

EXHIBIT 16

McLawn, Ronald W.
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5/17/2007

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

AMGEN, INC.,

Plaintiff,

v.

Civil Action No.
05-CV-12237-WGY

F. HOFFMANN-LA ROCHE, LTD.,
a Swiss Company, ROCHE
DIAGNOSTICS GmbH, a German
Company, and HOFFMANN-LA
ROCHE, INC., a New Jersey
Corporation,

Defendants.

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DEPOSITION OF RONALD W. MCLAWHON, M.D., PH.D.

SAN DIEGO, CALIFORNIA

MAY 17, 2007

(This transcript
contains testimony
designated confidential as
per Section 5(c) of the
Amended Protective Order.
Please treat the entire
transcript in accordance
with the protective order.)

Reported by: Harry Alan Palter, CSR NO. 7708

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1	A.	It could be immunologic	09:10:24
2		reactivity.	09:10:31
3		It could be biologic activity,	09:10:32
4		as measured by various methods -- a bioassay,	09:10:35
5		an in vitro assay.	09:10:42
6	Q.	Anything else?	09:10:46
7	A.	Those are the primary methods.	09:10:46
8	Q.	What methods would be used to	09:10:51
9		measure immunological reactivity?	09:10:53
10	A.	There are a variety of methods	09:10:56
11		at this point available.	09:10:58
12		Radioimmunoassay, historically.	09:11:00
13		More recently, enzyme-amino	09:11:02
14		assays or enzyme-linked amino assays.	09:11:06
15		There are chemoluminescent	09:11:09
16		amino assays available.	09:11:12
17		A variety of immunoassay	09:11:14
18		formats that can detect immunoreactive.	09:11:18
19	Q.	And when you say	09:11:28
20		"immunoreactive," what do you mean by	09:11:29
21		"immunoreactive"?	09:11:31
22	A.	That there's a specific epitope	09:11:32
23		or sequence, through three-dimensional	09:11:39
24		quaternary structure of erythropoietin that's	09:11:46
25		recognized by an antibody; an antibody that's	09:11:49

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1	used as a reagent in those immunoassay	09:11:54
2	systems.	09:11:58
3	Q. The specific epitope that's	09:12:01
4	recognized, would that change, depending on	09:12:03
5	the antibody?	09:12:07
6	A. Yes, it could.	09:12:07
7	Q. Let's focus on RIA.	09:12:13
8	What types of antibodies are	09:12:18
9	used in RIA assays?	09:12:19
10	A. Variety of antibodies are used.	09:12:22
11	Polyclonal, monoclonal,	09:12:26
12	different species.	09:12:28
13	Q. And would those recognize	09:12:32
14	different epitopes?	09:12:34
15	A. They could.	09:12:35
16	Q. Would it make a difference	09:12:39
17	between the assays if they recognize	09:12:40
18	different epitopes?	09:12:44
19	DR. FLOWERS: Objection.	09:12:45
20	Vague and ambiguous.	09:12:45
21	BY DR. CARSON:	09:12:48
22	Q. Well, would there be any impact	09:12:48
23	in comparing one radioimmunoassay to another	09:12:50
24	if you used two different antibodies that	09:12:53
25	recognize different epitopes?	09:12:56

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1	DR. FLOWERS: Objection.	09:12:59
2	Calls for speculation.	09:12:59
3	THE WITNESS: Again, I would be	09:13:03
4	speculating on that. I -- I just --	09:13:04
5	BY DR. CARSON:	09:13:07
6	Q. So you have no opinion, one way	09:13:07
7	or the other?	09:13:12
8	A. (No audible response).	09:13:12
9	Q. You have to answer audibly.	09:13:12
10	I'm sorry.	09:13:13
11	A. Yes.	09:13:14
12	Q. The -- now, the immunoreactive	09:13:16
13	assays that you named, do they tell you	09:13:23
14	anything about the biological activity of the	09:13:26
15	sample that you're measuring?	09:13:28
16	A. Not directly, but they can	09:13:29
17	provide an indirect measure.	09:13:35
18	Q. An RIA assay, does that tell	09:13:37
19	you anything about the biological activity of	09:13:40
20	the sample that you're measuring?	09:13:42
21	A. Again, it can provide an	09:13:46
22	indirect measure.	09:13:51
23	Q. And when you say "an indirect	09:13:52
24	measure," what do you mean?	09:13:54
25	A. Any immunologic assay would be	09:13:55

