UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ELYSIUM HEALTH, INC.,
Petitioner,

v.

TRUSTEES OF DARTMOUTH COLLEGE,
Patent Owner.

Case IPR2017-01795
Patent 8,393,085 B2

Record of Oral Hearing
Held: September 28, 2018

Before SUSAN L. C. MITCHELL, CHRISTOPHER G. PAULRAJ, and JOHN E. SCHNEIDER, *Administrative Patent Judges*.

APPEARANCES:

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The above-entitled matter came on for hearing on Tuesday, October 2, 2018, commencing at 1:00 p.m., at the U.S. Patent and Trademark Office, 600 Dulany Street, Alexandria, Virginia.

P R O C E E D I N G S

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JUDGE MITCHELL: Good afternoon, everyone. We are here for a final hearing this afternoon in IPR2017-01795. I am Judge Mitchell, and seated to my right is Judge Paulraj, and appearing remotely is Judge Schneider. I would like to get appearances for the parties on the record. So if I could start with petitioner.

MR. JONES: Good afternoon, Your Honor. My name is Brendan Jones --

JUDGE MITCHELL: Sorry, if you could go to the podium, just because we have a remote judge and so he can hear. Sorry to run you around.

MR. JONES: No problem. I'm Brendan Jones. I'm the lead counsel for petitioners, Elysium Health, and with me today is my backup counsel, Don Ware.

JUDGE MITCHELL: Thank you. And for patent owner.

MR. ABRAMIC: Good afternoon, Your Honors. My name is John Abramic. I'm here on behalf of patent owner, Dartmouth. And with me is my colleague, Jamie Lucia.

JUDGE MITCHELL: Thank you and welcome. So I know we've set forth our procedure in our oral hearing order, but I'll just go over a few reminders at the beginning. So each party has 60 minutes of total time to present argument. And it's very important for the clarity of the record that if

you are referring to a slide or an exhibit, please make sure you give us the number so when we go back and look at the record, we can make sense of it. And also certainly especially for Judge Schneider, who is remote, he won't be able to see what you have here. But certainly we have the demonstratives, and he can follow along. But again, for him, make sure you say what slide number you are on or what you are referring to.

Petitioner has the burden of showing the unpatentability of the challenged claims. So the petitioner will go first to present its argument. And then patent owner will have the opportunity to present its response. And I know I was going to see, petitioner, do you have time that you would like to reserve for rebuttal?

MR. JONES: Yes, Your Honor. We'll probably reserve around 20 minutes for rebuttal.

JUDGE MITCHELL: Okay. I know we have a new procedure for patent owner. You can tell me now or wait for yours if your time -- if you would like to reserve some of your time for sur-reply.

MR. ABRAMIC: Thank you, Your Honor. Our plan was to reserve ten minutes for sur-rebuttal.

JUDGE MITCHELL: With that, petitioner, when you are ready.

MR. JONES: Good afternoon, Your Honors. As I introduced myself before, I'm Brendan Jones. I'm lead counsel for Elysium Health. With me today is Don Ware. So as everyone here knows, we've challenged the validity of all five issued claims of the '086 patent which names Dr.

Charles Brenner as the sole inventor. He was formerly of Dartmouth College.

The '086 patent describes discovery by Dr. Brenner of a new pathway in eukaryotic cells in which the eukaryotic cells are able to convert nicotinamide riboside into nicotinamide. That was a pathway that was previously known to be present in bacteria, but not in eukaryotics as far as the patent describes. This is somewhat important because the NAD+ is known to be a coenzyme involved in a number of biological processes. For example, NAD+ deficiency results in a disease called pellagra. That's a disease that ran rampant through the rural south during the turn of the last century due to a lack of NAD precursors in their diet. There's a version of pellagra of NAD deficiency that's also present in dogs called blacktongue.

Claim 1 of the '086 patent is pretty much as straightforward claim as you could imagine for this kind of case. There's a preamble. There's a pharmaceutical composition. There's a requirement that the composition needs to be formulated for oral administration, that a transition phrase comprising which of course is a term of art which really means including, and then what's in the composition is nicotinamide riboside in admixture with a carrier.

Now, as we'll talk later, this ends up being a very broad claim. Pharmaceutical composition is defined both in the spec and in the dependent claims as including compositions of food. The admixture with a carrier, admixture isn't even used in the spec, but it's general meaning is in mixture with, and a carrier is defined pretty broadly in the spec to include, among

other things, sugar such as lactose. So what's left is the presence of nicotinamide riboside. And as we've shown through various evidence and as was discovered by Dr. Brenner himself, nicotinamide riboside is actually present in milk.

The consequence of this is that a number of studies that occurred in the early part of the 20th century by Dr. Joseph Goldberger, actually, in which he was endeavoring to treat pellagra using milk products such as skim milk and buttermilk actually end up reading on the scope of these claims. In the first one, Goldberger, et al., which was published in 1928, so more than 90 years ago, so I think it qualifies as art under 102(b), this study describes the administration of skim milk to a number of dogs who are otherwise on the blacktongue diet that inevitably results in the dogs getting blacktongue. Most of the dogs that were subjected to this ended up not getting blacktongue. From this, Dr. Goldberger concluded that skim milk contained the pellagra-preventative factor.

A similar study from 1924 also by Dr. Goldberger and Goldberger and Tanner described the treatment of a number of women who were highly susceptible to pellagra with buttermilk. So buttermilk is the form of milk most commonly available in the rural south. It's the byproduct after milk is churned and butter is removed. When these patients were treated with buttermilk three times a day, none of them ended up getting pellagra when it was Dr. Goldberger's experience that under similar conditions in similar populations, you would expect at least half -- about half of them to get pellagra.

Now, the dispute here really comes down to one of claim construction. So oddly, it comes -- involves claim construction of a very innocuous seeming phrase. The phrase is "a pharmaceutical composition comprising nicotinamide riboside." On its face this phrase seems to be very straightforward in its language. As we said, pharmaceutical compositions include compositions such as food. Comprising is just a transition word that usually in the art means including. And nicotinamide riboside is a well-defined molecule in the art. Despite the plain language of this claim being very straightforward, patent owner has proposed a construction in which they have added the limitation that would require nicotinamide riboside to be in the formulation as the active agent.

JUDGE MITCHELL: Counsel, what do we make of pharmaceutical in that preamble pharmaceutical composition? Does that not add some weight to patent owner's argument?

MR. JONES: I don't think so. So pharmaceutical composition, to the extent it is a limiting -- to the extent it is limiting would imply that the composition as a whole has some kind of pharmaceutical property. It doesn't necessarily mean that any particular agent in the pharmaceutical composition has a pharmaceutical -- has a pharmaceutical effect.

JUDGE MITCHELL: But the only thing they have named, at least in claim 1, is the nicotinamide riboside. So wouldn't the assumption be when we're reading this claim, if it's a pharmaceutical composition, that we are talking about that as an active agent, the nicotinamide riboside?

MR. JONES: Your Honor, I think there are a couple problems with that. One is I think pharmaceutical composition more implies the intended use of the composition rather than a specific activity. And we'll get into that because it's not really clear what this nicotinamide riboside would need to be active for under the construction of the patent owner's.

The second problem is if they had intended -- there are all sorts of claims to pharmaceutical compositions that are out there, you can imagine, where, it comprises any kind of thing, a filler, excipient or anything else where it's not the active agent. So just because it's a pharmaceutical composition doesn't mean that the one thing that's named in it has to be the active agent.

And the third thing is, the third problem is saying that it's the active agent makes it really problematic because many pharmaceutical compositions don't have a single active agent. They might have multiple agents that act in congress to each other where neither one of them alone would be sufficient to treat the disease or they may have multiple active agents where there are redundant with each other and if you remove one, it doesn't really change the effect. Either way, even if pharmaceutical composition is a limiting and it would imply it has some kind of health-related activity, then it still wouldn't be sufficient to impose, to incorporate into the argument -- into the construction the limitation that the nicotinamide riboside itself has to be the active agent. At best, it implies that the composition as a whole has to have some kind of activity.

JUDGE MITCHELL: Can I ask you, do you have a position as to whether a pharmaceutical composition is limiting?

MR. JONES: So we haven't taken a definitive position on this because we didn't feel it was relevant to the outcome of the case. I do think this is a classic case where the pharmaceutical composition is describing the intended use of the composition, especially in this context where there's no specific disease or anything listed here. I don't know how you would say that it has -- if you are given just a pill, right, that has nicotinamide riboside in it, you would say, well, is this a pharmaceutical composition? I think, yeah, probably because it's a pill, which is pharmaceutical form of something. But you don't know whether or not it has an activity and might have an activity against some diseases and not have activities against others. When we start importing these activities, these specific activities into it, you are really looking at more method claims. If this was a method of treatment claim, then maybe it would have more weight.

JUDGE MITCHELL: So your position is because it's not naming a particular disease to be treated, then we can't really know whether nicotinamide riboside is the active agent?

MR. JONES: Exactly. And I'll actually jump ahead because I have a couple slides here that actually address this. So this was actually one of the things that we were confused about when we read the initial response by the patent owner. That was if it has to be an active agent, what does it have to be active for. And the response doesn't actually say one way or another what activity this nicotinamide riboside would have to have. So we

asked the patent owner's expert, Dr. Zhou, what does it mean to have an active ingredient. And Dr. Zhou, if you looked at page 31, you see that he's using active ingredient, active agent interchangeably.

JUDGE SCHNEIDER: Counsel, if you are referring to a specific slide, I would like to know.

MR. JONES: I apologize. I'm looking at slide 11 of 54. I jumped ahead and I didn't give you warning. So in this specific question that was asked of Dr. Zhou, what does it mean, active ingredient, Dr. Zhou answered that it exhibits or confers therapeutic or preventive effects. So this still doesn't tell us what preventative or therapeutic effect it needs to be. I don't think someone could look at a pill and know whether or not it exhibits any particular therapeutic or preventive effect. And if you actually look in the specification of the '086 application, it lists all sorts of diseases that could potentially be treated as method of treatment for using the pharmaceutical compositions, but it doesn't give any specific disease and doesn't show any actual treatment.

And when asked whether or not this active agent would require it to be an effective amount in the pill, in other words, whether there would need to be enough of the active agent in the pill, enough of the composition in the pill in order to actually treat the disease, Dr. Zhou confusingly said that he did not think this was part of claim 1 at all.

