefits and a negative sign for the adverse drug reactions.

$$EU(\neg D) = \sum_{j} [P_{\neg D}(j) \cdot U_{\neg D}(j)]$$

The expected utility of drug rejection is the sum of the utility times probability products for all relevant attributes $\{j_1 \ldots j_n\}$ associated with this option: the negative consequences of not treating the illness with the drug on one side, and the avoidance of drug side effects on the other.

For any drug to be approved, the expected utility associated with it must be superior to that of not approving it. The ecological uncertainty affecting the risk-benefit assessment increases to the extent that the difference among the inequality factors approaches zero; i.e., when EU(D) ≈ EU(¬D). This might be due to compensatory attributes present in both the risk and the benefit side.

Whenever a new risk possibly associated to the drug is detected (development risk), a risk-benefit assessment needs to be made in order to determine whether this risk asks for intervention (for instance access restriction, approval suspension or product withdrawal) or not. If the risk-benefit balance remains favourable for the product, then the detected risk can be considered irrelevant. Instead, if the newly detected risk changes the risk-benefit balance so as to make it unfavourable, then appropriate measures need to be considered. Provided that, especially in the phase of signal generation, the causal connection between drug and ADR is uncertain, risk prevention/minimization measures should be determined by taking into account both the importance of the unbalance and by the evidence of causality.

AMG § 5 prescribes that safety measures should be undertaken whenever there is well-founded suspicion that by adequate use, the drug will produce damaging effects exceeding a *tolerable threshold*: the greater the unbalance, the lower the probability of association between expected damage and candidate cause. However, this threshold cannot be just the unfavourable balance in the risk-benefit, as this way the probability of the hypothesis of causal link between danger source and damage—which is the cornerstone of the principle of well-founded suspicion—does not enter the decision to intervene or not.

In the following two sections we propose that the precautionary criterion for safety intervention and pharmaceutical policy stated in § 5 of AMG be translated in the terms of the maximum entropy principle within an objective Bayesian approach. To state it informally, the principle of well-founded suspicion prescribes that the decision-maker believes in the existence of a causal link between drug and damage proportionally to the positive unbalance of the risk-benefit assessment. In other words, the higher the unbalance of therapeutic benefit against suspected damage, the stronger the belief that there is a causal link between drug and damage. Thus, it is not the result of the risk-benefit

analysis *alone* that triggers action, but the *belief* in a (suspected) causal link between drug and damage, which is based on a risk-benefit analysis.

4. **Bayesian epistemology to rescue?**

In this section we suggest that Bayesian epistemology offers promising conceptual and formal tools for the principle of well-founded suspicion. As will become clearer in the discussion, the advantage of Bayesian epistemology, and in particular objective Bayesian epistemology, is twofold. First, objective Bayesianism allows us to deal with probabilistic inferences, particularly with those that are supposed to trigger action, such as pharmaceutical decisions. Second, objective Bayesianism reflects the precautionary stance that has to accompany causal attribution (for instance about the danger of a drug) and the decisions to be taken as a consequence of such attribution.

4.1 **A crash course in Bayesian epistemology**

Bayesianism is an epistemological position concerning scientific reasoning, but also reasoning more broadly construed.[19] The core of Bayesianism has been formulated in the framework of the formal theory of probability. Thus, the two main assumptions behind Bayesianism are that (i) aspects of scientific reasoning, for instance, confirmation of a hypothesis or of a theory, can be quantified and constrained by the formal principles of probability theory; (ii) Bayesianism provides an account of how we should learn from experience. The formal apparatus of probability theory[20] serves to impose coherence constraints on rational degrees of belief and, typically, uses conditionalisation as a fundamental probabilistic inference rule for updating probability values according to Bayes' theorem.[21] Bayesianism is also taken to be a methodology that allows inductive reasoning from data, that is, probabilities of hypotheses in the light of data. Of course, not all reasoning in science is formalised in terms of probability theory nor is all reasoning inductive in character. The extent to which the core assumptions of Bayesianism really grasp the essential features of scientific reasoning goes beyond the scope of the present paper. What will be key for the following discussion is that Bayesianism explicitly deals with uncertain reasoning (which is exactly what happens in pharmaceutical contexts) and that, since it deals with how to learn from experience, a particular version of it (objective Bayesianism) will be useful when it comes to make decisions (such as in drug regulation).