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1	tied to the use of some type of standard or	09:14:00
2	calibrator.	09:14:04
3	Most of those standards or	09:14:05
4	calibrators are, in fact, traceable back to a	09:14:07
5	biological assay.	09:14:11
6	Q. Now, when you say it's tied to	09:14:17
7	a standard or a calibrator, what do you mean?	09:14:22
8	A. There is erythropoietin	09:14:24
9	preparation that is used that has been	09:14:29
10	assayed, or tested, either directly in a	09:14:31
11	biological assay or bioassay, or against a	09:14:37
12	previous preparation that has been tested	09:14:42
13	against biological assays.	09:14:45
14	So it's reference to that	09:14:47
15	material, and there's known activity	09:14:49
16	associated with that.	09:14:52
17	Q. And when that procedure is	09:14:54
18	done, what type of value does that give you?	09:14:57
19	Is that what's referred to as	09:15:00
20	"specific activity"?	09:15:02
21	A. That's what -- no.	09:15:02
22	That's what's referred to	09:15:04
23	typically as "units."	09:15:06
24	Many times it's portrayed as	09:15:07
25	"units per milliliter."	09:15:10

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1	Q.	Just so I --	09:15:12
2	A.	Or "milliunits per milliliter."	09:15:13
3	Q.	And what does that "units per	09:15:17
4		milliliter" refer to?	09:15:22
5	A.	That would refer to that	09:15:23
6		preparation's ability to produce a certain	09:15:25
7		effect -- again, traceable, maybe directly in	09:15:30
8		a biological assay or traceable back to that	09:15:36
9		biological assay by looking at other	09:15:40
10		materials that have been compared to the	09:15:42
11		biological assay.	09:15:45
12		So typically, at this point,	09:15:49
13		most of these standards are traceable to a	09:15:51
14		World Health Organization preparation of some	09:15:56
15		type.	09:16:07
16	Q.	So it's traceable to a	09:16:07
17		biological activity?	09:16:09
18	A.	Hmm-hmm.	09:16:09
19	Q.	Now, would the biological	09:16:17
20		activity that the standards can be traced	09:16:19
21		to -- would that be the same in each case,	09:16:23
22		for every standard?	09:16:25
23	A.	Could you rephrase that	09:16:26
24		question?	09:16:29
25	Q.	I'm just trying to figure	09:16:30

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1	out -- you said that the standard could be	09:16:31
2	traceable to a biological activity.	09:16:34
3	A. Hmm-hmm.	09:16:36
4	Q. So when you say that, what do	09:16:37
5	you mean that it can be traceable to a	09:16:41
6	biological activity?	09:16:43
7	A. This material has been tested	09:16:45
8	in some way, either directly or indirectly,	09:16:50
9	in a bioassay system, polycythemic mouse	09:16:52
10	system.	09:16:57
11	Q. And so what type of a number do	09:16:58
12	you get from that?	09:17:01
13	Just units per --	09:17:03
14	A. It would be units.	09:17:04
15	Q. -- units per ml?	09:17:06
16	A. Hmm-hmm.	09:17:07
17	Q. Now, you also said that -- what	09:17:25
18	types of assays would be available to	09:17:35
19	determine the biological activity of an	09:17:37
20	erythropoietin sample?	09:17:41
21	A. The classic one is the	09:17:43
22	polycythemic mouse.	09:17:46
23	Q. Are there any others?	09:17:52
24	A. That's the one that has been	09:17:55
25	used most often.	09:17:58

