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Re: Comments on “Myriad/Mayo” Guidelines<sup>1</sup>

These comments are in response to the “2014 Procedure for Subject Matter Eligibility Analysis of Claims Reciting or Involving Laws of Nature/Natural Principles, Natural Phenomena, And/Or Natural Products,” (“Guidelines”) that the Office issued following the Supreme Court’s decisions in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U. S. \_\_\_ (2012), and *Association for Molecular Pathology, et al. v. Myriad Genetics, Inc., et al.* 569 U.S. \_\_\_ (2013). Specifically, these comments will address the category of laws of nature/natural principles and explain how the Office’s interpretation of those categories is erroneous.

In *Mayo*, Prometheus Labs was the exclusive licensee of US patents 6,355,623 and 6,680,302. The patents describe a protocol to determine a safe and effective dosage for thiopurine, a medication used to treat autoimmune diseases such as Crohn's disease and ulcerative colitis. These medications metabolize in the patient's body to 6-thioguanine ("6-TG"). The different rates at which they metabolize make it difficult for physicians to determine whether a given dose was too high (and thus toxic) or too low (and thus ineffective). The Prometheus' patent's claims identify the range for safe and effective dosages as those which result in a concentration of 6-TG between about 230 pmol and about 400 pmol per  $8 \times 10^8$  red blood cells (“R.B.C.”). The patents claim no underlying biological process that accounts for the differences in metabolization. The Supreme Court ruled that Prometheus’ claims were not eligible for patent protection, holding that Prometheus did nothing more than identify a “law of nature.”

However, the Court’s analysis that the claims recite a law of nature is based on a misunderstanding, and that misunderstanding has not only been carried over into the Guidelines but extended far beyond the Court's decisions.

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<sup>1</sup> These comments are my own, and do not reflect the opinions of Fenwick & West LLP, or any of its clients.

### What is a Law of Nature?

To understand what counts as a law of nature, we must distinguish three types of statements:

*Accidental generalization*: All robins' eggs observed to date are greenish-blue.

*Universal truth*: Every robin's egg, both those observed in the past and those to be observed in the future, is greenish-blue.

*Law-like statement*: It is a law that robins' eggs are greenish blue.

An *accidental generalization* summarizes past experience--every robin's egg found to date has been greenish-blue--and leaves open the possibility that some robin's egg found in the future will not be greenish-blue. *Correlation does not imply causation*. An assertion that something is a law of nature simply *because* every observation of relevance has certain properties (*e.g.*, all the robins' eggs observed are greenish-blue) is never sufficient.

A *universal truth* is stronger than an accidental generalization. The statement requires more than just that every observed robin's egg has been greenish-blue. It *predicts* that every one in the future will be the same color. This assertion has more force, but it provides no *reason that necessitates* this result. Intuitively, a robin's egg could be, *e.g.*, pale white, due to genetic mutation. Merely stating the relationship in conditional form—"If *x* is a robin's egg, then *x* is greenish-blue"--does not make it a law of nature.

A *law-like statement* means something *more* than just the accidental generalization or the predictions of a universal truth. For a law-like statement to be *necessary*, it *must* be true for some reason or property.

Without distinguishing among accidental generalizations, universal truths, and law-like statements, one cannot explain what makes a law of nature or a natural principle. "Any alleged account of laws that failed to ground a distinction between lawful and accidental regularities is obviously mistaken."<sup>2</sup>

The question of "what is a law of nature" thus becomes "what properties are required of a law-like statement to make it a *law of nature*?" The kinds for properties typically discussed as necessary conditions include:

- a. *Universality*: the statement is true under any and all conditions and thus is independent of contingent facts. Continuing the above example, there would have to be no examples of robin's eggs that are not greenish blue for the statement to be a law of nature; otherwise the statement is merely an accidental generalization.
- b. *Necessity*: the statement expresses something that *must* be true and not just true by definition (*e.g.*, "all humans are mammals") or by mathematics (*e.g.*, "there is no largest

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<sup>2</sup> B. Loewer, "Humean Supervenience," in J. Carroll, ed. "Readings on Laws of Nature," (2004), p. 187.

prime number”). This requirement is *physical*, *natural*, or *nomological* necessity. Loosely speaking, is there something that makes it necessary that all robins’ eggs are blue? Necessity is what distinguishes a law-like statement from a (mere) universal truth.