I can understand why this would be a problem, because as we said, there's no specific disease here. If you are talking about a method of treatment claim, then saying that some compound is the active agent or that

it is an effective amount of it to treat a specific disease, then maybe it's reasonable to have that limitation there because you can actually test, okay, or maybe one of skill in the art would know you need to have this much of the compound in order to treat that disease. But when you are just looking at a pill without any connection with any kind of activity or disease, then whether or not -- I mean, for example, if it would require 10 milligrams of something to treat the disease, then if you had a pill with 10 milligrams, I suppose, would be the active agent. If you had a pill with 5 milligrams, then maybe it wouldn't be an active agent. But then, of course, we are dealing with two pills of 5 milligrams and then maybe you have enough. So when you are talking about a composition of matter, when you start importing these activity limitations into there without defining what the activity is, it renders a claim really nonsensical and impossible to show infringement or anticipation.

JUDGE SCHNEIDER: Counsel, going back to the term "pharmaceutical," I note that patent owner has submitted Exhibit 2004 which is a McGraw-Hill scientific dictionary. And there the definition for pharmaceutical includes a chemical produced industrially for a medicinal drug which is useful in preventive or therapeutic treatment of a physical, mental or behavioral condition.

Now, that would sort of imply that you have got to actually make something up rather than milk which just occurs naturally. How does that fit into your definition that milk is a pharmaceutical composition?

MR. JONES: So first it's pretty clear that even from claim 2 of this which says that the nicotinamide riboside is isolated from a natural or synthetic source that these claims don't actually require the physical or chemical manufacture of any of the agents within here. I think what ends up happening is the claims -- I mean, we need to look at what the patent owner says himself. And in claim 4 he expressly says that it's a formulation that comprises a food. And I think when you look at that and in the specification where it talks about oral formulations can be in the form of food, then I think especially when you are talking about something like this skim milk or buttermilk where there are pieces removed from the food by essentially the hand of man in order to create a different formulation, then you are looking at something that if it's used pharmaceutically, then it could be a pharmaceutical formulation.

And also, I just wanted to add that that definition, I don't think, is really applicable here. And that's a definition for the word "pharmaceutical," which is a noun. That's one thing. I think in this case, a pharmaceutical composition, the pharmaceutical is being used as an adjective to describe the composition itself. In other words, getting the intended use of the composition for pharmaceutical purposes. Not that it necessarily contains a particular pharmaceutical.

JUDGE PAULRAJ: Counsel, you bring up the intended use argument. I mean, one of the well established principles about intended use or at least preamble limitations such as this is that if it does breathe life and meaning into the rest of the claims, it should be given some weight. I'm

having some trouble as to why we should ignore pharmaceutical all together. If the idea here is that you are trying to treat some disease and you said the claims don't require a disease, require any particular disease to be treated, but the specification, the very first paragraph of the specification talks about pellagra and some other diseases, why shouldn't we consider that in the context of interpreting this claim?

MR. JONES: Your Honor, I think it's a very legitimate argument, and I think the case law goes both ways as to whether or not something like this would be a limiting preamble. But my point is not that pharmaceutical composition can't be a limiting preamble. It's not even that it doesn't have a limitation. What's not here is -- I mean, if you look at the language of claim 1 itself which I am going -- I'll just go to our other construction, so slide 7. So pharmaceutical composition comprising nicotinamide riboside. So I'm not trying to read out of this limitation the word "pharmaceutical composition" because as I said, a food can be a pharmaceutical composition if it's being used to supplement someone's diet in order to treat a disease or disorder.

What I'm reading out is that the requirement, the imported limitation that nicotinamide riboside specifically needs to be an active agent in the food. I think if they wanted -- first of all, as I said, I think out of the context of a particular disease, it's impossible to say whether one thing is an active agent or not because whether it's an active agent is going to depend on the context in which it is used.

Secondly, I think the plain meaning of this language dictates that all that is required is a pharmaceutical composition which the composition, maybe it needs to have some kind of at least therapeutic purpose, and that it needs to have within it nicotinamide riboside. There's no nexus that says the nicotinamide riboside needs to effectuate that therapeutic purpose. As I said, this is a claim to a composition of matter. Not a method of treatment. So there's no way to know whether or not in some composition of matter whether a particular compound has a particular therapeutic purpose.

JUDGE PAULRAJ: What is an active agent as you understand it to be in patent owner's proposed construction?

MR. JONES: That's a good question. And I'm honestly not really sure. I can tell you that there are disclosure, there's disclosure throughout the specification where it talks about methods of use where it says a method of use of nicotinamide riboside in order to treat a specific disease and then nicotinamide riboside needs to be added in an effective amount. So in that case I think it makes sense to have there be an active agent there or an effective amount where you have a specific method of treating a particular disease. You can see whether, okay, is this agent actually using to treat that disease.

But in a pure pharmaceutical composition like claim 1 is, devoid of any disease or method of treatment, I don't know if there's any way to say whether something is an active agent. And just to give an example, active agent is, of course, something that's pulled out of pharmaceutical language. When you go to the drugstore, you'll see the active agents in this compound

are this, this and this. In that context they have particular indications they are talking about. So that active agent is attributed to a specific indication. If there's no indication or requirement, there's no active agent -- there's nothing inherently an active agent in a pill.

JUDGE PAULRAJ: So then would you agree that at least under patent owner's construction, nicotinamide riboside is not an active agent and just milk or buttermilk as it occurs naturally?

MR. JONES: No, I don't agree with that either necessarily. I believe that by far the most likely conclusion you would reach from Goldberger or from -- from either of the Goldberger articles is that the nicotinamide riboside in the milk was contributing to the NAD+ biosynthesis in these patients.

JUDGE PAULRAJ: Let me follow up with a question I asked you before. Is what you consider to be an active agent something that contributes to the treatment of some type of disease condition, whether or not it's recognized or highlighted like you would see in a pill bottle or a label? In this case even though we have milk and buttermilk and it's naturally occurring product, is it your position that NR is an active agent because it contributes to the treatment of pellagra or blacktongue? Is that your position?

MR. JONES: Your Honor, I completely agree that in the methods that are being practiced by Goldberger in these examples in which he's actually treating pellagra or blacktongue, then nicotinamide riboside is almost certainly acting as an active agent here based on what we know

scientifically. What I'm saying is that in the actual claims themselves, there's no requirement for an active agent.

JUDGE PAULRAJ: I understand your position that at least the claims don't recite the term "active agent." We are trying to figure out whether pharmaceutical composition would be understood to require the nicotinamide riboside as an active agent. So let me flat out ask you, what is your understanding of active agent? If I were to ask you how do you define active agent, what is your answer?

MR. JONES: So in the context of a specific treatment, I think an active agent is the combination -- is either the individual or combination of compounds that mediate the effect. However, I don't think active agent is applicable to just a pharmaceutical composition devoid of actually being used for something because I don't think -- there's no activity there. It's just sitting there. I don't think there is an active agent in a pill as it sits there on a desk.

And I think part of looking at your question is whether or not nicotinamide riboside needs to be read in as an active agent into this claim. And I think one of the things that's illustrative of this, I'm on slide 8, is there are two uses of the word "pharmaceutical composition" in the body of the '086 patent. In the first one, it doesn't have anything to do with nicotinamide riboside itself. It actually describes using a pharmaceutical composition comprising nucleic acids, including the nicotinamide riboside kinase protein, the vectors containing that or the NRK polypeptides that can be administered to a subject.

So I believe above this comment it also mentions nicotinamide riboside. But this passage does not actually include reference to pharmaceutical compositions comprising nicotinamide riboside.

And the second use is, I think, a little bit illustrative. It says a physician -- it's on the patent in column 31 where it says a physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of a pharmaceutical composition required for prevention or treatment of an animal subject or human. So there are two things. One is this is again talking about the determining what the effective amount of the pharmaceutical composition is in the context of a disease or animal to be treated.

JUDGE SCHNEIDER: Counsel, what about the teachings in column 4 beginning about line 19 where it says that the method involves administering to a patient having a disease or condition associated with the nicotinamide riboside kinase pathway and NAD+ biosynthesis, an effective amount of nicotinamide riboside composition so that the signs or symptoms of the disease or condition are prevented or reduced, doesn't that directly tie the nicotinamide riboside to treating a specific disease and showing that the NR is the active agent?

MR. JONES: Your Honor, in this case it's exactly what I was talking about where they are actually talking about actual therapeutic use of a particular disease where there's an active agent that's in the composition because it's being used for a specific purpose. The nicotinamide riboside, absent anything else, doesn't have an active agent because it's not doing

anything active. It's only when the composition is put to a specific method of use where it's actually curing or treating a disease that any of the agents have any activity. There's no imbued activity.

JUDGE SCHNEIDER: How do you divorce the composition from the method? I mean, here it's talking about a composition that has an effective amount of NR present in it.

MR. JONES: So in the context of the method, it has an effective amount. The problem with effective amount here is that that's going to be a different value depending on what you are trying to treat. So for one disease it's going to be a small amount and another disease it's going to be a large amount. So absent a specific disease, there's no knowing what the effective amount is. The metes and bounds of the claim, you are just given a pill and trying to figure out whether this falls within the scope of the claim. There would be no way of telling whether or not this pill falls within the scope of the claim because there would be no way of knowing whether it has an effective amount unless you know a particular disease to test.

JUDGE SCHNEIDER: So you are saying basically by putting in either active agent or effective amount, you render the claim indefinite. Is that what you're saying?

MR. JONES: Yes. I think if you actually added effective amount into these purely composition claims without a disease or disorder without saying it has to be an effective amount for what, then the claim ends up being meaningless and indefinite. I just don't think looking at the plain meaning of this phrase that there's any need to complicate. So this is a very

straightforward phrase which would have a very bright line test of whether or not something infringes or not. It's a pharmaceutical composition comprising nicotinamide riboside. You look at a pharmaceutical composition, say does this contain nicotinamide riboside? Yes, it falls within the scope of this element; no, it doesn't fall within the scope of the element.

By adding this limitation to active agent, you make something that was inherently very simple and straightforward based on its plain language and make it impossibly complex. And I'll draw your attention to slide number 14 of the demonstratives.

And this was when we were trying to figure out from Dr. Zhou exactly what you would need to do in order to find out whether or not an active agent is in -- whether nicotinamide riboside is an active agent in claim 1. The answer he gives is that that's not -- let's see. It's what they claim or report the activity. Then I need to show the evidence of whether the experimental procedure shows without NR. So he's tying the desired activity to an experiment to show whether it has NR or not. Then he says, There are many, many complicated experiments one has to conduct to see, for example, whether NR and the absence of NR has the same effect or not. It's, you know, hundreds and thousands of experiments one has to conduct, and there's always caveats on how to interpret the data.

I just don't think when you have something as simple as a pharmaceutical composition comprising nicotinamide riboside that there's any need to import a limitation that takes it from a straightforward

construction that everyone would understand and be able to tell whether or not something fell within the scope of and make it this impossibly complex test in which you'd need to do dozens of complicated experiments to try and figure out whether it has activity for any possible disease or disorder. I just don't think if that construction was out there that there would be any way of showing whether or not a particular composition actually falls within the scope of the claims.