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1	Q.	And what units or what	09:18:00
2		designation would the activity that was	09:18:05
3		generated from a polycythemic mouse assay be	09:18:08
4		designated in?	09:18:11
5		How would you refer to the	09:18:14
6		results that you would get from a	09:18:15
7		polycythemic mouse assay?	09:18:16
8	A.	Again, it would be the use of	09:18:19
9		units.	09:18:23
10	Q.	So it would be units per ml,	09:18:23
11		again?	09:18:25
12	A.	It could be units per ml, yes.	09:18:25
13	Q.	In running an RIA assay today,	09:18:31
14		in order to generate units per ml, would you	09:18:53
15		need to have a standard?	09:18:59
16		DR. FLOWERS: Objection.	09:19:01
17		Vague and ambiguous.	09:19:01
18		THE WITNESS: Again, could you	09:19:05
19		rephrase that question?	09:19:06
20		BY DR. CARSON:	09:19:08
21	Q.	If you were running an RIA	09:19:08
22		assay today, in order to generate a measure	09:19:10
23		in units per ml, would you need to have some	09:19:13
24		sort of a standard to correlate your RIA	09:19:15
25		results against?	09:19:18

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1	against.	16:59:51
2	So it could be in milligrams or	16:59:51
3	it could be grams. It could be millimoles,	16:59:54
4	too.	16:59:58
5	Q. If you ran an unknown against a	16:59:59
6	standard that was calibrated in terms of mass	17:00:02
7	and the urine in that sample was not pure,	17:00:07
8	would that give an accurate reading as to the	17:00:11
9	mass of the unknown?	17:00:14
10	A. So long as the material in	17:00:16
11	there is immunoreactive in the same way that	17:00:18
12	it is to the standard.	17:00:21
13	If it's not, then you	17:00:25
14	potentially would have an issue.	17:00:27
15	One makes the assumption that	17:00:33
16	whatever you're measuring is an unknown is	17:00:35
17	equally immunoreactive. You draw those	17:00:38
18	conclusions.	17:00:44
19	Q. Now, if these calibrations	17:00:47
20	we're talking about, are these already done	17:00:50
21	for you in connection with the type of kit	17:00:53
22	that you use to generate the results that	17:00:54
23	were provided in McLawhon Exhibit 1?	17:00:57
24	A. Yes.	17:01:00
25	Q. Okay.	17:01:01

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1	A.	The manufacturer supplies them	17:01:02
2		and assigns the values.	17:01:06
3		DR. CARSON: I'll ask the	17:01:31
4		reporter to mark as Exhibit 27 a	17:01:32
5		publication by Dr. Sherwood and	17:01:38
6		Goldwasser entitled "Radioimmunoassay	17:01:42
7		For Erythropoietin."	17:01:45
8		(Exhibit 27 marked)	17:01:47
9		BY DR. CARSON:	17:02:19
10	Q.	Dr. McLawhon, the reporter's	17:02:20
11		placed before you what's been marked as	17:02:22
12		McLawhon Exhibit 27.	17:02:26
13		Is this a document you	17:02:27
14		considered in connection with coming to your	17:02:28
15		expert opinion reflected as McLawhon	17:02:30
16		Exhibit 18?	17:02:37
17	A.	Yes, it is.	17:02:46
18	Q.	What's reported in this paper?	17:02:49
19	A.	This is a description of the	17:02:53
20		radioimmunoassay for erythropoietin using	17:03:01
21		human urinary erythropoietin as the	17:03:04
22		immunogen.	17:03:09
23		And human erythropoietin as the	17:03:12
24		tracer and its primary standard.	17:03:16
25	Q.	Now, is this the -- was	17:03:31

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1	Dr. Goldwasser the individual who established	17:03:38
2	RIA to be used in assaying EPO samples?	17:03:42
3	A. He's one of the earlier	17:03:48
4	leaders, yes.	17:03:50
5	Q. If you could direct your	17:04:21
6	attention to McLawhon Exhibit 18 -- I'm	17:04:23
7	looking at paragraph 96.	17:04:26
8	You state there, "The unit was	17:04:43
9	originally designated by Dr. Goldwasser and	17:04:45
10	his colleagues to represent a selected amount	17:04:49
11	of erythropoietic activity, i.e., a certain	17:04:51
12	degree of erythropoietic response in a	17:04:55
13	'starved' rat equivalent to the response	17:04:58
14	solicited by the administration of five	17:05:01
15	micromoles of cobaltous chloride."	17:05:03
16	So as designated by	17:05:09
17	Dr. Goldwasser, did the unit refer to	17:05:13
18	biological activity?	17:05:17
19	A. It was an <u>arbitrary</u> unit based	17:05:18
20	on the biological activity in the starved	17:05:24
21	rat, at that time.	17:05:26
22	It was later, then, adopted by	17:05:28
23	international committees as the standard --	17:05:30
24	as the unit of measure that is subsequently	17:05:33
25	referenced in later publications.	17:05:38

