The Hon. Michelle K. Lee
Deputy Under Secretary of Commerce
Acting Director
United States Patent and Trademark Office

Via email to myriad-mayo_2014@uspto.gov

Re: March 4, 2014, Guidance For Determining Subject Matter Eligibility Of Claims Reciting Or Involving Laws of Nature, Natural Phenomena, & Natural Products

July 31, 2014

Dear Acting Director Lee,

The undersigned national and regional biotechnology industry associations appreciate this opportunity to comment on the USPTO's March 4 guidance for the determination of subject matter eligibility of claims relating to products and processes derived from natural sources or materials (the "Guidance"). We write to express our concern over the recent judicial and administrative expansion of nonstatutory patent law governing the patent-eligibility of certain classes of biotechnology inventions in the United States, as manifested in the PTO's March 4 Guidance.

Together, our associations represent thousands of biotech businesses, academic and nonprofit research centers, technology transfer organizations and other entities dedicated to biotechnological innovation throughout the world. Our increasingly global industry provides breakthrough products and technologies that combat debilitating and rare diseases, reduce our environmental footprint, provide food security, use less and cleaner energy, and drive economic growth.

Internationally harmonized, science-based regulatory and legal frameworks are important for competitiveness and innovation to ensure faster and more equitable access to new biotech products and processes for patients, farmers and consumers around the world. It is in this context that we note with concern the significant departure from internationally accepted norms of patentability that would be established by the Guidance, particularly with regard to industrial, agricultural, and pharmaceutical preparations of naturally-derived substances, compositions, and processes.

Inventive preparations based on naturally-occurring substances have historically been of great importance in biotechnology, and innovation in this area has been spurred, at least in part, by the availability of patent protection. This is true for every sector of biotechnology. Examples include

vaccine antigens, crop protection products,[1] plant biotechnology and breeding,[2] industrial enzymes,[3] immunosuppressive drugs,[4] anticancer compounds,[5] and antibiotic drugs.[6]

In the continual search for new therapies, the use of patented, naturally-occurring substances is not just a historical phenomenon but continues to be important today. For example, romidepsin was approved by the U.S. Food and Drug Administration in 2009 for the treatment of cutaneous T-cell lymphoma. It was first reported in the scientific literature in 1994 as an isolate from *Chromobacterium violaceum* from a soil sample obtained in Yamagata Prefecture, Japan (see US patent 4,977,138). Two natural marine antitumor compounds, trabectedin and aplidine (see US patent 5,834,586) were discovered in the sea squirts *Ecteinascidia turbinata* and *Aplidium albicans*, respectively. Both are in active clinical development, with trabectedin having been approved in 2007 for commercial marketing in Europe under the trade name Yondelis®. In 2012, ingenol mebutate, a natural compound extracted from *Euphorbia peplus* plants, was approved by FDA and EMA under the trade name Picato® for the topical treatment of actinic keratosis (see e.g. US patent 7,410,656).

As these examples from the oncology area indicate, preparations of novel and unobvious naturally occurring molecules continue to be an important source for drug discovery. Indeed, naturally-occurring molecules and their close derivatives have contributed an estimated 36% of all first-in-class small molecules approved by the FDA between 1999 and 2008.[7] In oncology, such naturally-derived chemotherapeutic agents have been described as an important second rail in the fight against cancer that supplements the parallel development of highly-targeted oncology treatments using antibodies or fully-synthetic small molecules.[8]

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[1] Numerous commercial crop protection products, such as enriched or purified preparations of selected strains and combinations of *Bacillus thuringiensis* or *B. subtilis* are used in organic insect control; *B. pumilus* is used as a biofungicide. Naturally-occurring fermentation products such as spinosad and avermectin are commercially marketed for insect and mite control.

[2] Genetic elements such as promoters, intronic nucleotide sequences, non-coding RNA as well as naturally expressed sequences are widely used in plant biotechnology and breeding activities in major crops including corn, wheat, soybean, rice, tobacco, rape seed, potato, sugar beet, and others.

[3] Phytase, an enzyme included in animal feed, significantly reduces the inability of some livestock to digest phytate in grain, which causes environmental pollution from fecal phosphate. Progress in this area has been facilitated by the invention of a phytase enzyme from the microbe *E. coli* and patent protection of isolated DNA. See U.S. Patent No. 6,190,897. Glucoamylase, an enzyme from the fungus *Trichoderma reesei* that efficiently releases glucose sugars from carbohydrates, allows for better production of biofuels such as ethanol. See U.S. Patent No. 7,413,887.