I wanted to -- if you have specific further questions, I'm happy to go on, but I also wanted to be able to talk a little bit about isolated during this. And would that be okay for me to move on or is there something else you wanted me to particularly address?

JUDGE PAULRAJ: Is isolated still at issue in this case, counsel?

MR. JONES: I believe isolated is still an issue because claim 2 was --

JUDGE PAULRAJ: We brought that back in after our post-SAS decision; is that right?

MR. JONES: Yes. So of course, I am jumping ahead to slide 44 here. And this is a slide that shows the language of claim 2 which describes -- I built it as an independent form for context. So it has the language of claim 1 and then the added limitation to claim 2 which is wherein, the nicotinamide riboside is isolated from a natural or synthetic source.

So in this case I understand the Board, of course, came out with the construction in its institution decision in which -- here it is on slide 45, the very next slide. So our proposed construction was based on the express

definition of "isolated molecule" in the specification which is that is separated or substantially free from at least some of the other components of the naturally occurring organism. The Board's construction is very similar, except for it adds this limitation such that it constitutes at least 25 percent weight/weight of the composition.

Now, there are a couple -- moving on to slide 46, I pulled out the actual language of the paragraph from which both of these values is obtained. So you can see in the top highlighted part, it says, As used herein, isolated molecule, and then it says, means a molecule separated or substantially free from at least some other components in the naturally occurring system. This is very clearly a definition saying exactly what an isolated molecule means.

Of course, isolated molecules is fairly broad, includes nicotinamide riboside which is, of course, a molecule, as well as polypeptides and nucleic acids.

Later in the paragraph, it says, when the isolated molecule is a polypeptide, said polypeptide is at least 25 percent. So in this the patent owner is -- or the draftsman is specifically saying that if it is a polypeptide, one type of molecule, it's at least 25 percent pure by weight. Implicitly, if only the polypeptide has to be 25 percent pure, then there's no requirement for the other types of molecules to be 25 percent pure. If the idea was that all molecules were 25 percent pure, the sentence would just read an isolated molecule is a molecule that's at least 25 percent pure. If it was all molecules except for nucleic acids, it would say an isolated molecule is a molecule

that's not an nucleic acid that is at least 25 percent pure. This definition does not directly read into the meaning of isolated in the sense of nicotinamide riboside.

JUDGE PAULRAJ: I think we recognized the fact that that sentence, that last sentence does talk about when the isolated molecule is a polypeptide. But as we did note in our institution decision, it does provide some guidance and context about that prior sentence that you have highlighted as to what might be considered separated or substantially free. Why, when we read that paragraph as a whole, shouldn't the skilled artisan take into account, well, it does define isolated molecule means a molecule that is separated or substantially free, now we need to know what's separated or substantially free means? That's a relatively big term. But then two sentences down or the very next sentence, it says at least with respect to polypeptides it needs to be at least 25 percent, 50 percent or more. Why draw a distinction between isolated polypeptide versus isolated nucleotides?

MR. JONES: Your Honor, that's a good question. So if you look at the definition above, it's really about what the isolated molecule is being separated from. It's not about what is a final composition. And there's a reason for this. I think we all know that these patents were drafted in a pre-Myriad world where in order to impose a hand of man onto claims, they would -- petitioners would put in the isolated limitation and say that it's not being surrounded by its natural constituents. That's what it was getting at there.

The reason why when it specifies the polypeptide, very clearly there's a reason why they called out the polypeptide and didn't say all molecules.

And I can also give as another example, so if you imagine, for example, if you have nicotinamide riboside in water and you have 5 milliliters of water and assuming it is soluble enough you have 25 percent by weight nicotinamide riboside so that it's now an isolated nicotinamide riboside is 25 percent by weight, it has nothing else around it that it can be associated with, and then if you add another 5 milliliters of water to that, all of a sudden you have a 12.5 percent nicotinamide riboside in the water by weight. And now if we adopt the construction where the isolated molecule has to be at least 25 percent by weight, even though this is completely separated from all its natural components, you are now looking at something that's no longer isolated from a natural or synthetic source because it's been diluted down below the 25 percent threshold.

I just don't think there's any support in the record for a particular 25 percent threshold for isolation in the context of nicotinamide riboside. I think that is particularly true when you understand that nicotinamide riboside can be -- is contemplated as being formulated for oral administration and including as being orally administered as part of food. I don't think it's particularly reasonable to be orally administering a food that is 25 percent nicotinamide riboside. I mean, I think 25 percent makes context maybe in the context of a pill, but once you get to other forms of oral administration, then because of the type of administration, it no longer

makes sense to have this 25 percent threshold. Did that answer your question?

JUDGE PAULRAJ: Somewhat. I wanted you to kind of -- we haven't discussed examples in the patent. Are there any examples in the patent where just nicotinamide riboside itself was present in an amount less than 25 percent of the composition?

MR. JONES: Yes, Your Honor. There is the discussion of using the fractionated whey.

JUDGE PAULRAJ: In example 2?

MR. JONES: Example 2. And in which -- so whey is, of course, a milk product, and this is how they identified milk as a source of nicotinamide riboside. I think it's pretty safe to say that a fractionated whey composition, especially when you take into account the levels of nicotinamide riboside present in milk based on Trammell I, that it's going to be far below 25 percent.

JUDGE PAULRAJ: That example doesn't actually tell you what the percentage is. Are you just making an assumption here? Where should I look at to say this is teaching me that you can have NR at a percentage less than 25 percent?

MR. JONES: Unfortunately, these examples don't actually give anything about the amount by weight of any of these compositions. And I don't think they even really relate to pharmaceutical compositions at all. Example 1 is just listing strains. Example 2 is talking about nicotinamide riboside weight preparations, which it doesn't say how much is in there, but

based on the small amounts that are -- of nicotinamide riboside that are present in milk and the amount of volume that's actually here in the whey, it seems very unlikely that it is going to be 25 percent. It wasn't a question, so we didn't actually do the calculations coming into the hearing.

The third example is just looking at the yeast library and again doesn't look at -- isn't actually looking for nicotinamide riboside as a pharmaceutical composition. Again, the example 4 is doing -- so example 4 is using 500 micromolar nicotinamide riboside which in 100 millimolar NACL and among other things, I think, I'm pretty sure if you actually set out to do the arithmetic here that 500 millimolar would be far less than 25 percent by weight. NRK gene and CDNA cloning enzyme purification, again, this is just showing that the gene is present in humans. So yeah, there's no express example, but there's also no examples of pharmaceutical compositions being used to treat anything here either.

JUDGE PAULRAJ: Thank you.

MR. JONES: And then the one other point I wanted to make, I'm on slide 48, in the context of isolated, if you actually look at it in the context of just it needs to be separated from some significant amount of something with which it naturally occurs, thereby, for example, imposing the hand of man here, then what we are looking at here is skim milk and buttermilk. I learned much more about dairy sciences during this case than I ever thought I would in my job, but one thing I know is that skim milk is where you remove practically all cream from the milk and you retain the water soluble vitamins including B complex vitamins such as nicotinamide riboside in the

liquid part. And as it points out here, this contains about the same number of calories as the cream itself. So you are actually removing half the caloric content and almost all the cream from the milk in order to produce skim milk, which I think would definitely satisfy the hand of man approach for just looking at whether or not this is a natural product from the old pre Myriad days.

Buttermilk, likewise, you are dealing with churned milk in which the cream, the fatty content is turned to butter and pulled out of the solution and all the water soluble fraction remains. So once again with buttermilk, I think you are again looking at something where a substantial part of its natural environment is being removed from the nicotinamide riboside by essentially a human process, and you are getting away from something that's actually naturally occurring.

So I think both the skim milk that's being administered in Goldberger, et al., and the buttermilk that's being administered in Goldberger and Tanner, both have an actual process by which the nicotinamide riboside is separated from other components of its natural state.

Then I think that's it, unless you have a specific question rather than turning to a new topic. It seems to make sense to reserve my time for rebuttal. But I'm, of course, happy to spend a little bit more of my time if any of you have any particular questions that you would like me to answer.

JUDGE PAULRAJ: I have no questions.

JUDGE MITCHELL: Thank you.

JUDGE SCHNEIDER: I'm fine, thank you.

MR. JONES: Thank you for this opportunity.

MR. ABRAMIC: Good afternoon, Your Honors. My name is John Abramic. I'm here on behalf of patent owner. And my plan today is to talk about claim 1, the issues that surround claim 1, the construction of pharmaceutical composition comprising nicotinamide riboside, both the claim construction and anticipation issues on that claim, and then turn things over to my colleague to talk about the issues with claim 2 and isolated.

And I'm going to start at slide 4. The issue here is the construction of the phrase "pharmaceutical composition comprising nicotinamide riboside." And the real issue here is whether or not the nicotinamide riboside -- which I have been referring to as NR throughout this case, if I say NR, it's because I have learned that as shorthand. And the issue is whether the NR is active in claim 1. And we believe that NR has to be active in claim 1. And petitioners --

JUDGE SCHNEIDER: Counsel where does the word "active" appear in claim 1? It just says comprising. You are asking us to read a limitation into the claims, are you not?

MR. ABRAMIC: No, I don't think I'm asking you to read a limitation into the claims. I'm asking the Board to construe the claims in light of the surrounding claim elements, in light of the specification and in light of what one of ordinary skill in the art would understand about this invention when reading the specification.

You bring up an important point, Your Honor, and that is the issue about the word "comprising," because I'm going to turn to what I think is the

primary argument from petitioner. And this is on slide 5. And their primary argument is the only thing we need to look at is the word "comprising." And they cite the law of comprising and say that comprising means including, and we can stop there. And we don't dispute that the word "comprising" is open-ended. That means the claim can include other elements. So our construction is consistent with the open-endedness of the word "comprising," but I think there are a couple of flaws with petitioner's argument, and that is this notion that all you do is consider the word "comprising" and that law controls and you stop there.

I would like to read something, a quote from a case, a Federal Circuit case. And this is Raytheon versus Sony. And the cite is 727 Fed 662, and the pinpoint is at 672. And in that case the Court, the Federal Circuit acknowledged that comprising means open-ended, but then it said this, quote, But the term comprising does not displace or otherwise allow one to disregard the patent specification. As we repeatedly have emphasized, the claims must be read in view of the specification which is always highly relevant to the claim construction analysis and is the single best guide to the meaning of a disputed term.

So we don't stop the analysis at the word "comprising."

JUDGE SCHNEIDER: So what term imports active ingredient or active agent? If you want to import the term "active agent" in there, what term is in dispute that would import the term "active agent"? Certainly not comprising.