- c. *Explanation*: the statement explains the phenomena and all instances. A law of nature about the particular color of robins’ eggs would provide an explanation as to why and how this occurs.
- d. *Prediction*: the statement makes predictions about future instances, which predictions can be confirmed (or disconfirmed). Will all robins’ eggs that are found in the future be greenish-blue?
- e. *Inference*: the statement supports inferences from sets of facts to further sets of facts that can be confirmed. Given the color of robins’ eggs, can we infer any other useful facts?
- f. *Counterfactuals*: a statement like “It is law that robins’ eggs are greenish blue” must be true in *counterfactual* examples where there are no robins’ eggs at all.
- g. *Objectivity*: whether a statement is a law of nature does not depend on any human knowledge, belief, interest, need, or other subjective or pragmatic consideration. Thus, if it is a law that robins’ eggs are greenish-blue, it does not depend any of our beliefs about robins, our perception of what is greenish-blue, or whether it is useful to humans that robins’ eggs have this color.
- h. *Scientific*: a statement should be discoverable by scientists; it is what scientists would consider a law.

In general the more of these properties that are met by a given statement of a possible law of nature, the stronger the case for that conclusion.<sup>3</sup>

Importantly, scientific facts are not laws in themselves because once the laws that describe the facts are identified, the individual facts are not needed. For example, given the Ideal Gas Law,  $PV=nRT$ , expressing the relationship in an ideal gas between pressure, temperature, volume, and moles, it is unnecessary to hold that all of the facts covered by the law are also laws of nature, e.g., that one liter of argon contain 0.043 moles at one atmosphere of pressure, has a temperature of 10° C. Thus, it would be a mistake to categorize a patent claim making use of a particular scientific fact about the properties of composition of matter, process, or the like as reciting a law of nature.

The question of whether there are laws in biology is one of the oldest questions in the philosophy of biology. Biology is distinct from physics because biological systems are the result of evolutionary processes. Different biological outcomes are inherent in the operation of evolution and have several sources: 1) random mutation, which is necessary for any adaptation, 2) variances in the environment that present selection pressure, and 3) the existence of multiple different functionally equivalent adaptations. Stephen Jay Gould, in *Wonderful Life: The Burgess Shale and the Nature of History* (1989), puts it vividly: “evolution is like a videotape that, if replayed over and over, would have a different ending every time.”

Humans and the particulars of human biology are just as evolutionarily contingent as any other biological outcome, and this contingency affects not merely superficial generalizations,

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<sup>3</sup> For a detailed analysis of the properties of laws of nature, see B. van Fraassen, *Laws and Symmetry*, p. 26 (1989).

like “Humans are relatively hairless,” but even fundamental biological processes, such as the Krebs Cycle, which is used by almost all aerobic organisms to generate energy through the oxidization of acetate derived from carbohydrates, fats and proteins into carbon dioxide and water. The cycle can be described purely as a sequence of eight specific chemical reactions. Describing the cycle in terms of chemical reactions does not make it any less a contingent outcome of evolution since it “depends on genetically based aspects of those organisms, like their ability to synthesize the enzymes that facilitate the various reactions of the cycle.”<sup>4</sup> The evolutionary contingency is further evidenced by the fact that there are aerobic organisms that bypass one or more the steps, precisely because they evolved different enzymatic pathways. Thus, what first appears as a lawful generalization of chemistry, morphs into an almost-but-not-quite universal truth about aerobic organisms.

All generalizations about the living world are simply mathematical, physical, or chemical generalizations or the deductive consequences thereof, or contingent outcomes of evolution. Accordingly, examiners must be cautious to avoid too quickly assuming that every claim reciting a biological or chemical process recites a law of nature. As the Supreme Court has recently stated, “we tread carefully in construing this exclusionary principle lest it swallow all of patent law. At some level, “all inventions . . . embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas.”” *Alice Corp. v CLS Bank*, 134 S. Ct. 2347, 2354 (2014).

