cyanobacteria, and insecticidal compositions, as well as specific embodiments of these main categories of inventions.

Eleven prior art references were cited in support of the rejection of the claimed invention. The principal reference disclosed successful expression in a cyanobacterium of a chimeric gene. Specifically, the reference disclosed the expression in cyanobacteria of a chimeric gene comprising a chloroplast promoter sequence fused to a gene encoding the enzyme chloramphenicol acetyl transferase (CAT). As the court noted, "[i]mportantly, Dzelzkalns teaches the use of the CAT gene as a "marker" gene"; rather than for the expression of a specific protein. Secondary references disclosed the expression of the insecticidally active proteins of Bacillus in heterologous hosts to increase the yield of recovery of such proteins.

The Federal Circuit reversed the rejections based on § 103 (*note*: rejections of the broad claims on the basis of lack of enablement under § 112 were upheld). The explanation provided by the court was as follows:

Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. See *In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).* Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure.

We agree with appellants that the PTO has not established the prima facie obviousness of the claimed subject matter. The prior art simply does not disclose or suggest the expression in cyanobacteria of a chimeric gene encoding an insecticidally active protein, or convey to those of ordinary skill a reasonable expectation of success in doing so. More particularly, there is no suggestion in Dzelzkalns, the primary reference cited against all claims, of substituting in the disclosed plasmid a structural gene encoding Bacillus insecticidal proteins for the CAT gene utilized for selection purposes. The expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria for unrelated purposes.

The court then distinguished In re O'Farrell by pointing out that (a) there was no suggestion, implicit or explicit, in the prior art to suggest the presently claimed invention and (b) nothing in the prior art references would have created a reasonable expectation of success in the expression of a Bacillus protein in cyanobacteria.

4. *In re Bell, 991 F.2d 781, 26 USPQ2d 1529 (Fed.Cir. 1993).*

The claimed invention was directed to nucleotide sequences (DNA and RNA) that code for human insulin-like growth factors I and II (IGF), single chain serum proteins.

The claims were rejected by the PTO on the basis of prior art disclosures that showed the amino acid sequences of human insulin-like growth factors I and II, in combination with a patent disclosing a method of cloning genes using amino acid sequence information.

The patent disclosing the generic method of cloning genes emphasized the value in relying on unique codons that code for amino acids to increase the likelihood of success in isolating a gene encoding the amino acid sequence.

The court's analysis focused on the logic of the PTO's rejection, which, in the court's interpretation, was grounded on the proposition that knowledge of the genetic code would render any nucleotide sequence that encodes an amino acid sequence obvious in view of a disclosure of the amino acid sequence. The Federal Circuit specifically rejected this proposition, stating:

It may be true that, knowing the structure of the protein, one can use the genetic code to hypothesize possible structures for the corresponding gene and that one thus has the potential for obtaining that gene. However, because of the degeneracy of the genetic code, there are a vast number of nucleotide sequences that might code for a specific protein. In the case of IGF, Bell has argued without contradiction that the Rinderknecht amino acid sequences could be coded for by more than 10^{36} different nucleotide sequences, only a few of which are the human sequences that Bell now claims. Therefore, given the nearly infinite number of possibilities suggested by the prior art, and the failure of the cited prior art to suggest which of those possibilities is the human sequence, the claimed sequences would not have been obvious.

The court also characterized the supporting reference of the patent that disclosed the generic cloning method as "teaching away" from the invention. In doing so, the court emphasized that the patent suggested use of probes with large numbers of unique codons to increase the likelihood of success in isolating the gene. In the patent application, the applicants used a probe with only one unique codon. On that basis, the court found that the PTO had improperly combined the patent with the references disclosing the amino acid sequences of IGF I and II proteins.[10]

5. *In re Deuel, 51 F.3d 1552, 34 USPQ 2d 1210 (Fed. Cir. 1995).*

The claims covered DNA and cDNA sequences encoding bovine and human heparin binding growth factors.

The PTO rejected the claims as being obvious over references that disclosed isolation and N-terminal sequencing of heparin-binding brain mitogen proteins from bovine and human sources, in combination with teachings that showed general methods for isolating nucleotide sequences using N-terminal amino acid sequence information. The disclosure of the primary prior art reference indicated that the proteins isolated were specific to brain tissue.