MR. ABRAMIC: Your Honor, I don't believe we are importing any sort of limitation. But I think the reason that active agent is in the claim is a result of the surrounding claim language, both pharmaceutical which isn't -- the technique that petitioners use is they break the claim apart into each of its constituent elements. And when my capable colleague had the claim up, he talked about each individual word, gave it its broadest meaning, and then they stitch it back together. What we need to do, what the Federal Circuit has said is do a claim construction analysis, we need to look at the specification, we need to look at the surrounding claim language. And I'm going to move to --

JUDGE SCHNEIDER: What language do you point to that suggests reading active agent? I mean, pharmaceutical composition in your own specification includes foods, correct?

MR. ABRAMIC: A pharmaceutical can be a food, but that doesn't mean that every food meets the requirements of claim 1.

JUDGE SCHNEIDER: I agree with that. But a pharmaceutical is also something that treats a condition and alleviates it. And milk, as shown by Goldberger, treated and alleviated a condition; is that correct?

MR. ABRAMIC: It did, but we don't know what the active agent was in that milk.

JUDGE SCHNEIDER: But again, where do we find the word "active agent" or what part of the claim do we look to, to import "active agent?"

MR. ABRAMIC: So two answers to that. If you are talking about, Your Honor, what part of the claim, the first is the word "pharmaceutical." We know that the word "pharmaceutical" has meaning. It breathes life and meaning into the claim, but it also provides antecedent basis in the claim. We can't just ignore the word "pharmaceutical." And a pharmaceutical is a compound that provides a therapeutic benefit. There is no dispute there. There was no dispute about that from petitioner.

JUDGE SCHNEIDER: And the milk here provided a therapeutical benefit. So it meets that definition of pharmaceutical; is that correct?

MR. ABRAMIC: No, I don't believe that a milk in and of itself is a pharmaceutical. Certainly it's not --

JUDGE SCHNEIDER: The milk that was used in Goldberger treated or prevented pellagra or blacktongue in dogs. Those are conditions that relate to NAD+, and using that milk, that was the conclusion at least that Goldberger had that it contained an ingredient that prevented or treated pellagra or blacktongue; is that correct?

MR. ABRAMIC: Certainly, but we are not just looking at the word "pharmaceutical" in the claim.

JUDGE SCHNEIDER: I'm sorry, am I correct in my reading of Goldberger?

MR. ABRAMIC: You are correct in your reading of Goldberger that milk was given to dogs and blacktongue was treated. You are correct.

JUDGE SCHNEIDER: And for the second Goldberger which was pellagra.

MR. ABRAMIC: Correct. There is no difference between the two prior arts in our view in terms of the substance of the arguments. The issue is whether the milk in Goldberger or the buttermilk in Goldberger and Tanner meets the requirements of claim 1 and whether or not the NR in that milk was active.

JUDGE SCHNEIDER: Again, where are we reading active into the claim?

MR. ABRAMIC: Okay. So Your Honor, first we know that it's a pharmaceutical composition. We know that a pharmaceutical composition has to have "an active." After pharmaceutical composition --

JUDGE SCHNEIDER: Where is that definition?

MR. ABRAMIC: What is that definition?

JUDGE SCHNEIDER: That pharmaceutical composition has to have "an active."

MR. ABRAMIC: On page 6 or slide 6, there's a citation to expert testimony and also to several references that talk about the fundamental concept that a pharmaceutical has an active ingredient. Because as we've talked about here, a pharmaceutical is something that treats a condition, you need an active in order to treat a condition. And this is not a point that's in dispute in this record.

JUDGE SCHNEIDER: And how do we tie that to saying that NR has to be the active ingredient?

MR. ABRAMIC: So first what we'll do is we'll look at the specification. And we know we have to look at the specification, and the

substance that's identified in the claim after the phrase "pharmaceutical composition" is nicotinamide riboside. And so we need to go to specification to see what the spec says about nicotinamide riboside. And in every instance when you look at the specification, what we learn about looking at the specification is that this is an invention about treating disease with an increase in NAD+. So NAD+ is what's treating the disease. And nicotinamide riboside leads to the increase in NAD+. So nicotinamide riboside is one of the actives identified in the specification that leads to this increase in NAD+.

And when we go to the specification --

JUDGE SCHNEIDER: Milk contains nicotinamide riboside, does it not?

MR. ABRAMIC: Milk can contain nicotinamide riboside.

JUDGE SCHNEIDER: Have you shown any examples where milk does not have NR present?

MR. ABRAMIC: We have not shown a reference where milk -- where nicotinamide riboside was not present. But there has been no reference of record cited where nicotinamide riboside in milk was shown to be active.

JUDGE SCHNEIDER: Well, the question -- that wasn't my question. I'm saying does it show -- you said the milk might not have nicotinamide riboside. My question is was there a reference that says that it is absent in milk? Trammell teaches that it is a component of it and is a precursor of NAD+; is that correct?

MR. ABRAMIC: Trammell teaches that nicotinamide riboside is a component of the milk that was studied in Trammell. But it also establishes that nicotinamide riboside can degrade in milk. And so we don't know whether or not any NR that may have been in the milk of Goldberger ever degraded.

JUDGE SCHNEIDER: Goldberger used fresh milk, though. He says it was milk within 24 hours.

MR. ABRAMIC: That's true, but we don't know how much NR may have been in Goldberger at the outset. What Trammell 1 showed was that there are varying degrees of NR.

JUDGE SCHNEIDER: But there's still NR present even after degrading. It wasn't completely absent in Trammell. It went from like 4 milligrams down to 2 milligrams. So there was still NR present.

MR. ABRAMIC: And that's in the milk that was studied in Trammell. We can't say with absolute certainty that there was NR in the milk in Goldberger and Goldberger and Tanner. But the one thing we also can say is there's certainly no evidence that to the extent there was any NR in the milk of the prior art that it was active. And this gets back to this notion that nicotinamide riboside, every time in the specification that nicotinamide riboside is discussed, it's talked about in the context of administering NR to treat something.

JUDGE PAULRAJ: Counsel, let me ask you the same question I asked petitioner's counsel. How do you define active agent in your proposed construction?

MR. ABRAMIC: An active agent is the substance that's in the composition that leads to the therapeutic benefit. It's the substance in this composition that is leading to the NAD+.

JUDGE PAULRAJ: So when we are talking about this particular composition, therapeutic benefit is the NAD+ biosynthesis; is that right? Increased NAD+ biosynthesis?

MR. ABRAMIC: Correct, because it's the increased NAD+ that is providing the therapeutic benefit, and that's what's disclosed in the patent specification.

JUDGE PAULRAJ: All right. I'll leave it at that.

MR. ABRAMIC: So what we see is every reference, there isn't a single portion or petitioners have not cited a single spot in the specification where nicotinamide riboside is identified as some inactive excipient. It's just not there.

I have just moved to slide 8, and the reason that these portions of the slides or these snippets of the patent specification are here is because petitioner has said ignore these parts of the specification because they use the phrase "effective amount," and effective amount is not in the claims. We agree effective amount is not a limitation in the claims, but that's not a reason to ignore the specification. The fact that the specification is talking about an effective amount of nicotinamide riboside means that the specification is treating nicotinamide riboside as an active, as an active agent. And the definition for effective amount is in the snip on the bottom left of this slide where it says an effective amount of nicotinamide riboside is

one which prevents, reduces or alleviates, it's the amount that you need in order to treat the condition. That's how you talk about an active agent. And there are consistent and repeated references to nicotinamide riboside in this specification, and every time it's talking about --

JUDGE SCHNEIDER: Counsel, is the phrase "active agent" itself ever used in the specification?

MR. ABRAMIC: Yes. So if we go to --

JUDGE SCHNEIDER: Yes or no? Can you point it to me, please?

MR. ABRAMIC: Yes. So I have just picked up slide 10. And so you'll see that at the start of -- and this is at column 28, lines 49 through 67 of the patent. At the top of that section of the specification, there's a listing of what the patent describes as the compounds of the invention, the compounds that are involved in this NAD+ synthesis, and one of them is nicotinamide riboside. And it says that the method of the invention can be conveniently used or administered in a composition containing the active agent in combination with a pharmaceutically acceptable carrier.

And this goes to, Judge Schneider, another one of your questions about what in the claim brings this active agent into the claim. Well, it's not just the pharmaceutical composition. It's the fact that the nicotinamide riboside is an admixture with a carrier. And when we go with the specification -- and on this slide that is the portion of the specification that defines carrier. The highlighting on the bottom of the slide is the actual definition that the Board used to the define carrier. But what we see in the

top portion of this slide is that the composition can contain the active agent in combination with a pharmaceutically acceptable carrier. So you can use a carrier. And the carrier is paired with the active agent in the specification. Why? Because that's what a carrier does.

JUDGE PAULRAJ: Counsel, let me focus on the first sentence in the slide there. So one portion that you didn't highlight there is the word "dietary supplements" and "related prodrugs." So here it does seem to be more narrowly focused on NR in the presence of dietary supplements or prodrugs. How do you -- why is it appropriate to take that statement to apply to any pharmaceutical composition? The claim language is a little broader than what's referenced here; is that right?

MR. ABRAMIC: I'm sorry, I'm not following the question.

JUDGE PAULRAJ: So let me break it down. So where in this paragraph or elsewhere in the specification can you tie the concept of NR as an active agent with the claim term "pharmaceutical composition"?

MR. ABRAMIC: Sure. So if we talk about pharmaceutical composition, and I moved to slide 9 -- and this goes to one of the portions of the specification that talks about pharmaceutical composition, and this kind of goes to petitioner's argument that they only want to look at the portions of the specification that talk about pharmaceutical composition. And if you look at the highlighted text there, it talks about pharmaceutical composition, an effective amount of the pharmaceutical composition. And petitioner says, well, this doesn't say NR, so that's why we can't import NR into the claims.

But if you look up at the top of the specification there, and it's just one paragraph above the highlighted portion, it talks about the compound is administered to the subject in an effective amount. Again, the compound is the active agent that the inventor is using to administer in an effective amount.

And the next sentence says dosages of active compounds can be determined by the methods known in the art. It talks about pharmaceutical composition below in terms of the effective amount of the pharmaceutical composition, and then right in the preceding paragraph, it talks about an effective amount of the compound. Well, the compound of the invention, the compound of the invention are the compounds or the NAD+ precursors, and NR is this NAD+ precursor.