#### Does Prometheus’ Claim Recite a Law of Nature?

We can consider whether Prometheus’ claim recites a law of nature under the variously described criteria. Here is the claim:

1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:

- (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
- (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,

wherein the level of 6-thioguanine less than about 230 pmol per  $8 \times 10^8$  red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and

wherein the level of 6-thioguanine greater than about 400 pmol per  $8 \times 10^8$  red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

The Supreme Court’s analysis of this claim in its entirety is:

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<sup>4</sup> Beatty, “The Evolutionary Contingency Thesis,” in Sober , ed. “Conceptual Issues in Evolutionary Biology,” Third Ed. (2006) MIT Press, p. 217-247, at p. 219.

Prometheus' patents set forth laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm. Claim 1, for example, states that *if* the levels of 6-TG in the blood (of a patient who has taken a dose of a thiopurine drug) exceed about 400 pmol per  $8 \times 10^8$  red blood cells, *then* the administered dose is likely to produce toxic side effects. While it takes a human action (the administration of a thiopurine drug) to trigger a manifestation of this relation in a particular person, *the relation itself exists in principle apart from any human action. The relation is a consequence of the ways in which thiopurine compounds are metabolized by the body—entirely natural processes.* And so a patent that simply describes that relation sets forth a natural law.

The Supreme Court assumes that the claimed dosage-toxicity relationship is a law of nature. The structure of the Court's reasoning is as follows:

- 1) there is a *natural relationship* between the concentration of the metabolite and its effective/toxic dosages;
- 2) expressing this relationship in *if...then* form is important because it operates as a prediction of what will happen; and
- 3) the relationship exists apart from human action.

First, let us find the “natural relationship” between 6-TG and effective and toxic doses, which formed the basis for the alleged law of nature. As stated in the '623 patent, this relationship is based on two studies of patients who received daily administrations of 6-mercaptopurine (6-MP) or AZA for at least four months. One study had 89 patients; the other had 93. Hepatic, pancreatic, and hematological tests for toxicity were obtained every three months. The results of the first study are shown in Table 1 (from the '623 patent):

TABLE 1

Group	n	median 6-TG	6-TG >225	median 6-MMP
Responders	58	295	45/58 (78%)	3094
Non-responders	31	184*	8/31 (26%)	2048
Hepatic toxicity	7	258	5/7	9211**
Pancreatic toxicity	6	211	2/6	2342
Hematologic toxicity	6	414+	5/5	7042
p Values		*<0.001 +<0.03	‡<0.001	**<0.001

In the first study, 58 patients showed specific clinical improvement. Of these, 78% (45) had 6-TG levels >225 pmol per  $8 \times 10^8$  RBC. In the second study (not shown here), 78% of patients

above a median 6-TG of 230 pmol/8x10<sup>8</sup> RBC responded to treatment. From these findings come the claim limitation that 6-TG less than “about 230” “indicates a need” to increase the dosage.

Now consider the toxicity level. Table I shows that just six people out of 89 (6.74%) experienced hematologic toxicity; for them the median 6-TG level was 414 pmol per 8x10<sup>8</sup> RBC. There is no direct statistical evidence that the concentration should be *about 400*; the number was most certainly selected by the patent attorney to give some leeway in the patent claim. These six patients are very impressive, since they (no doubt unknowingly) form the smallest sample of data upon which a “law of nature” has ever rested.

The inventors of ‘623 patent, Drs. Siedman and Theoret, made no claim that they discovered any law of nature—instead it was the Supreme Court that gave this imprimatur to the claim. One would think that, if the inventors believed they had discovered something as fundamental as a law of nature, they would have said so.