Bayesianism, as an epistemological position about scientific reasoning, is accompanied by an interpretation of probability in terms of rational degrees of belief. Here, probabilities are quantitative expressions of the strengths of an agent's beliefs. Such an interpretation was famously championed by de Finetti (1937) and Ramsey (1926), who analysed probabilities in terms of betting behaviour: probabilities are identified in terms of the betting odds that a rational agent is willing to accept. Without going into unnecessary technicalities, it can be

formally argued (by means of the so-called 'Dutch book theorems'[22]) that conforming to the probability calculus is a necessary condition for rationality.

According to *strictly subjective* Bayesian epistemology, it is sufficient that an agent's degrees of belief satisfy the axioms of probability. Other than that, the agent is free to adopt whichever degrees of belief she wished. The typical objection is that this account leads to arbitrariness: two agents may assign different probability values to the same event (given the same background information) and be equally rational, provided that they do not violate the axioms of probability. A solution to the objection of arbitrariness is attempted by empirically-based and objective Bayesian epistemology.

In a nutshell, these two positions impose further constraints on an agent's degrees of belief before they can be deemed rational. Early proponents were Salmon (1967) and Jaynes (1957). There are two types of constraints: empirical and logical. Those constraints amount to taking into account any information and lack of information, when shaping degrees of belief.

Salmon emphasises the role of empirical constraints and requires knowledge of relative frequencies to assign prior probability values. This characterises *empirically-based* subjective Bayesian epistemology. The frequency interpretation is yet another interpretation of probability, traditionally classed as an empirical or physical interpretation of probability. Physical probabilities, unlike Bayesian probabilities, take probabilities to be quantitative expressions of some features of the world, not of our knowledge or belief about them. A simple form of the frequency interpretation states that the probability of an attribute *A* in a finite reference class *B* is the relative frequency of the actual occurrence of *A* within *B*. Further developments of the frequency interpretation are due to von Mises (1928) and Reichenbach (1935), who considered infinite reference classes and identified probabilities with the limiting relative frequency of events or attributes therein.

Jaynes (1957) goes beyond this empirically-based approach and puts forward a maximum entropy principle, which might be thought of as an extension of the principle of indifference.[23] This is known as *objective* Bayesian epistemology. Thus, whilst empirically-based Bayesian epistemology contents itself with the adoption of empirical constraints, i.e. knowledge of observed frequencies is sufficient to shape degrees of belief, the objective Bayesian approach requires that *both* empirical and logical constraints be satisfied. Also, although both the empirically-based and objective Bayesian interpretations shape degrees of belief using knowledge of observed frequencies, the two interpretations significantly differ in that the objective Bayesian approach requires choosing the middling or most equivocal probability value in case of lack of evidence (e.g., concerning observed frequencies; see Williamson 2006). We shall explain objective Bayesianism in more detail in the next section.

It is worth noting that Bayesian interpretations, whether subjective, empirically-based or objective, interpret single-case rather than generic probabilities. (On the other hand the frequency interpretation of probability only makes sense of probabilities of generic or repeatably-instantiatable outcomes.) In fact, degrees of belief are associated with bets and a bet in a generic outcome does not make sense. This turns out to be a useful feature of Bayesianism in general, because decisions in pharmaceutical contexts are single-case and therefore a Bayesian interpretation of probability ipso facto proves to be better suited than other approaches (notably, frequentism).

4.2 **Objective Bayesianism**

Objective Bayesianism has been subject to several criticisms since its inception by Edwin Jaynes (1957). The approach has been criticised for a variety of reasons, ranging from the foundational and motivational—e.g., it is hard to articulate how evidence constrains degrees of beliefs—to more technical ones—e.g., a worry that using the maximum entropy principle engenders serious computational problems. Recently, the approach has been defended and developed by Williamson (2005, 2006 and 2010). The peculiar features of objective Bayesianism, in Williamson's approach, are the following. *First*, it doesn't require a separate updating rule, as probabilities can be determined afresh on each change of evidence (though updates are often consistent with the results of conditionalisation). *Second*, probabilities are not fully determined by evidence—language and context also play important role in shaping degrees of belief, and even when these are taken into account there may remain some room for subjective choice. Objective Bayesianism is characterised by three norms: the Probability Norm, the Calibration Norm, and the Equivocation Norm. Of the three, the Equivocation Norm is key to the suitability of the objective Bayesian framework formalising the principle of well-founded suspicion.