Now, we don't contend that NR is the only active that's identified in the specification. NR is one of the actives identified in the specification, but we are construing claim 1. We are construing claim 1, and in claim 1, NR is specified. And in claim 1, NR is paired with the carrier. And the specification says you use a carrier with the active agent. There's nothing in the specification that says you use a carrier with some inactive excipient. That doesn't make sense. And there's nothing in the specification that says that nicotinamide riboside can be an inactive excipient. So when you look --

JUDGE SCHNEIDER: Counsel, if we accept your definition or your proposed construction that the word "active agent" should be construed in the claim, doesn't the milk in Goldberger still meet that limitation? I mean, granted, Goldberger doesn't specifically talk about NR, but there is

evidence that NR is present in milk. Goldberger does show that it treated an NR-related disorder in an effective amount, so it met that limitation. So why is Goldberger not anticipatory?

MR. ABRAMIC: Because there is no evidence that to the extent that there was NR in the Goldberger milk that that NR was active.

JUDGE SCHNEIDER: But giving the milk to the patient treated the disorder. And NR is the compound that treats that disorder, is it not?

MR. ABRAMIC: It's not the only compound that treats that disorder.

JUDGE SCHNEIDER: What other compounds are present in the milk there that would meet that limitation and would be active?

MR. ABRAMIC: Tryptophan is in milk, Your Honor, and it's one of the identified compounds in the specification as an NAD+ precursor. So --

JUDGE SCHNEIDER: But the relative amounts of tryptophan are relatively low compared to NR; is that correct?

MR. ABRAMIC: I don't believe so, Your Honor. I believe that our expert -- I'm not going to give you an answer to that question, but I don't think that's accurate. But I do know that tryptophan is an NAD+ precursor. And I do know that there is no evidence of record that NR in Goldberger was actually active.

And the Trammell reference, it is undisputed that the Trammell reference on its face says that the nicotinamide riboside in Trammell was bound to another molecule.

JUDGE SCHNEIDER: Doesn't it also recommend further recent research to maximize NR concentration in milk? That would suggest that NR is somehow active in there. Why would you look at something that was inactive in concentration for further research? This is at the last page of the Trammell I reference which is 374 of the document, Elysium Exhibit 107, page 6.

MR. ABRAMIC: Your Honor, that statement is exactly why there is no evidence that the NR was inherently active in Goldberger.

JUDGE SCHNEIDER: Why would you recommend doing further research on NR if you didn't have expectation it is active?

MR. ABRAMIC: There is no actual proof. And what the conclusion was is that we need to look at this more. And there was another conclusion --

JUDGE SCHNEIDER: Why would you look at it more if you didn't have at least a suspicion that it was an active component? If it's inert the way you say it is and that's what Trammell teaches, why would you bother doing any more research on it?

MR. ABRAMIC: Maybe you do have a suspicion, Your Honor, but a suspicion isn't good enough for inherency. Probabilities aren't good enough for inherency. You need to know with absolute certainty that the NR in Goldberger was active. And we don't have that evidence in this case. All we can say is that it might have been active. And what I think I hear Your Honor suggesting is, well, maybe probably it was active. That's not good enough for inherency. And we don't have evidence in this record that

any NR that was in Goldberger or Goldberger and Tanner was active, that it wasn't bound to another molecule and --

JUDGE PAULRAJ: So let me follow up on that, counsel. To the extent that NR in buttermilk or skim milk would not be active, it would only be inactive in the situation where it's spoiled or it's gone bad somehow. Is that right? Is that what the record establishes?

MR. ABRAMIC: No, Your Honor. I think you are talking about the issue of degradation as to whether or not there is NR in the milk. So if the NR has degraded, then I think there would no longer be NR in the milk. But I think what you are driving at is what is the evidence of record to conclude that the milk in Goldberger or any NR may not have been active.

JUDGE PAULRAJ: And fresh milk at that, fresh milk within 24 hours.

MR. ABRAMIC: I'm on slide 22, Your Honor. And this is petitioner's expert's testimony talking about the Trammell reference. And the Trammell reference is the one that shows the NR in the milk was bound to another compound. And the testimony from Dr. Baur is that when you have an active that's bound to another molecule, it can be rendered inactive.

JUDGE SCHNEIDER: It can be rendered inactive?

MR. ABRAMIC: Absolutely, Your Honor.

JUDGE SCHNEIDER: So what you are suggesting is that NR milk, based upon the Trammell reference, is never active?

MR. ABRAMIC: No. What I'm suggesting, Your Honor --

JUDGE SCHNEIDER: Trammell says that NR in milk is bound, so therefore, it's never active?

MR. ABRAMIC: What I'm suggesting, Your Honor, is that Trammell cannot be used to prove that any NR in the 1920s prior art was active. Trammell can't be used to prove that because Trammell shows that NR can be bound in milk.

And we got to talk about the burdens of proof here. I cannot prove that any NR in the prior art was not active. I admit I can't prove that. But they can't prove that any NR in the prior art was active. And that's the issue. It's their burden of proof here, and they've failed to meet that burden.

JUDGE SCHNEIDER: So it all really rests on whether or not we import "active agent" into the claims.

MR. ABRAMIC: For that particular argument, for whether or not the NR in the prior art was active, then the answer to the question is yes. For the issue of whether or not they have established that there actually was NR in that 1920s milk, when it wouldn't depend on whether or not you import "active agent." But I don't think --

JUDGE SCHNEIDER: Wait a minute. If we are not going to import "active agent" into the claims, what is the issue with whether or not milk contains NR?

MR. ABRAMIC: Because there's no proof that there was actually NR in the milk of Goldberger and Goldberger and Tanner. All they have are present day references stating that NR was in the milk that was tested.

I just want to go back and address one of the issues that was raised by petitioners. And I'm on slide 12. This has to do with claim 4. So we have claim 1 there which is the claim we've all been talking about. And then claim 4 is a dependent claim further comprising one or more of tryptophan, nicotinic acid or nicotinamide. And petitioners have argued that our construction of claim 4 is inconsistent with our construction of claim 1.

First of all, we have not proposed the construction for claim 4. And the issue is whether or not those three additional components have to be active or not. They could be active. They don't have to be active. We haven't proposed the construction. Our construction, our argument is that in claim 1, because you have a pharmaceutical composition that identifies NR that's tied to the carrier that in claim 1 nicotinamide riboside has to be the active, but it can include additional components. And so it doesn't matter whether or not the Board were to construe claim 4 to require tryptophan, nicotinic acid or nicotinamide to be active.

Regardless, nicotinamide riboside in claim 1 is an active ingredient. And the specification provides some guidance here. If you look at the portion of the spec cited there, that's from column 28, lines 36 through 48, the first paragraph there talks about an effective amount of nicotinamide riboside. It's talking about a nicotinamide riboside composition. And then the second paragraph there says that you can add some of these other compounds if you want to alter NAD+ metabolism. So you can add those compounds to another compound or to another composition where nicotinamide riboside is the active agent.

And to the extent -- and what petitioners argue is, well, it would be inconsistent to say that the ingredients specified in claim 4 don't have to be active, whereas, nicotinamide riboside would have to be active. And I don't believe that that would be inconsistent because in claim 1, the nicotinamide riboside is the composition that is tied to the carrier. And we saw from the specification that the active agent is the thing that is tied to the carrier. So I don't believe it would be inconsistent for the Board to conclude that the ingredients in claim 4 don't have to be active. But again, I don't think that that is something that needs to be addressed.

But I want to bring up one other thing that petitioner raised. And counsel made a statement that our construction, and our construction is composition containing NR as the active agent, and petitioner said, well, it wouldn't make sense for claim 1 to cover one active agent and only one active agent. And we agree because of the word "comprising," other components could be a part of the claim. We did not intend with our construction to suggest that NR has to be the only active agent. So the reason for the "the" in our construction there is because it's the active agent that is paired with the carrier in the claim. But to the extent that the Board were to read our proposed construction, which is composition containing NR as the active agent, to suggest that claim 1 would only cover a composition where there's a single active agent, then we would propose that the correct construction would be composition containing NR as an active agent.

JUDGE PAULRAJ: Counsel, how do you reconcile your construction and your general arguments with dependent claim 3 and the

specification's reference to food, that the compound can be in the form of food?

MR. ABRAMIC: Sure. I have claim 3 on the screen here on slide 3. So claim 3 is a dependent claim. So claim 3 has to include all of the limitations of claim 1. We know that. And so what claim 3 says is that this pharmaceutical composition of claim 1 can take the form of food. We don't dispute that. But that doesn't mean that all food is a pharmaceutical composition of claim 1. We still have to meet the requirements of claim 1. And one of the requirements of claim 1 is that you have a composition where NR is the active ingredient.

JUDGE PAULRAJ: Give me an example or a food where you would have food that meets your claim construction.

MR. ABRAMIC: Food that meets my claim construction. So there is water that has unbound NR in it in admixture with a carrier formulated for oral administration.

JUDGE PAULRAJ: So where the NR is added specifically to water purposefully?

MR. ABRAMIC: I believe that that's -- you could say that because it says pharmaceutical composition that that is a component of a pharmaceutical composition. And it is something that we kind of made that argument in our preliminary response, but I don't think the Board needs to go that far with its construction because as long as you have NR that's active in the food, you know that it's active, then it's an active agent in that composition.

JUDGE SCHNEIDER: What if milk had been fortified with NR? Let's say we had milk and we add NR to it in an amount -- assume we have a milk that has no NR in it or it's bound or it's inactive, and we take an active amount of NR and add it to milk and then administer it. Would that meet the pharmaceutical composition of claim 1?

MR. ABRAMIC: If the NR that was added was available, right. And it's interesting that you bring that up, Your Honor, because there is an example of that in the declaration that was submitted, and I'm trying to get there, the Brenner declaration. And I'm on slide 30 now. And this is a document that petitioners have said proves that the NR in the milk of Goldberger was active. They cite several articles that establish that unbound NR was active. It increased NAD+.

And this, by the way, a segue here, I don't know how you can say that it would be impossible or indefinite when petitioners are presenting evidence that shows when a certain substance increases NAD+.

But back to the point and the question you asked, Your Honor, and that is all of the references that they cite that showed an increase in NAD+ were compositions where NR was something else. It wasn't NR in milk. And this particular one shown on slide 30, this was Dr. Brenner doing exactly what you suggested, adding NR to milk.

And the top snip is from the reply brief of petitioners. You can see they say Brenner submitted a declaration to the Patent Office during prosecution of the '086 patent's parent application in which he asserted that NR added to milk is bioavailable. And the snip on the bottom of this slide,

you can see that each compound was prepared in 20 milliliters Lactaid milk. He added unbound NR to the milk.

So this reference doesn't prove that NR naturally occurring in milk was active. But if you added unbound NR to milk and established that that increased NAD+, then you have active NR in the composition.

JUDGE PAULRAJ: Is this dependent on your construction of admixture?

MR. ABRAMIC: No. None of this is dependent on the construction of admixture.