Applying some of the above criteria shows what Drs. Siedman and Theoret “discovered”—if they *discovered* anything at all—was an *accidental generalization*. First, as Table I shows, neither the effective nor the toxic dosages approach anywhere near *universality*. While the effective dose need not result in a 6-TG level of about 230 in, say, 99% of patients, being effective for less than 80% seems a rather weak condition, especially when 26% of the non-responders had a 6-TG level greater than 225. Indeed, it is easy to see that the claimed “about” could have been shifted one way or the other by five or ten pmol with little impact. Real “laws of nature” are not so malleable. Similarly, it can be argued that the claimed minimum dosage level could have been set lower, perhaps to 220 pmol per 8x10<sup>8</sup> RBC. That would have provided superficial support for the assertion that the level was “universal.” Finally, the fact that the confidence level for this finding was p<0.001 simply means there is less than one chance in 1000 that this is a random outcome. Thus, it may be a strong correlation, but that does not tell us that it is a *necessary* one.

The toxic dosage is even more suspect, as just six people experienced toxicity in the first study, and the toxic level of *about 400* was not the average but the median level. With a sample that small, the median can be an unreliable measure of central tendency. Thus, for another group in another study, the results not merely could have, but very likely would have, been different to a noticeable degree. Indeed, this is acknowledged in the *Prometheus* decision itself: Mayo's research led them to pick 450 pmol per 8x10<sup>8</sup> RBC as the toxic level. Are there then *two* laws of nature of 6-TG toxicity, Prometheus’ Law and Mayo’s?

Nor does the *natural relationship* have any *necessity*. In line with the laws of biology, the particular ability of humans to metabolize 6-MP or AZA into 6-TG at all is a historical accident of evolution. Given that 26% of the patients in the first study metabolized these drugs too poorly to have any therapeutic effect, it is not beyond reason to think we could evolved to be entirely unable to metabolize 6-MP or AZA. But we do not even need this strong an outcome; we need consider only that humans could certainly have evolved so that the effective or toxic dosages were different from that which was claimed, say both higher by 25%.

The claimed natural law does not *explain* anything either. There is no causal explanation why the dosages are effective or toxic; there is only a statement of what they are. Once the causal mechanism is discovered, the particular levels may fall away as unnecessary.

Predictive power also marks a law of nature. Here, Prometheus' claim does provide a prediction. From the data in Table I and Bayes' Theorem, we can determine the probability that a patient will demonstrate a clinical response to 6-TG, given a concentration above 225 pmol  $8 \times 10^3$  RBC, is approximately 85%. That means about 15% of the time patients treated in accordance with the patent's claim will not show any clinical response at 225 pmol  $8 \times 10^3$  RBC. In that case, what is a doctor to do? As Table I shows there were seven patients who did not respond and who developed hepatic toxicity; of these, five (71%) had 6-TG levels greater than 225. Thus, if the doctor increases their dosage, there is a significant probability that the patient will have a toxic reaction to 6-TG at level well below the claimed "about 400." Thus, on its face, claim 1 does not present a certain predictive path for treatment.

The next criterion above is *objectivity*, that the claimed law does not depend on human knowledge, beliefs, needs or other pragmatic concerns—in short that, like  $E=mc^2$  or  $F=ma$ , it is true regardless of any facts about the human condition. Here the Supreme Court's assertion of lawhood fails miserably: The claimed law is based on a human need to modify a dosage of drugs for a specific disease, drugs that were invented by humans in the first place. No other generally accepted law of nature in physics, chemistry, etc., has any such intimate connection to an unmistakably subjective human need. Even the Supreme Court in *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U. S. 127 (1948), did not fasten upon such a human-centric law of nature.

Finally, we come to the "scientific" requirement, what scientists would consider a law of nature. Ernst Mayr, a leading 20th biologist who contributed to what is called the "Modern Synthesis" of evolutionary theory tells us:

The question has been raised in recent years whether or not laws are as important in biology as they seem to be in the physical sciences. Some philosophers...deny that there are any universal laws in biology...other philosophers...have emphatically defended the existence of biological laws. Biologists have paid virtually no attention to the argument, implying that this question is of little relevance to the working biologist... If one looks at a modern textbook of almost any branch of biology, one may not encounter the term "law" even a single time.<sup>5</sup>

In short, biologists have little use for calling statements laws of nature—they get on with their work quite nicely without such a label. In the case of Prometheus, workers in the field would most certainly not label the relationship a law of nature.