[4] Three major immunosuppressive drugs used to prevent organ rejection of transplant recipients were all discovered in natural, soil-dwelling microbes. Cyclosporine A was first discovered in a soil sample from Norway; tacrolimus (Prograf®) is produced by the bacterium *Streptomyces tsukubaensis*, first discovered in a soil sample from northern Japan (see U.S. Patent No. 4,894,366), and sirolimus (Rapamune®)(see US patent 3,929,992) is produced by the bacterium *Streptomyces hygroscopicus*, which was famously discovered in a soil sample from Easter Island.

[5] A large proportion of early cytostatic drugs were discovered, isolated and derived from botanical or microbial sources, such as vincristine, vinblastine, vinorelbine, vindesine, camptothecin, irinothecan, topothecan, paclitaxel, docetaxel, etoposide, teniposide, doxorubicin, daunorubicin, idarubicin and epirubicin.

[6] Many antibacterial and antifungal medicines were first isolated and patented from natural sources, see. e.g. amphotericin b (US2908611), streptomycin (US2449866), actinomycin (2378876), neomycin (2799620).

[7] Swinney DC and Anthony J, How were new medicines discovered? Nat. Rev. Drug Discov. 10 (2011) 507-519.

[8] Basmadjian et al, Cancer Wars: Natural Products Strike Back. Frontiers in Chemistry 2 (2014) 1-18.

Antibiotics represent another area of drug development where naturally-derived products play an important role in addressing critical emerging medical needs. FDA antibiotic approval numbers illustrate the problem. There were 16 new systemic antibiotics approved from 1983 to 1987. Approvals declined to 10 from 1993 to 1997, to five from 2003 to 2007, and to just two between 2009 and 2012.[9] Yet, new antibiotics are urgently needed. In its Action Plan against the rising threats from antimicrobial resistance of November 2011, the European Commission called for "unprecedented collaborative research and development efforts to bring new antibiotics to patients."[10] In May of this year, the World Health Organization released a major report on antimicrobial resistance, with Dr. Keiji Fukuda, WHO's Assistant Director-General for Health Security, commenting: "Without urgent, coordinated action by many stakeholders, the world is headed for a post-antibiotic era, in which common infections and minor injuries which have been treatable for decades can once again kill." Amongst a range of urgently-needed measures, WHO emphasized the need to develop new diagnostics, antibiotics and other tools to allow healthcare professionals to stay ahead of emerging resistance.[11]

As described in the submission by Cubist Pharmaceuticals Inc.,[12] naturally-occurring antibacterial substances play an important role in addressing this emerging problem. Among the relatively few new antibiotic drugs that were approved during the past decade, for example, are the bacterial fermentation products daptomycin and fidaxomicin, the latter having been approved as a first-in-class molecule only in 2011. Over the coming decade, the importance of naturally-occurring substances as sources for new antibiotic drug development will only increase, as advances in bioprospecting, in understanding microbial physiology and bacterial biosynthetic gene clusters, and in analytical techniques provide fertile areas for critically-needed research to unlock the untapped potential of naturally-occurring antibacterial substances.[13]

The use of naturally-occurring substances and the practical application of newly discovered biomarkers is playing out with equal importance in the area of diagnostics and personalized therapy. We live at a time when molecular biology, bioinformatics and medicine are converging at a rapid pace, and have the potential to create a revolution comparable to the discovery of penicillin or streptomycin, and their implications for the fight against bacterial infections. These inventions saved millions of lives, and created a foundation for medical advances based on sound scientific research. We saw this again with the scientific breakthroughs regarding the diagnosis and treatment of patients with HIV or HPV infections, which was honored with the Nobel Prize for Medicine in 2008 [14] and opened the door to the next revolution of medicine that is called personalized medicine. This new revolution is anchored in scientific advances in studying the reasons why patients having the same medical condition respond differently to the same

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[9] https://www.biocentury.com/biotech-pharma-news/coverstory/2012-11-19/gain-act-fda-stance-only-first-steps-to-refilling-antibiotic-pipeline-in-us-a1

[10] http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf

[11] http://www.who.int/drugresistance/documents/surveillancereport/en/

[12] http://www.uspto.gov/patents/law/comments/mm-e-cubist20140507.pdf

[13] Wright GD, Something Old, Something New: Revisiting Natural Products in Antibiotic Drug Discovery. Can. J. Microbiol.60 (2014) 147-154.