JUDGE PAULRAJ: So where do you get the limitation or requirement that you need to somehow purposefully add NR in order to meet your claim requirements?

MR. ABRAMIC: That ties to the sense, Your Honor, that you just brought up in terms of the pharmaceutical composition, does it have to be something that -- a pharmaceutical composition is something that one thinks of as something that is purposefully made. It goes to Judge Schneider's question about an industrially produced chemical. It goes to this notion or this struggle that I think we are all having with how can this claim cover milk. Milk was disclosed in the patent specification as a source of NR, a source from which NR can be isolated. And it was disclosed in the spec. And what we have to do, what Phillips has said what we have to do for claim construction is to get to what the applicant regarded as his or her invention.

JUDGE PAULRAJ: Let me pause you right there because you mentioned the magic case law, Phillips here. Why should we consider Phillips when this is a BRI case?

MR. ABRAMIC: Because Phillips discusses what you look at when you are construing a claim.

JUDGE PAULRAJ: Is this a situation where the claim construction standard might make a difference?

MR. ABRAMIC: I don't think so, Your Honor, because I think in light of all of the specification, in light of all the statements about what NR is doing and it's acting as an active agent, in light of the fact that it's tied in, in the claim with a carrier, I think that under either standard it would be unreasonable to conclude that claim 1 should be read to cover on any compound where NR is some inactive ingredient. There's no support in the specification for that. Even under the broadest reasonable interpretation, you still have to look at the specification. You still have to consider what that specification means.

And I think maybe one of the most telling things to look at -- and I'm on slide 13 now. This is testimony from petitioner's expert. And what we see here is multiple times where petitioner's expert conceded that the active agent in the claims is NR. In the testimony on the left, the line of questioning related to pharmaceutical composition in the claims. And that's clear from earlier pages 16 and 17 of the deposition transcript. And you can see the question and answer, In this case, the active agent would be nicotinamide riboside, correct? Yes.

And the top right snip you have their expert confirming explicitly that nicotinamide riboside is the active agent of claim 1. And petitioners have brushed this testimony off and said, well, that's misleading testimony. They snuck nicotinamide riboside or active agent into the questions. I think it's clear from this record and the fact that it happened three times that it wasn't misleading. These are standalone questions where a person of ordinary skill in the art gave his sense that the claim in the '086 patent was to nicotinamide riboside as an active component.

JUDGE SCHNEIDER: Go back to your discussion about food being a pharmaceutical composition. What about -- and I realize we are talking about a different disorder here, but what about oranges which contain vitamin C which was used before we isolated vitamin C to treat scurvy? Wouldn't that be a pharmaceutical composition? It has an active ingredient, vitamin C, which is used to treat a disorder or prevent a disorder. It's a food. It wasn't added to the orange. It naturally occurs in the orange.

MR. ABRAMIC: But in your hypothetical, Your Honor, that active ingredient that you identified was active. There is proof in your hypothetical that the ingredient that caused the therapeutic benefit was active. And we don't have that in this case.

JUDGE SCHNEIDER: So I think there may be evidence in the record, but we will hear from petitioner on that. But assuming we find that the NR -- we incorporate your word "active agent" into claim 1 and we find that there is evidence that NR is active in milk, wouldn't that meet the requirements of the claim?

MR. ABRAMIC: If you found that there was evidence that the NR, that NR was active in milk, natural milk, not NR added to milk, but then you would still have to say that somehow that evidence that you are talking about, Your Honor, which isn't in this record, but you'd still have to find some way to say that that evidence then proves that the milk that was consumed in the 1920s for those prior art was also active. And those are two gigantic leaps that I don't think you can make based on the law of inherency.

I'm going to turn things over now, unless the Board has more questions. Thank you.

MS. LUCIA: Good afternoon, Your Honors. As Mr. Abramic said, I'm just going to address briefly the "isolated" term. And I have gone to slide 3 briefly. That's the slide where we have all of the claims from the patent. And isolated appears only in claim 2, and it reads, The pharmaceutical composition of claim 1 wherein the nicotinamide riboside is isolated from a natural or synthetic source.

And what petitioner wants the Board to do here is to take back the construction it used in this case and use its broader construction. So let's take a look at the Board's construction which I have here on slide 36. And of course, we discussed this before, but I'll raise it again. The nicotinamide riboside is separated or substantially free from at least some of the other components associated with the source of the molecule such that it constitutes at least 25 percent weight/weight of the composition.

And petitioner's proposed construction, the only difference would be that they would take out the purity level that the Board has added in here,

that 25 percent number. And contrary to petitioner's argument, Your Honors did not misread any portion of the specification, including the portion that I have cited here on slide 36 which is from the patent at page 8, column 9, lines 1 through 12. We've looked at this earlier, but first, this portion of the specification, as I think Mr. Jones even conceded, discusses molecules more generally even though it does identify some exemplary compounds in the paragraph we have here. And even though the 25 percent value that the petitioner objects to discusses polypeptides specifically, I think the Board correctly pointed out that a person of ordinary skill in the art would read this specification more broadly to require some type of purity level for any compound of the particular invention. And I think that's exactly right.

In other contexts, the petitioner has conceded that the patent's discussion of isolated is not so limited as they would like it to be. In their reply, paper 33 at page 16, they even talk about that the patent discusses, quote, isolated molecules, end quote. And again, I think that's right. In order for this to make sense, we have to consider what does isolated mean. How pure does it have to be from the source from which you are isolating it for use in the claimed pharmaceutical compositions.

In any event, the Board's construction already accounts for this difference between polypeptides and nicotinamide riboside, which we'll see on slide 37. So this is just a portion of Your Honors' analysis leading to the construction of isolated. And as Judge Paulraj, you mentioned during Mr. Jones' presentation, you pointed out that the patent does discuss specific purity levels for a single molecule but that a person of ordinary skill in the

art would understand that some minimal level would have to apply to other isolated molecules of the invention. And of course, in this patent, that isolated molecule is nicotinamide riboside.

Now, petitioner had an expert, that expert, Dr. Baur, submitted a declaration in connection with the petition. To the extent petitioner or Dr. Baur had any objection to the Board's conclusion that a person of ordinary skill in the art would read the specification this way, they could have put in an additional declaration and explaining that disagreement and why the Board got it wrong. But the Board didn't get it wrong here and they didn't put in any type of counter declaration to explain why they think that's true.

JUDGE MITCHELL: So are you saying that petitioner then has waived this argument?

MS. LUCIA: I think it was available to them to -- Your Honors were quite clear in terms of how you got from the specification portion that we had on the prior slide 36 and why you drew the conclusion that a person of ordinary skill in the art would read it that way. They had a person of ordinary skill in the art on the payroll. They could have said, well, our person of ordinary skill in the art disagrees with your reading. I think that that's telling. I don't know that I would go so far as to say a waiver, but in the event that they had that opportunity, I think they should have done so.

So what petitioner wants to do is to contort this specification to permit a result where any molecule other than a polypeptide can be less than 25 percent pure. And I'm going to keep on saying this, but a person of ordinary skill in the art, there's no evidence that a person of ordinary skill in

the art would take such a broad reading of either the term "isolated" or the related concept of purity.

I want to address a couple of points that Mr. Jones made on this. He gave a water example, and petitioner has touched on this in their reply claiming that Your Honors had drawn the definition of isolated to be with respect to the ultimate composition. And I think that's a misreading of the Board's construction. So I think that that example that he gave about nicotinamide riboside being in the water, that's a question of how pure the nicotinamide riboside is in the final composition. Whereas, the Board's analysis and the specification is talking about the purity level of the molecule when it's isolated from the source from which you got it. And we'll look at more of that here in a moment.

Second, there was some discussion of a couple of examples, both example 2 and example 4. And I think Mr. Jones mentioned that that example doesn't relate to the pharmaceutical composition. And in fact, I think he mentioned that that particular example is about the method for identifying the source of the nicotinamide riboside. And that, again, I'm going to get into that more and explain why that is not going to be relevant to this question of whether or not there's some disclosure about the purity of nicotinamide riboside. Same thing with example 4. That was about an assay. So it's just not applicable to that particular question.

At the end of the day, we know what isolated can't mean. It can't mean that the nicotinamide riboside that's in milk inside of a cow's udder is not isolated but that when you take it from the cow's udder, that same

nicotinamide riboside in that same milk is now isolated. Now, he gave some examples about removing fat to make the milk, but their broader construction would lead to that same result of the difference between the cow's milk in and outside of the udder.

JUDGE SCHNEIDER: What if we had an example that Goldberger uses skim milk which a fat fraction has been removed? So something has been taken away. So it's not the same as the milk coming right out of the udder. It has been processed to some extent. If there was evidence that the NR was present at 25 percent, and I'm not saying there is, I haven't looked for it, was present at 25 percent, would that still beat your isolating claim?

MS. LUCIA: I mean, it's interesting. I think that Your Honors did actually look for this evidence and found in the anticipation analysis that there was no evidence and that in fact, the evidence was that it was significantly less pure than what the requirement was. But if there is -- if the evidence is showing that you are actually trying to extract the nicotinamide riboside from that composition for use in the pharmaceutical compositions that are claimed here, but again, petitioner hasn't met that burden to provide you any evidence to draw that conclusion.

So I would like to turn back to the specification. I'm on slide 38. And this portion of the specification, again, is still talking about cow's milk. Cow's milk as a source of nicotinamide riboside is no secret. So in column 4, lines 1 through 13, they are talking about that method for identifying a natural or synthetic source for nicotinamide riboside. This is precisely that

method that I was talking about that you were discussing with respect to example 2.

JUDGE SCHNEIDER: How do you reconcile the statement that in one embodiment the natural source is cow's milk with your argument your co-counsel made is that the milk at least in Trammell was bound and wasn't active? Here you are saying I can get what I need by going to cow's milk, but there's no discussion here that says you have to then unbind it to make it active. You are just saying I can get what I need, the nicotinamide riboside, from milk.

MS. LUCIA: The specification has a lot to say about how hard it is to do that. So if we go to slide 39, this portion of the specification is talking about it identifies the types of synthetic sources of nicotinamide riboside where it can get that from various chemical companies. It goes on to say that then you can test natural sources for the presence of nicotinamide riboside, and I think that's precisely what Trammell 1 was doing. They were trying to see, let's take a look at some milk and see which NAD+ precursors are present in that reference, and then they reported that results.

Now, if you wanted to do some additional work, you are going to have to extract those precursors from the milk. So that's what this next highlighted portion is about. It says isolated extracts of the natural sources can be prepared using standard methods. Now, I didn't highlight the rest of that, but this is talking about centrifuging and you are going to fractionate it so that you can remove all the other portions of the milk to get to the actual compound that you're going to use, that compound being NR.