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<sup>5</sup> Mayr, "The Growth of Biological Thought: Diversity, Evolution, and Inheritance," (1989), Cambridge: Belknap Press, p. 19, p. 37. Mayr supports his critique of universal laws in biology in a section headed "Erroneous Search for Laws," in which he gives four specific examples of how four "ill-founded endeavors" to make biology "obey definite laws." See, Mayr, p. 846-847.

I have sketched out a number of reasons that Prometheus' claim is not a law of nature, any more than (and indeed quite possibly less than) than it is a law of nature that robins' eggs are greenish blue. Natural relationships surround us, but being *natural* does not make them *laws* of nature. Einstein famously said "God does not play dice with the world," but it can be equally said that God did turn every possible correlation in human biology into a law.

While the Supreme Court is certainly our highest judicial authority and is charged with stating what the law is, that authority is directed to defining the words and meaning of statutes. Thus, the Court can define legal terms like *probable cause* or *contributory infringement*. But the Court is without authority to reach into the domain of science or technology and define a "law of nature" in a manner inconsistent with the scientific community. The Supreme Court can no more define a something to be a law of nature than it can define *that*  $\pi$  is equal to three. It would be utterly bizarre for a court or the USPTO to declare something a law of nature (and thereby invalidate patent or deny a patent application) only to have the scientific community discover that the so-called law does not hold all. The history of science is littered with false theories and mistaken identifications of laws of nature.

Perhaps than Prometheus' claim sets forth something less than a law of nature, a "natural principle"? Unfortunately, the Supreme Court's caselaw does not support this distinction. The term "natural principles," originated in *Funk Brothers*. The Court stated that

Discovery of the fact that certain strains of each species of these bacteria can be mixed without harmful effect to the properties of either is a discovery of their qualities of non-inhibition. It is no more than the discovery of some of the handiwork of nature, and hence is not patentable. The aggregation of select strains of the several species into one product is an application of that newly discovered natural principle. But however ingenious the discovery of that natural principle may have been, the application of it is hardly more than an advance in the packaging of the inoculants. *Funk Brothers*, 333 U.S. at 131 (emphasis added).

It is clear that the Court is using "natural principle" as another way of saying "law of nature," and not as a different or lesser category. Even if there are natural principles that are less than laws of nature, then these are either accidental generalizations or universal truths. In short, these would at best scientific facts, such as the properties or attributes of biological or chemical systems. But the Supreme Court certainly did not intend to exclude all patents that make use of scientific facts, since these are essential the development of technology. There are thousands upon thousands of patents that recite specific limitations directed to the physical, chemical, biological, or other attributes used in products or processes. Again, the judicial exception would "swallow" the patent law if every claim that recited such properties was deemed directed to a natural principle.

Accordingly, the USPTO should not treat attempt to distinguish between laws of nature and natural principles, and my comments will treat them as being identical.

### Discussion of Example Claims

The Guidelines provide two claim examples dealing with laws of nature and natural principles. I will review these examples in light of the foregoing analysis.

### III. F. Process Claim Involving a Natural Principle and Reciting Natural Products

Claim: A method for determining whether a human patient has degenerative disease X, comprising:

obtaining a blood sample from a human patient;

determining whether misfolded protein ABC is present in the blood sample, wherein said determining is performed by contacting the blood sample with antibody XYZ and detecting whether binding occurs between misfolded protein ABC and antibody XYZ using flow cytometry, wherein antibody XYZ binds to an epitope that is present on misfolded protein ABC but not on normal protein ABC; and

diagnosing the patient as having degenerative disease X if misfolded protein ABC was determined to be present in the blood sample.

The Guidelines go on to state “the correlation between the presence of misfolded protein ABC in blood and degenerative disease X is a natural principle,” and therefore, the claim is directed to the judicial exception.

