				1			3
				1	09:00:31	1	THE COURT: Good morning. Please, take your
08:57:17	1	IN THE UNITED STATES	DISTRICT COURT		09:00:34	2	seats. We are going to have to be here I am not sure
	2	IN AND FOR THE DISTRI	CT OF DELAWARE		09:00:47	3	exactly how long, actually. I know some work is being done
	3		-		09:00:50	4	on the audiovisual system in my courtroom, which is has
	4	PFIZER INC. and UCB PHARMA GMBH,)	Civil Action		09:00:55	5	really plaguing us of late. Fortunately, Judge Robinson is
	5	, Plaintiffs,))				6	
	6	v.)			09:01:00	_	on vacation. I am going to have to get used to this very
	7	ALKEM LABORATORIES LTD., et al.,)	NO. 13-1110 (GMS)		09:01:03	7	different configuration that her predecessor and mine, Rod
	8	Defendants.)	CONSOLIDATED		09:01:09	8	McKelvie, decided to build. He is gone now, so I can't say
	9		-		09:01:12	9	too much about him.
	10	Wilmington, Monday, July 9:00 a	13, 2015		09:01:14	10	Let's start out with introductions. Mr.
	12	Day 1 of			09:01:16	11	Blumenfeld.
	13		-		09:01:17	12	MR. BLUMENFELD: Good morning, Your Honor.
	14	BEFORE: HONORABLE GREGORY M. SLE	ET, U.S.D.C.J.		09:01:21	13	Jack Blumenfeld from Morris Nichols for the
	15	APPEARANCES :			09:01:23	14	plaintiffs' Pfizer and UCB. Can you hear?
	16	JACK B. BLUMENFELD, ESQ. Morris Nichols Arsht & T	unnell LLP		09:01:27	15	THE COURT: This is strange. Can the folks in
	17	-and- JAMES S. TRAINOR, JR., E	sq.,		09:01:33	16	the well of the court hear?
	18	JEFFREY J. OELKE, ESQ., ROBERT E. COUNIHAN, ESQ.	1		09:01:36	17	MR. BLUMENFELD: I will speak up and get a
	19	RYAN JOHNSON, ESQ., and LAURA MORAN, ESQ.			09:01:39	18	little closer to the mike. I guess we will all try to do
	20	White & Case LLP (New York, NY)				19	that.
	21	Counse	l for Plaintiffs		09:01:42		At counsel table from White & Case are Jeff
	22					21	
09:22:24	23				09:01:46		Oelke, Jim Trainor, and behind them are Robert Counihan and
09:33:40	24					22	Lauren Moran.
	25				09:01:53		(Counsel respond "Good morning.")
					09:01:54	24	MR. BLUMENFELD: Also from White & Case.
ļ				2	09:01:56	25	In the first row, Stephane Drouin, Jurgen Hassa
	1 API	PEARANCES CONTINUED:		2			4
	2	KELLY E. FARNAN, ESQ.			09:02:02	1	from UCB. And in the second row Chase Romick, who is here
	3	Richards, Layton & Finger, P -and-	.A.		09:02:07	2	from Pfizer.
	4	RACHEL K. HUNNICUTT, ESQ NEAL SETH, ESQ.	., and		09:02:07	3	THE COURT: Good morning.
	5	Wiley Rein LLP (New York, NY)			09:02:09	4	Ms. Farnan.
	-	Counsel for Defer			09:02:10	5	MS. FARNAN: I will start, Your Honor. Good
	6	Alkem Laboratori	es Llu.		09:02:11	6	morning. Kelly Farnan from Richards Layton Finger. I am
	7	ADAM W. POFF, ESQ., and PILAR KRAMAN, ESQ.			09:02:13	7	representing Accord and Amneal and Alkem. I also have with
	8	Young Conaway Stargatt & T -and-	aylor LLP		09:02:18	8	me my colleague from my office Christine Hayes.
	9	KRISTEN VINK VENEGAS, ES SHON LO, ESQ.	Q., and		09:02:20	9	THE COURT: Good morning.
	10	McDermott Will & Emery LLC (Chicago, IL)	:		09:02:20		MS. FARNAN: Then on behalf of Accord and Amneal
	11		idant Sandoz Inc.				I am working with Sughrue Mion, we have Mike Dzwonczyk,
,	12	KELLY E. FARNAN, ESQ., and			09:02:23	11	
	13	CHRISTINE HAYNES, ESQ. Richards, Layton & Finger, P	.A.			12	Renita Rathinham, and Alton Hare is in the back.
	14	-and- MICHAEL R. DZWONCZYK, ES			09:02:33		Also here on behalf of Amneal from the company
	15	RENITA A. RATHINAM, ESQ.,			09:02:36	14	in the back as well, Ken Cappel, Brian Sommese, and Lars
		ALTON L. HARE, ESQ. Sughrue Mion, PLLC			09:02:36	15	Tavolla.
	16	(Washington, D.C.) Counsel for Defer			09:02:44	16	THE COURT: Good morning.
	17	Counterclaimant Healthcare Inc., U			09:02:45	17	MS. FARNAN: I also represent Alkem, Your Honor.
			al Pharmaceuticals,		09:02:47	18	And I am working with Wiley Rein. At counsel table is
1	18	Inc.			1	19	Rachel Hunnicutt and Neal Seth.