Simply put, the Probability Norm says that an agent's degrees of belief should be representable by a probability function defined over the sentences of her language. The Calibration Norm states that those degrees of belief should fit with her evidence – in particular, should match empirical probabilities where known. Finally, the Equivocation Norm says that in case more than one probability function is compatible with evidence, the agent should choose one that is not too extreme – i.e., should choose one that equivocates sufficiently between the basic possibilities expressible in her language.

The first norm would be unproblematically endorsed by all Bayesians; the second norm would certainly be endorsed by empirically-based Bayesians, since they require degrees of beliefs to be shaped upon available evidence. The third norm is what sets objective Bayesianism apart from other flavours of Bayesianism. It requires that the agent's probability function be sufficiently close to the *equivocator*, which is the probability function that gives the same probability to each of the basic possibilities that the agent can express. Suppose the agent can

express elementary propositions $A_1,...,A_n$. Then the basic possibilities ('possible worlds') that she can express take the form $\pm A_1 \wedge \cdots \wedge \pm A_n$, where each instance of $\pm A_i$ is either just A_i or its negation, $\neg A_i$. Distance between probability functions is measured by Kullback-Leibler divergence,

$$d(P,Q) = \sum_{\pm A_1 \wedge \cdots \wedge \pm A_n} P(\pm A_1 \wedge \cdots \wedge \pm A_n) \log \frac{P(\pm A_1 \wedge \cdots \wedge \pm A_n)}{Q(\pm A_1 \wedge \cdots \wedge \pm A_n)}.$$

Probability functions that are sufficiently close to the equivocator are those that have sufficiently high entropy:

$$H(P) = - \sum_{\pm A_1 \wedge \cdots \wedge \pm A_n} P(\pm A_1 \wedge \cdots \wedge \pm A_n) \log P(\pm A_1 \wedge \cdots \wedge \pm A_n).$$

As to what counts as *sufficiently* high entropy is a pragmatic question, guided by considerations to do with the required accuracy of predictions and so on. In the extreme case we have Jaynes' *Maximum Entropy Principle*, which says that the agent's degrees of belief should be representable by a probability function, from all those that are calibrated with evidence, that has maximum entropy. Since this is the standard formulation of objective Bayesianism, we shall presume this formulation in what follows.

5. **An objective Bayesian formalisation of the principle of well founded suspicion**

As we mentioned earlier, the principle of well-founded suspicion in pharmaceutical regulation can be considered as an instantiation of the precautionary principle. The precautionary principle can be stated in very simple terms as follows: the decision to withdraw a drug should not wait until strong causal links between drug and harm are established with certainty, but action may follow already from the *well-founded suspicion* of causal link between the two. Before the sentence of the Contergan case (section 2), the German legal system required a *proven* causality nexus between danger source and possible damage in order to allow for administrative or punitive actions. As mentioned earlier, with the Contergan sentence, the legal system shifted from a danger avoidance system (Gefahrabwehr), where causal connection needs to be certain, to a risk prevention system (Risikovorsorge), where a *hypothesis* of causal connection suffices for intervention. According to the precautionary principle, then, withdrawal should be considered as soon as harm is suspected. Stated in these terms, the precautionary principle introduced into legal and administrative theory the concept of *probabilistic* causal links.

Since according to the precautionary principle, the causal connection between danger source and effect need not be certain and scientifically proven, administrative actions, such as suspension or prohibition of the drug under

consideration, can be enforced *before* scientific proof is eventually provided. The threshold point for action is established by reference to the risk/benefit assessment on the one hand and to the probability of causal connection on the other: the higher the risk in comparison to the benefit, the lower the probability of causal connection between potential damage and suspected source can be in order to allow for risk prevention/minimization strategies.

Now, there are several reasons why objective Bayesianism is a good candidate for formalising the principle. *First*, (health) technologies are always surrounded by a considerable amount of uncertainty in relation to their medium-long term effects. By providing a machinery of probabilistic inference, objective Bayesianism can put these considerations into practice. *Second*, the precautionary principle is very generally formulated, and even its pharmaceutical concretization, "the principle of well-founded suspicion" does not provide any concrete reference point that can help to establish the tolerance threshold in a standard fashion. Withdrawal decisions are made on the basis of a consensus procedure grounded on empirical data, expert opinions and contextual factors (availability of alternative treatments, pressure of interest groups, influence of patient groups and public opinion): this may lead to biased procedures thwarting any precautionary effort. *Third*, objective Bayesianism formally takes into account not only all available evidence, but also lack of evidence, precisely in the spirit of the precautionary principle. This has to do with the Equivocation Norm. In the following we present how this works concretely.