JUDGE SCHNEIDER: Where does it suggest that you have to remove a bound element to the nicotinamide riboside? I don't see that, and saying what we are talking about separating out the NR, but nothing is talking about having to remove the bound compound that your counsel talked about which render the NR inactive.

MS. LUCIA: I think, Your Honor, this is consistent with that. And certainly it's not using those exact words that you are using, but if you are going to take an extract out of the milk, and if what you are trying to get is the specific nicotinamide riboside molecule, and quite frankly, it would probably be more pure than 25 percent if you are going to put it in a pharmaceutical composition, in order to get that molecule out of an extract of cow's milk, you are going to have to do the things that the specification mentions in column 26, line 64 through 27:12, which is, like I said, you are going to have to grind it down and you are going to have to centrifuge it to remove the cellular debris. And so those types of things will -- to the extent your NR is bound to other molecules within the milk, those are the processes to the extent you need to unbind that NR to get just the NR molecule itself.

And if I may, I'm just going to touch on a couple of items here because our time is running short. I'll skip that for you. So let's go to slide 40. So even though the petitioner wants the Board to ignore how a person of ordinary skill in the art would read the specification, even their own expert, Dr. Baur, seems to understand this related concept of a purified precursor. So what I have on slide 40 is from page 10 of Baur's declaration, paragraph 15, where he says that symptomatic cases of pellagra would be treated with

purified precursors. When asked about that phrase at his deposition, he confirmed that purified precursors in the context of this '086 patent meant that the nicotinamide riboside would at least be enriched. What he meant by that was if there were other molecules present in addition to the nicotinamide riboside, they would be, quote, for instance, to compound it into a pill, end quote.

And that's exactly what we have here in the '086 patent claims. In claim 2, we have the pharmaceutical composition of claim 1 wherein the nicotinamide riboside is isolated from a natural or synthetic source. And as Mr. Abramic explained, that nicotinamide riboside is at least an active agent in the pharmaceutical composition of claim 1.

So Your Honors, I see that my time is up. Thank you.

JUDGE MITCHELL: Thank you.

MR. JONES: Thank you, Your Honor. So there are a number of points that my colleagues have raised during their argument that I would like to address now. And of course, to the extent you have any specific questions for me, I, as always, will welcome and be happy to the answer them.

But I thought I would deal with that last point first since it's kind of fresh in our mind as far as isolated. One thing that surprised me that my colleague said was that this 25 percent composition doesn't appear to be -- 25 percent purity doesn't appear to be the requirement for the purity of the final pharmaceutical composition we are dealing with here but needs to be the purity of the composition when it is initially isolated. So to me that sounds like what we are getting at here is a product by a process claim. And

maybe this is a product by a process claim element, that it needs to be isolated from a natural or synthetic source. As you know, for a product by a process claim, in order to practice a product by a process, you need to actually practice the process. But in order to anticipate the product by a process, all you need to do is be identical to the composition of the process.

I ask you that if we had purified the nicotinamide riboside from milk such that it was 25 percent pure in whatever state, maybe it's bound, maybe it's not bound, then you add more components back to it, don't you end up with the exact same thing that you began with? You end up with milk. I just don't think that to the extent this was product by a process claim, I don't think it would cover claims products that are less than 25 percent pure. I don't think that would actually read out the milk in the actual claim because there would be no physical structural difference between the skim milk from which cream is removed and something that was 25 percent pure and then milk is re-added to it.

With respect to the active agent, I just wanted to point out a couple things. First I wanted to just remind everyone that we are dealing with the broadest reasonable construction here. We are construing a pharmaceutical composition comprising nicotinamide riboside to mean that the pharmaceutical composition contains nicotinamide riboside and doesn't have any kind of imported element of the nicotinamide riboside needing to have some specific activity for some particular disease.

JUDGE PAULRAJ: But when you take into account -- let's focus on the word "reasonable" here. And under broadest reasonable

interpretation, it still needs to be reasonable as far as the construction we come up with. Against the backdrop that milk was known forever, skim milk was known probably forever as well, buttermilk was known forever, and the specification expressly references the fact that NR was isolated or obtained from milk, why is it reasonable here to read the claim language in a way that would expressly read on milk that was recognized in the prior art or in the patent as prior art?

MR. JONES: What I don't think that the patentee or the examiner or anyone else had before them were these Goldberger references or the context of pellagra and milk being used in order to treat a specific disease or disorder. So absent that knowledge, putting together that milk, that skim milk would be a pharmaceutical composition probably hadn't occurred to them.

JUDGE PAULRAJ: Well, didn't you just spend the first half of your argument saying how the claims don't require treatment of any particular disease? So if a pharmaceutical composition is just any composition that can include NR, again, if that's how we are supposed to read this claim, I want to go back and say why would it matter whether or not the examiner knew that milk could be used to treat pellagra or any other disease?

MR. JONES: Well, as we talked about, there's the pharmaceutical composition in admixture with a carrier. So there are lots of different parts to this claim. And if you recall, the context where milk was brought up during the prosecution was actually in the prosecution of the parent. And

the way the patent owner got over that claim was to add the limitation wherein the milk -- into the independent claim add the limitation wherein the -- actually, it was the isolated nicotinamide riboside composition increases the NAD+ when orally administered. So that's how they overcame the prior art at that time, and they submitted that declaration that said for the surprising result that nicotinamide riboside is orally bioavailable at the time.

So I don't think milk was ever brought up in the way that you are intending. It's actually brought up only as a side comment where the examiner said, well, nicotinamide riboside would be expected to be orally bioavailable because it's present in milk. And they responded by saying, well, it has this surprising property that's even more bioavailable than nicotinamide, which is the other component in milk. Nicotinamide riboside is 40 percent of the NAD+ precursor in milk and nicotinamide is 60 percent.

And I think we aren't -- I don't think it's legitimate -- I don't think claim construction should be about trying to construe claims in order to avoid the prior art that's before you. The question is in light of the plain language of the claims and in light of the specification, what would be the reasonable construction here? And I think the plain language of the claims is very straightforward and very clear and doesn't call for any kind of added limitation here. There's certainly no express definition of pharmaceutical composition comprising nicotinamide riboside in the spec. There's no disavowment of pharmaceutical compositions where are nicotinamide riboside is not the active agent.

And I would also like to bring to your -- sorry. Was that referring to isolated or active agent?

JUDGE PAULRAJ: You did bring in isolated in terms of your answers, but I was going to raise the point that, well, at least for claims 1 and the other claim 2, it doesn't seem like isolated is at issue. Are you trying to somehow import isolated at this time into your construction?

MR. JONES: I apologize for the confusion. Being up here on the spot, you jumble your words. I was actually referring to the claims of the parent application where milk was brought into it. In that case those claims actually -- the independent claims actually had the word "isolated" in the independent claims. So that's why I brought it up. I was just providing context to the prosecution history.

But I wanted to point out that to the extent that active agent requires, as my colleague said, that it leads to NAD+ increase in order to get that therapeutic benefit, I would like to point out, and I'm on slide 51, that claim 5 actually adds this limitation wherein the pharmaceutical composition increases NAD+ biosynthesis upon oral administration. So if that was actually a requirement for independent claim 1, this dependent claim doesn't really add anything to it because if the nicotinamide riboside in the independent claim increase NAD biosynthesis, then obviously, the composition as a whole would increase NAD biosynthesis.

To the extent you have -- I'm going to address a couple of the slides that the petitioner -- sorry, the patent owner showed before you. And one of them I wanted to address was they raised slide 8, which is the --

patent owner slide 8 which has a bunch of quotes from the specification about the effective amount of administering the composition.

What I would like to point out here is in the upper left-hand portion it's talking about, Moreover, the present invention is a method of preventing or treating a disease or a condition associated with nicotinamide riboside kinase biosynthesis. The method involves administering to a patient having a disease or condition. So once again, when we are talking about an effective amount or active agent, we are actually talking about a method of treatment claim. We are not talking about a composition of matter claim and just reinforces the point that without actual treatment, there is no active ingredient. It doesn't really mean anything.

If you look at the passage to the right which is from page 17 of the patent, 27:60-28:15, it again talks, Thus -- in the middle, thus, the present invention is further a method of preventing or treating a disease or condition with the nicotinamide riboside kinase pathway by administering an effective amount of nicotinamide riboside composition. So once again, talking about the effective amount in the context of treating a disease.

If you look at the lower left-hand panel which talks about an effective amount of nicotinamide riboside, it talks about it being the effective amount that prevents, reduces or alleviates or eliminates signs or symptoms of the disease or condition being prevented or treated. So once again, they are tying the effective amount to the disease or condition to be treated.

One of the things that really brings home this point is that it points out that such signs and symptoms can be evaluated by a skilled clinician before and after treatment with nicotinamide riboside to evaluate the effectiveness of treatment regime, and dosage can be adjusted accordingly. So what we are looking at here is the reason the effective amount is so tied to the method is because of the amount of this compound that is in the drug is going to depend on what is actually being treated.

This gets brought home in the next slide they presented, slide 9, where they took -- where we talked about the physician on the bottom, the highlighted passage we cited to the physician determining and prescribing the effective amount of the composition, and they added this paragraph above. But you'll notice it starts out, In the particular embodiments a compound is administered to the subject in an effective amount as the term is defined herein. So once again, they are talking about the effective amount being tied to the actual administration in order to treat.

You'll even see in the middle of this it talks about the effective dosage level will depend on a variety of factors, including the activity of the particular compound the present invention employed, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the duration, so on and so forth. So once again, you are talking about if it's an effective amount or an active agent, it's only active or effective depending on what is being treated. That term should only be applied to method of treatment claims. It

doesn't make sense to have there be an effective amount in the composition of matter claims.

I just wanted to finally point out the next slide, which is slide 10, which refers to these polypeptides, nucleic acids, dietary supplements, nicotinamide riboside, and it says that they can be conveniently used and administered in the composition containing the active agent or in combination with a pharmaceutically acceptable carrier. So two points here. One is that this isn't a requirement that these compounds be the active agent. This is saying that they can be used or administered in the composition. That's a permissive phrase. It doesn't say that all compositions need to have these as active agent. It's saying that they can be the active agent in a composition. Then of course, this also is tied to the use or administration of the composition, which means it's also tied to a specific method of treatment.

JUDGE SCHNEIDER: Counsel, I have a question relating to patent owner's argument relating to active ingredient. Do you have any evidence in the record, whether it be the Trammell or others that shows that the NR that's in milk is active or is metabolized to be an active agent?