This conclusion is incorrect. The correlation here, especially in its schematic form of an arbitrary protein ABC and arbitrary disease X, is not a law of nature. At best, the relationship between the presence of the misfolded protein and the disease is a universal truth, thus the detection of the misfolded protein using the antibody XYZ is used to predict the disease in a given subject. Even so, this does not rise to the level of necessity required for a law of nature. On the other hand, it could well be that this relationship is in fact a byproduct of some other process occurring in the body; that is the misfolded protein ABC and disease X are both caused by some as yet undiscovered agent, and their correlation is merely symptomatic of that agent’s operation. For example, the beta-amyloid plaques (a form of protein malformation) that form on the brain were once believed to be the cause of Alzheimer’s Disease due to the correlation between the presence of the plaques and the symptoms of the disease. However, there are studies identifying individuals who had the plaques but who did not have the disease, thereby suggesting that this relationship is not a universal truth, but only an accidental generalization. Thus, simply labeling this correlation between the misfolded protein ABC and disease X a law of nature/natural principle improperly ignores these complexities.

### G. Process Claims Involving A Natural Principle

Claim 1. A method for treating a mood disorder in a human patient, the mood disorder associated with neuronal activity in the patient’s brain, comprising:

exposing the patient to sunlight, wherein the exposure to sunlight alters the neuronal activity in the patient’s brain and mitigates the mood disorder.

Background: It is a well-documented natural principle that white light affects a person's mood. Exposure to white light changes neuronal activity in the brain, which changes a person's mood.

Analysis of Claim 1: The answers to Questions 1-2 in the above analysis are both "yes," because the claim is to a process, and because the claim recites judicial exceptions, e.g., the natural principle or phenomenon that white light affects human neuronal activity, and the natural phenomenon of sunlight.

It is not a law of nature that "white light affects human neuronal activity," and alters mood, any more than it law of nature that chocolate alters neuronal activity and makes people happy, or alcohol makes them drunk. Like the latter two, the impact of white light on neuronal activity is only the macroscopic result of more basic biological and chemical mechanisms.

Nor is it correct to say that this relationship is a natural phenomenon. Natural phenomena are more concerned with events occurring in the natural world (i.e., outside of the human body.).

A natural phenomenon is not a man-made event. Examples include sunrise, weather (fog, hurricanes, tornadoes), biological processes (decomposition, germination), physical processes (wave propagation, conservation of energy, erosion), tidal flow, and include natural disasters such as electromagnetic pulses, volcanic eruptions, earthquakes.

[http://en.wikipedia.org/wiki/Natural\\_phenomenon](http://en.wikipedia.org/wiki/Natural_phenomenon)

For example, lists of natural phenomena, such as <http://www.buzzfeed.com/simoncrerar/natural-phenomena-you-wont-believe-actually-exist> almost universally contain examples of the foregoing classes, and not processes relating to in the human body. Thus, a rejection under Section 101 is improper. If, as the background states, this so-called phenomena is "well-documented" then the Examiner can reject the claim under Section 102, potentially using Official Notice, and avoid the more problematic question of Section 101.

### Conclusion

The primary concern underlying the Court's Section 101 jurisprudence is preemption:

We have described the concern that drives this exclusionary principle as one of pre-emption. See, e.g., *Bilski*, supra, at 611-612 (upholding the patent "would pre-empt use of this approach in all fields, and would effectively grant a monopoly over an abstract idea"). Laws of nature, natural phenomena, and abstract ideas are " ' "the basic tools of scientific and technological work." ' " *Myriad*, supra, at \_\_\_\_." *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2354 (2014).

Thus, if a patent's recitation of a computer amounts to a mere instruction to "implemen[t]" an abstract idea "on . . . a computer," *Mayo*, supra, at \_\_\_\_, 132 S. Ct. 1289, 182 L. Ed. 2d 321, 337), that addition cannot impart patent eligibility. *This conclusion accords with the preemption concern that undergirds our §101 jurisprudence.* *Alice*, 134 S. Ct. at 2358 (emphasis added)

The Office should approach Section 101 by focusing on the preemptive impact of claims, relying on its own considerable scientific and technical knowledge, and using the Court's decisions as guidance for the overarching goal, and not as scientifically valid statements about the nature of reality.

Sincerely,

A handwritten signature in black ink, consisting of the letters 'AUS' stacked above 'RR', all enclosed within a hand-drawn oval.

ROBERT R. SACHS