5.1 **Precautionary principle, expected utility, and risk-benefit assessment**

Decisions concerning the approval, marketing, suspension, and withdrawal of pharmaceutical products are generally justified on the basis of a favourable (or unfavourable) risk-benefit balance. The expected benefits of a drug are weighed against its potential drawbacks and this comparison determines the decision outcome. In this respect, these decisions follow the general rule that an agent should act so as to maximise her expected utility. The example we propose below is by no means intended as the description of a particular case, but aims to provide a formalization which clearly distinguishes the different roles played by the risk-benefit evaluation (utilities) and by the causal assessment (probabilities associated with the various utilities) in risk management decisions, and thereby illustrates where the precautionary principle really intervenes along this process.

Suppose a drug has been licensed for market. Consider variable D which takes value d if the drug is taken as prescribed and value $\neg d$ otherwise. R signifies recovery (with values r and $\neg r$) and H signifies harm (taking value h if there is harm sufficient enough to warrant withdrawing a drug that caused that harm, and taking value $\neg h$ otherwise). W signifies withdrawal of the drug from market (with values w and $\neg w$).

Now since the drug has been licensed for market, there must be good evidence that

(i) the drug positively causes recovery, written, $D \rightarrow^{+} R$ and

(ii) the drug does not positively cause excessive harm, $\neg(D \rightarrow^{+} H)$.

(Here 'positively causes' is taken as the opposite of 'prevents', so that *D causes R* if and only if *D positively causes R* or *D prevents R* or is a *mixed cause* of *R*. A mixed cause sometimes positively causes and sometimes prevents.) Let us suppose that the evidence is such that the probability that *the drug positively causes recovery* reaches some threshold, $P(D \rightarrow^{+} R) \geq 1 - \delta$, and that the probability that the drug does not positively cause harm reaches another threshold, $P\big(\neg(D \rightarrow^{+} H)\big) \geq 1 - \varepsilon$, where δ and ε are small.

Consider a utility matrix for withdrawing the drug, given the case in which the drug positively causes harm and the case in which the drug does not positively cause harm:[24]

	$(D \rightarrow^{+} H)$	$\neg(D \rightarrow^{+} H)$
w	5	-10
¬w	-50	5

If $P(D \rightarrow^{+} H) = x$ then the expected utility of withdrawing the drug is

$EU(w) = 5x - 10(1 - x)$

$= 15x - 10$

While the expected utility of not withdrawing is

$EU(\neg w) = -50x + 5(1 - x)$

$= 5 - 45x$

According to the principle of maximising expected utility, one should withdraw the drug if $EU(w) > EU(\neg w)$, i.e., if

$15x - 10 > 5 - 45x$

i.e., if

$60x > 15$

i.e., if

$x > \frac{1}{4}$

This is indeed a precautionary approach: if the probability that the drug positively causes harm is more than ¼, the drug should be withdrawn. Only a little evidence of positive causality is required for withdrawal; the causal claim need neither be established beyond reasonable doubt nor even on balance of probabilities. Note however that, so far, nothing has had to be said about what the probabilities mean. The precautionary principle itself is thus independent of the interpretation of probability. As we shall now see though, the implementation of the precautionary principle does depend on the interpretation of probability.

5.2 **Objective Bayesianism and the precautionary principle**

In order to determine the conditions under which $P(D \rightarrow^{+} H) > 1/4$, an interpretation of probability and an interpretation of causality must be provided. And different interpretations will warrant different decisions. Since we are primarily interested in comparing interpretations of *probability*, let us take a simple probabilistic account of causality as our reference point: here $D \rightarrow^{+} H$ if and only if $P(h|d \wedge c) > P(h|\neg d \wedge c)$ for some state *c* of the other possible causes of *H*, and $P(h|d \wedge c') \geq P(h|\neg d \wedge c')$ for every other such state *c'*. (Accordingly a *preventative* lowers the probability of harm for some state *c* and raises it for none, while a *mixed cause* raises it in some contexts *c* and lowers it in others.)[25] Let us turn, then, to interpretations of probability.[26]

So far, we know that $P(\neg(D \rightarrow^{+} H) \geq 1 - \varepsilon$, i.e., $P(D \rightarrow^{+} H) \leq \varepsilon$. Consider first the case in which $\varepsilon > 1/4$.