MR. JONES: That's a good question. The fact is that before this case started, I don't believe anyone has ever suggested that the nicotinamide riboside in milk would be inactive. No one suggested that nicotinamide riboside in milk would not be present in any case. As you saw in Trammell, all the samples of milk had nicotinamide riboside, including the raw milk that was actually staphylococcus aureus positive. Even though there's positive for the bacteria, there's still nicotinamide riboside in there.

Now, as far as whether or not it has an active agent, it is functionally. You saw in Trammell that the -- well, you actually pointed out the language. They directly suggested that you would use -- that the binding of the compound to the active agent -- binding of the compound to nicotinamide riboside would actually protect it and convey benefits for it therapeutically.

And I'll also point out that --

JUDGE SCHNEIDER: Well, I'm looking at your slide 34, which is the second Trammell article.

MR. JONES: Yeah. So the second Trammell article, again, it shows that their belief that the NR is present is both present in milk and that the nicotinamide riboside is actually active in the treatment of pellagra. You'll see that it says dietary NAD+ precursors, which include tryptophan and the three vitamins -- and the three vitamins are nicotinic acid, nicotinamide and nicotinamide riboside -- prevent pellagra. So in this, Dr. Brenner, the inventor on this patent, is attributing the presence of these vitamins in milk to the actual treatment of pellagra.

JUDGE SCHNEIDER: It says milk is a source of NR.

MR. JONES: Yeah. And then I also wanted to point out on slide 35, so this is actually pulled from one of the parties-in-interest. ChromaDex is filing for their nicotinamide riboside product. It's for their GRAS, which is generally recognized as safe, FDA filing. So this is a filing to the FDA where they try and show that their dietary supplement is safe for consumption, and this is part of the evidence that they present for it. They

show that humans are exposed to NR via dietary sources such as milk. They point out that NR is the second-most abundant NAD precursor in milk after nicotinamide where NR levels in milk do not change significantly when milk is stored at room temperature for 24 hours. Thus, the estimated amount of NR ingested in humans is the equivalent of 710 milliliters per day. Three cups of cow's milk is about 545 micrograms per day. Now, if NR was completely inactive in milk, then how would this at all be relevant to the safety of NR administered to humans?

And finally, I would just like to point out, if you take a step back and take a look at the big picture, milk is an oral substance that's excreted by mammals in order to feed their young to provide nutrition. The reason why substances are present in milk is so that they can be passed on to their offspring when they are eating. It makes absolutely no sense for the mother to have inactivated NR present in their milk in order to convey any benefit to their child. I mean, honestly, this whole thing about nicotinamide riboside being inactive is not present in the art. There's no real reason to believe this is true. This is just a manufactured argument that's put together because otherwise you are looking at a direct anticipation by milk.

And big picture, I firmly believe that the broadest reasonable scope of this claim does not require the nicotinamide riboside itself to be the active agent in the pharmaceutical composition in which case whether or not it's bioavailable in the milk is a side show and a red herring and doesn't make sense.

Finally, I just wanted -- they brought up a number of slides where -- slides of a bunch of quotes from Dr. Baur's deposition in which -- about the active ingredient. And I just wanted to -- active agent. So I wanted to point out two things. All those quotes were talking in the context of Goldberger. So, yeah, Dr. Baur was saying that it was his opinion that in the context of Goldberger in these claims, nicotinamide riboside is an active agent. And none of those questions directly asked him, do you believe that claim 1 requires nicotinamide riboside to be an active agent. That question just wasn't asked. They could have asked that question if they wanted to.

And when they actually started talking to him about this activity with respect to claim 5, the one claim that actually does require some activity which is NAD+, he explained, I believe the sentence says -- he makes two different statements, one that nicotinamide riboside is contained in milk, and two, that milk increases NAD biosynthesis after administration but it doesn't require that the nicotinamide riboside be the reason for the increase. So Dr. Baur was very clear about his belief that there is two separate things here. One is that the milk itself increases the NAD biosynthesis and the other is that NR is present in milk and that the claims didn't require that NR be the reason for this increase.

I see I have about 30 seconds more and I just wondered whether or not there were any other specific issues I could address for you or clarify.

JUDGE MITCHELL: I do have a quick question. So if we say that the NR has to be active, we adopt what patent owner is saying, aren't you sort of turning an inherency argument on its head? You are saying,

well, there's nothing that says that this is not active in milk. But isn't it really your burden to show with inherency that, yes, it necessarily has to be an active agent in milk?

MR. JONES: Your Honor, I believe that our burden is by the preponderance of the evidence we need to show that the -- okay, assuming that you require the activity in milk, by the preponderance of the evidence we need to show that the nicotinamide riboside is necessarily active in milk. I think if you look at all the evidence as a whole, everything would lead one to believe that the nicotinamide riboside is active in milk. When you look at how the inventor himself is treating milk, how the parties-in-interest are classifying milk, how it's being classified in the art, and if you look at just the whole purpose of milk, I think if you take all that together, more likely than not by the preponderance of the evidence, nicotinamide riboside is necessarily active in milk.

JUDGE MITCHELL: Thank you.

MR. ABRAMIC: Your Honors, I would like to start with that last point that counsel just made, and that is the burden of proof and inherency. And I think the statement that he made was when you look at all of the evidence, that you would believe that the NR that may have been present in Goldberger was active. And I just want to show some more testimony from Dr. Baur.

And this is slide 31, and these are portions of his testimony talking about Goldberger, and these are from pages 15 and 16 of his deposition transcript. And the question is put to him, So the nicotinamide riboside in

milk is the ingredient that's increasing NAD+ biosynthesis in your opinion; is that correct?

I don't think that's proven.

Then down below, So you don't know what is increasing the NAD+ biosynthesis in the Goldberger reference?

No.

There is no proof that the NR in Goldberger was active and was increasing NAD+ biosynthesis. If all of this evidence were out there that would lead one of ordinary skill in the art to truly believe that the proof was there that the NR in the Goldberger reference was active, the response to this question would have been different. It would have been, well, yeah, I have got all these different references that talk about NR as a supplement in milk, and from that I can draw this conclusion that the NR in the Goldberger milk was active in increasing NAD+. But we don't have that.

JUDGE PAULRAJ: Counsel, under what circumstances would you have NR in milk not being active? Could you kind of describe how frequent or how unusual that would be?

MR. ABRAMIC: I don't have numbers for you, Your Honor, but what we do is we have the testimony from their expert that we showed previously where his response to the question -- and we know that NR is bound in milk. We know that from Trammell. And what Dr. Baur told us, and I'm on slide 22, is that there are molecules that exist that can inactivate compounds. And the answer was, I don't know whether or not the molecules that are in milk are inactivating NR. I certainly can't put a number on it, but

all we need is a possibility to defeat inherency. All we need is a possibility that that NR might not have been active.

JUDGE PAULRAJ: Isn't there case law saying that inherency can be defeated by just these outlier situations is really unusual circumstances? That wouldn't necessarily defeat inherency.

MR. ABRAMIC: But I don't think we have an outlier situation here. What we have is petitioner bringing us references from the 1920s and they are making a leap that there was NR in milk from the 1920s based off of references that are contemporary.

JUDGE PAULRAJ: Has milk changed since the 1920s?

MR. ABRAMIC: We don't have evidence in the record. It's not our burden to establish what was in milk in the 1920s. We have testimony from our own expert, and this wasn't cited in the documents, talking about how even in cold milk you can have NR degrade, and milk processing was different back then. So I'm not saying this is part of the record. We didn't cite it, but it would have been their burden. If they want to show that milk from 1920 was active, they would have had to establish -- and they want to use present day references to establish that milk back then had the same components and the same activity as milk present day, there should have been a record established to link it together and to do a better job of establishing it. Or maybe there's some other prior art reference they could have brought, but they chose this reference from the 1920s. And the evidence that they brought to establish that NR was active was a reference,

Trammell, that said that NR was bound to other compounds. And they have an expert who clearly admits that that can render NR inactive.

JUDGE PAULRAJ: Can you address the claim differentiation argument with respect to claim 5. If claim 5 specifically requires that the composition increase NAD biosynthesis, why should we incorporate that limitation, that activity limitation into claim 1?

MR. ABRAMIC: I think it's a very fine distinction, Your Honor. I think that with claim 1, you have to have an active compound that's active that's available to increase NAD+. Whereas, with claim 5, you actually have to have that increase in NAD+.

JUDGE PAULRAJ: What does that mean? What is available to increase NAD+?

MR. ABRAMIC: Available means to be in a state that if put in the body will lead to an increase in NAD+, because you don't know with a composition whether or not -- if you are just looking at a pill, you don't know whether or not you can have an active component. But with claim 5, you have an actual requirement that the NAD+ be increased.

JUDGE PAULRAJ: Is bound NR something that might be available even if it's bound to increase NAD biosynthesis?

MR. ABRAMIC: I think the testimony is that bound NR could increase NAD+ biosynthesis, but we don't know whether or not it could.

JUDGE SCHNEIDER: Sorry. Finish, counsel.

MR. ABRAMIC: The answer to the question is it could, I believe. We just don't know.

JUDGE SCHNEIDER: How do you reconcile that with Exhibit 1008, petitioner's slide 34 and slide 35, which is Exhibit 1023 that talk about milk being a source of NR, that NR is a precursor for NAD+? So if it's a source and it's bound and it's inactive, why would it be a source of that?

MR. ABRAMIC: Because it's a source from which you can extract isolated NR and obtain NR that is then active.

JUDGE SCHNEIDER: They are saying humans are exposed to NR by drinking milk. So why would you be concerned about exposure to NR if it's inactive?

MR. ABRAMIC: Well, you might be exposed to NR that's active or inactive. It doesn't necessarily -- just because humans --

JUDGE SCHNEIDER: Why in an FDA filing, if it's inactive, why would you be concerned about exposure to a compound that doesn't have any effect?

MR. ABRAMIC: I'm sorry, Your Honor, I'm not following.

JUDGE SCHNEIDER: In the FDA filing that's Exhibit 23, they talk about humans being exposed to NR in dietary sources and say it is the second-most abundant NAD precursor in milk after nicotinamide. If it's inactive, why would you even be worried about it, the exposure level of it?

MR. ABRAMIC: I think there is an assumption there that in milk, in some milk NR may be active, but there's no proof of it. And that's the issue that we have here. The issue is if there was NR in Goldberger and Goldberger and Tanner, was it active? And we just don't have proof there.

And an FDA statement today, a general statement about milk being a source of NR doesn't get you there. It doesn't give you that proof.

And that's all I have, Your Honors, unless there are other specific questions.

JUDGE PAULRAJ: Nothing.

JUDGE MITCHELL: Nothing for me.

MR. ABRAMIC: Thank you.

JUDGE MITCHELL: Thank you both so much. And this case is submitted.

(Whereupon, the proceedings at 3:08 p.m., were concluded.)

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