[14] http://www.nobelprize.org/nobel_prizes/medicine/laureates/2008/press.html

medicines. Our ability to link individual genetic variations to specific subtypes of a disease is increasingly driving choices of medical treatments and prognosis of outcome and disease progression. Many of these inventions are being made at U.S. universities for which the availability of patent protection is a key in their technology transfer strategy. The proposed Guidance, by its unfavorable treatment of these inventions, has the potential to seriously impair the scientific advances of U.S. universities over universities in e.g. Europe and Japan, which provide broader patent protection to inventors. In the end, this could lead to the United States falling behind in this extremely important area of research, one that has significant implications on drug discovery and development.

By singling out naturally-derived biotechnology inventions for special, disfavored treatment, the Guidance would establish peculiar disincentives for investment in research and development of entire categories of biotechnology. Under the Guidance, our member companies are already receiving rejections in the USPTO of applications for recombinant industrial enzymes, for pharmaceutical formulations having purified naturally-occurring substances as active ingredients, for methods of treatment using medicinal molecules, for diagnostic laboratory procedures, and other inventions that were neither considered nor discussed in the U.S. Supreme Court's decisions. Such rejections under the new Guidance, if they were to become systemic, would seriously impair investment incentives in new, socially beneficial technologies.

Research and development within the biotechnology industry comes at a high cost, and every idea that is funded comes with a greater likelihood of failure than success. Developing a single therapy requires an average, fully-capitalized investment of $1.2 billion, and the clinical testing period alone consumes more than 8 years on average. [15] Such investments are risky. For every successful biopharmaceutical product, thousands of candidates are designed, screened, and rejected after large investments have been made. Only a small minority of drugs even advance to human clinical trials and most of those fail to obtain regulatory approval. Investment therefore is predicated on the availability of patent protection that enables biotechnology businesses to attract capital and commercial partners in order to advance basic inventions - including those based on naturally-occurring substances and processes - from the laboratory to the marketplace and ultimately to generate an expected return on investment in the form of patent-protected products or services. In the United States alone, the biotechnology industry is responsible for more than 20 billion dollars of annual research investment and provides employment to hundreds of thousands of individuals. The overwhelming majority of this investment is through private funding.

The same holds true for the development of plant products in the seed industry, for instance with regard to genetically modified traits. It generally takes approximately 10-15 years on average to develop a plant product containing single or multiple traits including regulatory cultivation and/or import approval. Depending on the complexity of the trait(s), the cost for research, development and deregulation for one single plant product in the United States has been estimated to well exceed $ 100 million.[16]

[15] Joseph A. Di Masi and Henry G. Grabowski, The Cost of Biopharmaceutical R & D: Is Biotech Different? Manage. Decis. Econ. 28: 469-479, 2007).

[16] McDougall, P. "The Cost and Time Involved in the Discovery, Development and Authorization of a New Plant Biotechnology Derived Trait." Consultancy study, Crop Life International, Brussels,

Accordingly, it is extremely important that investment in biotechnological innovation is not discouraged by systematically erecting special hurdles to patent protection for all inventions that relate to naturally-derived substances and processes. We are concerned that the expansive scope of the Guidance reflects an investment-hostile extrapolation and expansion of nonstatutory U.S. patent law that was not required by the U.S. Supreme Court's decisions. In its *Myriad* decision, the Supreme Court clearly indicated that it neither meant to break new ground nor to revise its prior decisions. The Court's multiple cautionary statements about the narrowness of its holding and of all the questions it was explicitly *not* deciding, signal a narrow, incremental decision that should not compel broad changes in examination practice. In particular, we believe the Supreme Court's decisions do not require the application of a heightened patent-eligibility test to inventions such as combination products (especially in instances where the claimed combination occurs neither in a natural state nor in the prior art); methods of drug administration or the use of medicinal molecules for the treatment of disease; or purified naturally-occurring substances (such as antibiotics or vaccine antigens) which, in the claimed purified state, are for the first time provided for real-world practical uses and having industrial applicability not possessed in their natural, impure state.