A physical interpretation of probability, such as the frequency theory, would deem the physical probability that the drug raises the physical probability of harm to be some undetermined point within the interval $[0, \varepsilon]$. Since some points within the interval would trigger withdrawal and others would not, no decision can be made as to whether to withdraw the drug.

Consider next an empirically-based Bayesian interpretation of probability. Here an agent's rational degree of belief that the drug raises her rational degree of belief in harm is also some fixed point within the interval $[0, \varepsilon]$, but in this case the point in question is not out of reach of the agent—rather, the agent must simply choose some point within the interval. As long as the agent remains within the interval, all points are deemed equally rational. In this case a decision will be made as to whether to withdraw the drug, but the decision is entirely up to the subjective whim of the agent—it is not objectively determined as to which course should be taken.

Finally, consider an objective Bayesian interpretation. According to this interpretation, an agent should believe that the drug positively causes harm to the degree within the interval $[0, \varepsilon]$ that is as equivocal as possible. Here, 'as equivocal as possible' means *as close as possible to the value given by the maximally equivocal probability function (the equivocator)*. As explained above, the equivocator gives each basic possibility that the agent can express the same probability. As the basic possibilities take the form $P(h|\pm d \wedge c) = x$, it equivocates as to whether $P(h|d \wedge c) = \mathrm{x}$ is greater or less than $P(h|\neg d \wedge c) = y$ for any state *c* of the other possible causes of *H* – i.e., the equivocator gives probability ½ that $x \geq y$. If the agent supposes that there are *k* other causes of *H*, all binary variables, and therefore 2^k states of such causes, the maximally equivocal function yields the probability that the drug positively causes harm to be $(1/2)^{2^k}$. (That the drug is a preventative has probability $(1/2)^{2^k}$ and that it is a mixed

cause has probability $1-(\frac{1}{2})^{2^k-1}$.) Now there is a unique point in the interval $[o,\varepsilon]$ that is closest to $(1/2)^{2^k}$. The decision for withdrawal should be taken according to whether this point is greater than or less than ¼. The objective Bayesian interpretation has the advantage, then, that a decision will be taken, and that decision is objectively determined by her evidence.

Next consider the case in which $\varepsilon \leq 1/4$. In this case all the interpretations considered above will license the decision not to withdraw the drug, since no probability in the interval $[0,\varepsilon]$ exceeds the level ¼ that triggers withdrawal. What sets the interpretations apart here is the case in which new evidence becomes available. Suppose that new evidence *e* increases the interval for $P(D \rightarrow^{+} H)$ from $[0,\varepsilon]$ to $[0,\varepsilon']$, where $\varepsilon \leq 1/4 \leq \varepsilon'$. As before, a physical interpretation will not license any decision. The empirically-based Bayesian interpretation will again license some decision, and this decision is objectively determined by the evidence and the agent's prior degrees of belief: if, when conditionalising on *e*, the agent's degree of belief in positive causation increases above ¼ then the decision to withdraw the drug will be warranted, otherwise the drug should be retained. Note, however, that the prior probabilities—including the probabilities conditional on the evidence—are entirely subjective, so the decision as to whether to withdraw remains entirely subjective. Finally the objective Bayesian will again withdraw according to whether $(1/2)^{2^k}$ is greater than or less than ¼. In sum, then, the objective Bayesian interpretation has the same advantage in this case too: a decision will be taken, and that decision is objectively determined by the agent's evidence.

In conclusion, the precautionary principle arguably follows from the principle that one should act as to maximise expected utility. But the implementation of this principle depends on how probabilities and causal relationships are interpreted. Under a standard probabilistic account of causality, a physical interpretation of probability suffers in that there are situations in which no decision can be taken. This is a problem because in a court of law a decision *must* be taken on the basis of available evidence. On the other hand, a subjective Bayesian interpretation of probability always licences a decision, but in certain circumstances the decision taken is entirely a matter of subjective choice. Thus this interpretation can also fail to provide normative guidance. But an objective Bayesian interpretation licenses a decision that depends on the evidence. Only on an objective Bayesian account, then, can the precautionary principle be implemented in an objective way.

While we have presented this argument in the context of a specific utility table, it should be clear that the procedure is fully general. All that is required is that utilities can be set out in order to determine a threshold for withdrawal.