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1	So at some point, it started	17:05:43
2	out as an arbitrary unit because there was	17:05:44
3	nothing prior to that, and then this became	17:05:47
4	the definition for the unit -- now it was	17:05:48
5	accepted as a convention for biological	17:05:52
6	activity.	17:05:54
7	Q. You go on to state, however,	17:05:56
8	once that unit was agreed upon by the	17:05:58
9	international community to represent an EPO	17:05:59
10	activity or concentration in an RIA in vitro	17:06:03
11	or in vivo bioassay, it was no longer	17:06:05
12	arbitrary and misleading to call it	17:06:09
13	arbitrary.	17:06:12
14	What's the difference between	17:06:12
15	an EPO activity or a concentration in an RIA?	17:06:13
16	A. There would be no difference.	17:06:16
17	You're talking about a	17:06:20
18	concentration measure that's representing	17:06:21
19	activity per <u>units</u> of volume, units in	17:06:25
20	milliliters or liters, if you look at the	17:06:28
21	publication.	17:06:34
22	So it is a concentration	17:06:37
23	measure, in this case, using the reference	17:06:39
24	standard material that was in units.	17:06:42
25	Q. So "EPO activity" or	17:06:45

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1	"concentration in RIA" refer to the same	17:06:49
2	thing?	17:06:50
3	A. Hmm-hmm.	17:06:50
4	Q. Now, if you could direct your	17:06:57
5	attention back to McLawhon Exhibit 27, the	17:06:59
6	second page, which is page 866, under	17:07:04
7	"Bioassay Methods."	17:07:11
8	The last line of that section	17:07:14
9	says, "A unit of EPO is defined as the	17:07:16
10	activity contained in 1/10 of an ampule of	17:07:19
11	the international reference preparation."	17:07:22
12	What does that refer to?	17:07:25
13	A. (Examining document) This would	17:07:35
14	be 1/10 the ampule of the international	17:08:01
15	reference preparation and, and at that time,	17:08:04
16	that would be the -- it would be the second	17:08:08
17	international reference preparation.	17:08:14
18	Q. So that's referring to the	17:08:17
19	<u>second</u> international reference preparation?	17:08:19
20	And that international	17:08:25
21	reference preparation -- strike that.	17:08:27
22	So when Dr. Goldwasser stated	17:08:38
23	that a unit of EPO is defined as the activity	17:08:41
24	contained in 1/10 of an ampule of the	17:08:44
25	international reference preparation, isn't he	17:08:47

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1	defining unit as "activity"?	17:08:50
2	A. Restate that.	17:09:00
3	Q. Doesn't this statement say that	17:09:03
4	a unit of erythropoietin is defined as the	17:09:05
5	activity of the erythropoietin?	17:09:08
6	A. It is the activity, and it's in	17:09:12
7	the bioassay.	17:09:14
8	Q. So unit used in the bioassay	17:09:19
9	measures the activity in the EPO?	17:09:22
10	A. In this particular instance,	17:09:24
11	yes.	17:09:26
12	They also use the terminology	17:09:27
13	for units for the radioimmunoassay.	17:09:29
14	Q. What antibodies were used in	17:09:57
15	this paper in the radioimmunoassay?	17:09:59
16	A. Dr. Goldwasser's?	17:10:02
17	Q. Yes.	17:10:07
18	A. The Sherwood and Goldwasser	17:10:08
19	paper?	17:10:10
20	Q. What's been marked as McLawhon	17:10:11
21	Exhibit 27.	17:10:14
22	A. If you go under the	17:10:14
23	immunization paragraph on page -- is it 886.	17:10:19
24	"Antibodies to EPO were raised	17:10:24
25	in four male New Zealand white rabbits."	17:10:31