By subjecting such inventions to a heightened patentability analysis, the Guidance conspicuously departs from internationally accepted standards of patent-eligibility. Many valuable inventions that would be patentable in the patent offices of the U.S.'s major trading partners will nevertheless be rejected in the USPTO because they fail to pass an extrastatutory "significant differences" test that has no equivalent in the patent laws of other industrialized countries.[17] Doing so creates a deep disparity in substantive patent law whereby whole categories of socially beneficial inventions would face obstacles to patent protection in the United States but remain patentable among its major trading partners, with attendant harmful effects on the flow of investment, trade, and cross-border transfer of innovation. The U.S. Government, together with the governments of EU member states, Japan, Korea, Australia and other major U.S. trading partners have been making efforts over a considerable period of time to encourage more harmonization and the adoption of more uniform and consistent rules relating to intellectual property and, in particular, patents. Progress, although slow, has been significant. Such efforts have borne fruit through increased membership and use of the Patent Co-operation Treaty, the adoption of the Patent Formalities Treaty and Patent Law Treaty, and in the extension of WTO rules to intellectual property. Currently, in negotiations that are taking place, U.S. negotiators are hoping that other countries will sacrifice tradition for uniformity, for example by considering the adoption of harmonized grace periods for inventor disclosures. The effect of an unnecessarily broad interpretation of the Supreme Court's decisions such as is proposed under the new Guidance will be a serious setback to such efforts and to progress in achieving further steps on the road to harmonization and the benefits that this would bring to many countries, but in particular, to the United States.

Given the potentially deep impact of the Guidance, we are perplexed by the complete absence of a policy justification for why the USPTO adopted such a far-reaching interpretation of judicial

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Belgium, 2011. Available at: http://d1jkwdgw723xjf.cloudfront.net/wp-content/uploads/2014/04/Getting-a-Biotech-Crop-to-Market-Phillips-McDougall-Study.pdf

[17] For example, EU member states, under the Directive on the legal protection of biotechnological inventions 98/44(EU) Article 3(2), uniformly accept naturally occurring biological material as eligible for patent protection. As an alternative to the non-statutory "significant differences test", European law uses the well-established framework of novelty, inventive step and industrial applicability.

decisions and departed so profoundly from its own past policies and from internationally accepted practices. We believe that constructive criticism, helpful proposals and productive dialogue on the Guidance would be greatly facilitated by a sound, scientifically and economically-grounded policy discussion of what is actually sought to be accomplished. By requesting comments on its Guidance, the USPTO is appropriately beginning a public discussion over the best (re)interpretation of the often confusing and internally inconsistent body of judge-made extrastatutory patent law relating to subject matter eligibility that has developed in the United States. But what is also needed is a public dialogue not just over what the law "is," but over what the right policies *ought* to be. Undoubtedly, there is a real risk of "getting it wrong" when trying to extract generalizations and uniformly applicable principles from an unstable jurisprudence and from judicial decisions that stand in tension with each other. Should the USPTO resolve this uncertainty by denying patent protection to the broadest possible range of biotechnology, or would it perhaps be wiser to invoke extrastatutory exceptions only in really unambiguous cases, and leaving it to the courts or Congress to establish the outer bounds of the Supreme Court's pronouncements? We urge the USPTO to consider this question in the context of the overall purpose of patent law to promote the progress of science and the useful arts, and in light of consistent reminders by the U.S. Supreme Court that the statute is inclusive and the exceptions to it are narrow – not the other way round. We encourage the USPTO to convene further meetings with the stakeholder community to discuss internationally prevailing best practices in this area. We believe that our organizations could contribute helpful scientific and economic insights, as well as real-life experience with the many nuanced approaches taken in the patent offices of the United States' major trading partners.

Respectfully submitted,

ASEBIO – The Spanish Bioindustry Association
AusBiotech, Australia's Biotechnology Organisation
Belgian Biotechnology Industry Organisation
BIA, The UK BioIndustry Association
BIO Deutschland
BIOTECanada
Biotechnology Industry Organization
CropLife International
EuropaBio
HollandBIO
Japan Bioindustry Association
P-BIO, Portugal's Biotechnology Industry Organization