6. **Concluding remarks**

Drug decisions are especially difficult to make because of the high goods at stake, because of the uncertainty surrounding both the pharmaceutical products as well as the health damage eventually produced by the disease, and because of the related difficulty to establish a risk tolerance threshold. Whenever new risks *possibly* associated with a drug are detected, then the question is raised as to whether these can be considered to be part of the bargain, and if not, whether they are indeed conditioned by drug intake. According to the principle of well-founded suspicion, the causal nexus between drug and harm need not be certain in order for safety measures (such as new labeling or product retirement) to be enforced. Indeed, following the precautionary principle, the probability of a causal connection can be as low as the possibly associated harm is supposed or known to be severe. Thus the probability of the causal link constitutes the critical measure for intervention, together with the harm suspected to be associated with the drug. Provided that the former falls within a given interval, objective Bayesianism provides the formal tools for determining, within this interval, the probability value that is maximally equivocal, thereby grounding the decision both on the available evidence *and* on the lack of information, as required by a precautionary attitude.

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[1] For instance, information duties towards the public as well as towards the administrative authorities, quality controls both at the level of product design and manufacture, or privilege restrictions in the trial procedure for tort, strict or criminal liability. Restrictive norms have sometimes been accompanied by deontology codes of self-regulation from the side of the industry (Scheu, 2003: 59-60). See for instance in Germany the BPI-Code of conduct (Bundesverband der Pharmazeutischen Industrie: Federal Association of Pharmaceutical Industries).

[2] For a historical contextualization of this evolution see Scheu, 2003. A fundamental reference to the evolution of risk regulation is Di Fabio, 1994.

[3] See in this respect the report of the Committee for Medicinal Products for Human Use (CHMP) on benefit-risk assessment methods in the context of the evaluation of marketing authorization applications of medical products for human use /Doc. Ref. EMEA/CHMP/15404/2007) where it is recommended to "explore further development of methodologies for benefit/risk analysis, including a wide range of quantitative and semiquantitative tools" (p. 2). The document insists that "Quantitative approaches to benefit-risk assessment might also be useful for the continuous evaluation of products post-approval" (p.6) and that "There can be a number of theoretical and practical aspects of decision-making theory that can be useful to refine the CHMP assessment". It is furthermore acknowledged that "Most of these methods are still in the research domain and their validity and usefulness remain to be tested in various contexts" (p.4): http://www.emea.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/01/WC500069634.pdf. Another important document in this sense is the Report of CIOMS Woking Group IV (Council for International Organizations of Medical Sciences, Geneva 1998) "Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals": http://www.cioms.ch/publications/g4-benefit-risk.pdf, which also advances the use of formal decision theory in the decision-making process (p. 5) and recognizes the lack of generally agreed procedures or regulatory guidelines for conducting and acting upon benefit-risk assessment as well as of defined and tested algorithms or summary metrics (p. 13, 21, 55). The general aim is to

provide “techniques that are expected to yield a reproducible and transparent quantification and descriptions of risk attributable to drugs” (p. 35).

[4] Landesgericht (LG) Aachen, 18. 12. 1970 – 4 KMs 1/68, 15 – 115/67: Juristische Zeitung 507 (521).

[5] LG Aachen, 18. 12. 1970 – 4 KMs 1/68, 15 – 115/67: Juristische Zeitung 516.

[6] LG Aachen, 18. 12. 1970 – 4 KMs 1/68, 15 – 115/67: Juristische Zeitung 516.

[7] Scheu, 2003: 755.

[8] § 1 AMG: “Es ist der Zweck dieses Gesetzes, im Interesse einer ordnungsgemäßen Arzneimittelversorgung von Mensch und Tier für die Sicherheit im Verkehr mit Arzneimitteln, insbesondere für die Qualität, Wirksamkeit und Unbedenklichkeit der Arzneimittel nach Maßgabe der folgenden Vorschriften zu sorgen“.

[9] Authority for intervention is linked to this norm throughout the law: § 25 II S 1. Nr. 5 (approval) in connection with § 28 (special conditions), § 30 (approval withdrawal, revocation, suspension), and § 69 I S. 2 Nr. 4 (risk management interventions). Hart, 1998b: 168.

[10] § 5 II: “Bedenklich sind Arzneimittel, bei denen nach dem jeweiligen Stand der wissenschaftlichen Erkenntnisse der begründete Verdacht besteht, dass sie bei bestimmungsgemäßem Gebrauch schädliche Wirkungen haben, die über ein nach den Erkenntnissen der medizinischen Wissenschaft vertretbares Maß hinausgehen”.