In reversing the PTO, the court emphasized that the claimed invention was a "product" claim (i.e., discrete DNA and cDNA molecules). It then reasoned that the PTO's rejection was unsupportable because it rejected the claimed "products" based on a possible method of their production, rather than through a comparison of the physical characteristics of the claimed nucleotide sequences to prior art nucleotide sequences. The

[10] *In re Bell*, 991 F.2d at 785 ("we cannot say that Weissman "fairly suggests" that its teachings should be combined with those of Rinderknecht, since it nowhere suggests how to apply its teachings to amino acid sequences without unique codons.").

court emphasized that the prior art disclosures of partially sequenced proteins shared no structural similarities with the claimed nucleotide molecules, and, notwithstanding the general knowledge of the relationship between the protein and nucleotide sequence information, could not render the claimed nucleotide sequences obvious. The court reaffirmed its finding in Bell as follows:

We today reaffirm the principle, stated in Bell, that the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs. A prior art disclosure of a process reciting a particular compound or obvious variant thereof as a product of the process is, of course, another matter, raising issues of anticipation under 35 U.S.C. § 102 as well as obviousness under § 103. Moreover, where there is prior art that suggests a claimed compound, the existence, or lack thereof, of an enabling process for making that compound is surely a factor in any patentability determination. ...There must, however, still be prior art that suggests the claimed compound in order for a prima facie case of obviousness to be made out; as we have already indicated, that prior art was lacking here with respect to claims 5 and 7. Thus, even if, as the examiner stated, the existence of general cloning techniques, coupled with knowledge of a protein's structure, might have provided motivation to prepare a cDNA or made it obvious to prepare a cDNA, that does not necessarily make obvious a particular claimed cDNA. "Obvious to try" has long been held not to constitute obviousness. *In re O'Farrell,* 853 F.2d 894, 903, 7 USPQ2d 1673, 1680-81 (Fed. Cir. 1988). A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out. Thus, Maniatis's teachings, even in combination with Bohlen, fail to suggest the claimed invention.[11]

6. *In re Mayne, 104 F.3d 1339, 41 USPQ2d 1451 (Fed. Cir. 1997).*

The claims were directed to two genetically engineered "fusion" proteins consisting of a peptide (Met-Phe-Pro-Leu-) connected to an enterokinase cleavage site (-$(Asp)_4$-Lys-) which, in turn, was connected to either human or bovine growth hormone.

The claims were rejected as being obvious over prior art which taught the production of fusion proteins consisting of enzyme cleavage sites and human and bovine growth hormones, in combination with references that disclosed specific amino acid sequences of enterokinase cleavage sites and the full amino acid sequences of human and bovine growth hormones.

The Federal Circuit upheld the rejection of the claimed fusion proteins as being obvious over the prior art references cited. In doing so, the Court first emphasized that the cited references would have provided ample motivation and information for a person of ordinary skill to produce fusion proteins having enterokinase cleavage sites of a general form claimed by the applicant (i.e., having the X-$(Asp)_n$-Lys-Y, where X is a peptide and Y is the protein of interest). The court then noted that the distinction between the prior art and the claimed invention was a single amino acid substitution in the leading peptide sequence (i.e., Leucine was claimed instead of Isoleucine). The court sustained the rejection of the PTO that this substitution would have been obvious to a person of

[11] *In re Deuel,* 51 F.3d at 1559.

ordinary skill through reliance on the doctrine of "structural similarity."[12] Specifically, the court affirmed the PTO's argument that the well-known close physical similarity between the amino acids Isoleucine and Leucine would have provided ample motivation to a person of ordinary skill to modify the known peptide cleavage site by substituting Leucine.

(iii) Indicate whether specific difficulties have been encountered by your examining authority in applying the standard of inventive step/non-obviousness and the nature of the steps taken to address or resolve those difficulties.

As a general matter, the PTO has not experienced any significant difficulties in evaluating applications that claim biotechnology inventions for compliance with the requirement for non-obviousness. The ever-increasing body of law that governs § 103 determinations, particularly through cases concerning biotechnology and the closely related chemical and pharmaceutical technology areas, have provided ample guidance to PTO examiners in their evaluation of biotechnology inventions. The U.S. practice of precedential effect of cases related to § 103 regardless of the technical field of the invention has enabled the PTO to easily and successfully adapt to the ever evolving technological field of biotechnology.

The difficulties that have been encountered by the PTO relate more to the ability of the PTO to hire, train and retain experienced patent examiners who are able to examine applications in the field of biotechnology. The PTO has been very successful in overcoming its initial difficulties in this area through the hiring and extensive training of highly qualified biotechnology examiners. As such, the ability of experienced examiners to evaluate biotechnology inventions for purposes of compliance with 35 U.S.C. § 103 has not been a problem.

(l) Indicate whether, through the application of one or more conditions of patentability, products or compositions that are not considered to differ from their natural state, are generally found non-patentable in your country. Please explain the nature of tests, if any, that govern this issue in your system.

An invention that is claimed so as to define subject matter indistinguishable from subject matter found in nature cannot be patented under United States law. Depending on what has been claimed by the applicant and the degree of public disclosure of the subject matter, the claimed subject matter would fail to satisfy 35 U.S.C. § 101 and/or § 102.

- § 101 precludes the patenting of "naturally occurring" subject matter. The basis for this exclusion is that subject matter that is indistinguishable from what is found in nature has had no human intervention in its production, and as such is not a manufacture, composition of matter or machine as those terms have been used in 35 U.S.C. § 101 and construed by the courts.[13] The term "naturally occurring" is generally understood to mean subject matter which, as defined in the claim, cannot be distinguished from subject matter as it exists in nature. Where some distinction can be identified between the

[12] An extensive discussion of this doctrine, which evolved primarily in relation to chemical inventions, was provided by the Federal Circuit, sittin en banc, in the case of *In re Dillon,* 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990) (*en banc*).

[13] See, *Diamond v. Chakrabarty*, , 447 U.S. 303, 206 USPQ 193 (1980); In re Bergy, 596 F.2d 952, 201 USPQ 352 (CCPQ 1979). For a general overview on this topic, see Chisum, Chisum on Patents, § 1.02[7].

subject matter that is claimed (e.g., a purified composition containing bacteria in comparison to compositions containing the bacteria as they are found in nature), a rejection under section 101 is inappropriate, as the subject matter claimed is not identical to the subject matter found in nature.

- § 102 precludes the patenting of subject matter that was publicly known prior to the point in time that the inventor sought patent protection by filing an application. Public knowledge of subject matter that occurs in nature would preclude the patenting of the same subject matter as claimed by an applicant.

(m) Deposit of biological material:

(i) Indicate the general criteria that your examining authority uses to determine if a deposit of a sample is necessary to support enablement of an invention in the field of biotechnology.

Generally speaking, an applicant for a patent in the United States can be required to deposit a sample of a microorganism where, absent the act by the applicant of making the sample available to the public, it would not be possible for a person skilled in the relevant art to practice the patented invention without engaging in undue experimentation. Thus, a deposit will be required from an applicant when (a) the invention consists of a specific biological material (e.g., a cell line, yeast, fungus, a bacterium) or is dependent upon use of a specific biological material for its production or use and (b) the specific biological material is not readily available to the public or cannot be obtained from natural or other sources using information provided in the application. If it is determined that a deposit is necessary to satisfy the requirements of section 112, first paragraph (written description or enablement or both), the applicant will be required make a deposit that conforms to the requirements of 37 CFR 1.801 et seq.

A summary of the situations in which a deposit of a biological material will be mandated can found in sections 2404.01 and 2404.02 of the Manual of Patent Examining Procedure.

2404.01 - Biological Material that is Known and Readily Available to the Public

In an application where the invention required access to specific biological material, an applicant could show that the biological material is accessible because it is known and readily available to the public. The concepts of "known and readily available" are considered to reflect a level of public accessibility to a necessary component of an invention disclosure that is consistent with an ability to make and use the invention. To avoid the need for a deposit on this basis, the biological material must be both known and readily available - neither concept alone is sufficient. A material may be known in the sense that its existence has been published, but is not available to those who wish to obtain that particular known biological material. Likewise, a biological material may be available in the sense that those having possession of it would make it available upon request, but no one has been informed of its existence. The Board of Patent Appeals and Interferences has held that a description of the precise geographic location of marine tunicates, as a biological material, used in a claimed invention was adequate to satisfy the enablement requirement of 35 U.S.C. § 112. Ex parte Rinehart, 10 USPQ2d 1719 (Bd Pat. App. & Int. 1985). The term "readily" used in the phrase "known and readily