[11] http://www.fda.gov/regulatoryinformation/guidances/ucm122049.htm.

[12] German Medicine Act 1976 (Arzneimittelgesetz 1976); see also Scheu, 2003: 701.

[13] See the Enquete-Kommissions-Bericht “Schutz des Menschen und der Umwelt”: BT-DrS. 12/8260, cited in Scheu, 2003: 72. In addition to inherent epistemological limits, Scheu also mentions the objective information insufficiency regarding the risk profile of chemical products in general. For most of the chemical products on the market, fundamental data about chemical behavior and environmental consequences of their use are simply not available (Scheu, 2003: 80; see also Abraham, 2005).

[14] This evolution is the reflection of the development of the precautionary principle in different fields of technological risk regulation. See Di Fabio, 1994. See also Dettling, 2005: 165.

[15] A proposal in this direction has also been put forward by Waller & Evans (2002) for instance.

[16] See also Räpple, 1991: 50-57.

[17] This kind of uncertainty is termed “ecological” because it is not primarily originated by lack of knowledge but by an intrinsic indecision due to a preference tie-up (see also Osimani 2010, forthcoming and Delquié, 2008).

[18] See a.o. Hart, 2005; Osimani 2007 (chapter 2).

[19] The mathematical and philosophical literature on probability, the interpretation of probability, and Bayesianism is indeed vast. The unfamiliar but interested reader may look at the following references: Davidson (1981), Dubucs (1993), Eagle (2009), Gillies (2002), Howson and Urbach (1993), Williamson (2005 and 2010).

[20] In spite of its long history, probability theory was axiomatized by Kolmogorov only in 1933.

[21] In probability theory, the axioms state that (i) probabilities are non-negative real numbers, (ii) every tautology is assigned value 1, and (iii) the sum of the probabilities of two mutually inconsistent sentences is equal to the probability of their disjunction. The conditional probability of A given B is written P(A|B) and is defined as P(A|B)= P(A&B)/P(B) for nonzero P(B). Bayes’ theorem follows from the axioms and from the definition of conditional probability. It governs the inversion of a conditional probability and relates the posterior probability of B given A to the probability of A given B, provided that the prior probability of A and B are known or that a conventional procedure to determine them is accepted. Formally, Bayes’ theorem states that: P(B|A) = P(A|B)P(B)/P(A) for nonzero P(A). Priors are probability values assigned to an event or hypothesis in the absence of evidence or before evidence is collected. Posterior probabilities are then probability values computed by means of Bayes’ theorem taking into account evidence. See Howson and Urbach (1993) for a detailed exposition.

[22] See, e.g., de Finetti (1937).

[23] The principle of indifference states that whenever there is no evidence favouring one basic possibility over another, these possibilities have the same probability.

[24] This analysis supposes that the decision as to whether or not to withdraw the drug is taken solely on the basis of whether or not the drug is a positive cause of harm that is sufficiently great. But this analysis can be extended straightforwardly to decisions taken on the basis of whether the drug is a cause of harm that is sufficiently great (so that mixed causation is also taken into account). The utilities can be calculated via a variety of risk-benefit protocols (see also footnote 3 and related literature). In general, prolongation of life expectancy is one of the most common parameters considered in health technology assessment. More precisely, technologies are evaluated in terms of *quality adjusted* life expectancy. In the case of pharmaceutical products following parameters are taken into account. On the benefit side: efficacy, therapeutic importance, healing, symptoms relief, transitory vs permanent positive effect. On the risk side: severity, intensity, extension, duration (risk magnitude), risk type, severity of impact on life quality, reversibility, controllability, possibility of (early) detection, possible countermeasures. All these parameters jointly contribute to the final approval decision. A formal procedure should therefore aggregate them and weight them by the probability of the benefit and the risk respectively. The decision matrix proposed here is an ideal formalization of this procedure which only serves the theoretical purpose of showing where exactly the precautionary principle comes to its own.

[25] This kind of probabilistic analysis is in fact over-simplistic, as argued in Russo and Williamson (2007); Williamson (2009) and Russo and Williamson (2011). But it will serve our purposes as a simple reference point with which to compare interpretations of probability.

[26] The following analysis supposes that probabilities are all given the same interpretation, but can be extended to pluralistic accounts of probability.