	18 19	Inc.			09:02:51		Rachel Humilcutt and Near Seth.
		Inc. J. CLAYTON ATHEY, ESQ. Prickett, Jones & Elliott, P.A.			09:02:51 09:02:53		THE COURT: Good morning, counsel.
:	19	Inc. J. CLAYTON ATHEY, ESQ. Prickett, Jones & Elliott, P.A. -and- WILLIAM D. HARE, ESQ., and	1			20	
:	19 20	Inc. J. CLAYTON ATHEY, ESQ. Prickett, Jones & Elliott, P.A. -and-	1		09:02:53	20 21	THE COURT: Good morning, counsel.
	19 20 21 22	Inc. J. CLAYTON ATHEY, ESQ. Prickett, Jones & Elliott, P.A. -and- WILLIAM D. HARE, ESQ., and GABRIELA MATERASSI, ESQ.	1		09:02:53 09:02:55	20 21 22	THE COURT: Good morning, counsel. MS. FARNAN: Thank you, Your Honor. THE COURT: Mr. Poff?
	19 20 21	Inc. J. CLAYTON ATHEY, ESQ. Prickett, Jones & Elliott, P.A. -and- WILLIAM D. HARE, ESQ., and GABRIELA MATERASSI, ESQ. McNeely, Hare & War LLP	l Idants		09:02:53 09:02:55 09:02:56	20 21 22 23	THE COURT: Good morning, counsel. MS. FARNAN: Thank you, Your Honor.

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and and a second of the second of t	09:03:06	1 And from my office, Pilar Kraman.	09:06:15	1	or the '650 patent. It has a priority date of November 16,
with 4 MRLATHEY: Good morning, Your Monor. Clayton Second 5 Ather from Prickett, Jones & Ellist from the Amerigan with 6 Ather from Prickett, Jones & Ellist from the Amerigan Second 5 Second 6 Toward Hease sciences and the second	09:03:08	2 THE COURT: Good morning.	09:06:19	2	1999. And that patent concerns specific salt forms of
with a set of the probability of the method of using, of administering these sait form. with a today are William Hale and Gabriels with a set of administering these sait form. with a today are William Hale and Gabriels with a set of administering these sait form. with a today are William Hale and Gabriels with a set of administering these sait form. with a today are William Hale and Gabriels with a set of administering these sait form. with a set of administering these sait form. with a set of administering these sait form. with a set of administering these sait form. with a set of administering these sait form. with a set of administering these sait form. with a set of administering these sait form. with a set of administering these sait form. with a set of administering these sait form. with a set of administering these sait form. with a set of administering these sait form. with a set of administering these sait form. with a set of administering these sait form. with a set of administering these sait form. with a set of administering these sait form. with a set of administering these sait form. with a set of administering these sait form. with a set of administering these sait form. with a set of administering these sait form. with a set of administering these sait form. <tr< th=""><th>09:03:10</th><th>3 All right. Counsel.</th><th>09:06:25</th><th>3</th><th>compounds, and the asserted claims concern specific salt</th></tr<>	09:03:10	3 All right. Counsel.	09:06:25	3	compounds, and the asserted claims concern specific salt
1 Image: Section 1 Image: Section 2 Now, some of these claims do encompass more than 1 Materasi. Also from Ameriges, Domsthan Nichol. T Just feesterodine. The issue here will be about this 1 Materasi. Also from Ameriges, Domsthan Nichol. T Just feesterodine. The issue here will be about this 1 Materasi. Also from Ameriges, Domsthan Nichol. T Just feesterodine. The issue here will be about this 1 The COURT. Less start with the opening	09:03:14	4 MR. ATHEY: Good morning, Your Honor. Clayton	09:06:28	4	forms of fesoterodine, which we will talk about, and a
accor 7 Materiassi. Also from Amerigen, Jonathan Nichol. accor 7 Just festoradine. The Issue here will be about this accor 8 THE COURT: Good moming. accor 9 Festoradine. The Issue here will be about this accor 10 Connexel, are there any housekeeping matters we accor 10 compound, the stile the structure of the accor 12 MR. DEWE: I on't believe set ogin? accor 11 highlighted a few things here just to give a short preview accor 13 MR. DEWE: Your Henor, I have some sildes. The COURT: Let's start with the opening accor 15 or at teast it's blue on my side. I am not sure if it's accor 14 THE COURT: No. Buckson will take these from fibe for you. Your Honor. The tearger group is one location accor 16 MR. DEWE: Your Henor, I have some sides. fibe for you. Your Honor. The tearger group is one location accor 13 accor 14 Your some sides. fibe for you. Your Honor. The tearger group is one location accor 14 THE COURT: No. Buckson will take these for fibe for you. Your Honor. The tearger group is one location accor	09:03:18	5 Athey from Prickett, Jones & Elliott from the Amerigen	09:06:31	5	method of using, of administering those salt forms.
min 8 THE COURT: Good morning. min 9 I think that's It. Bight? min Coursed, are there any housekeeping matters we min meed to talk about before we begin? min MB. OELKE: I don't believe so, Your Honor. min MB. OELKE: No the ond effectation. min MB. OELKE: Your Honor, I have some silde. min MB. OELKE: Your Honor, I have some silde. min MB. OELKE: Your Honor, I have some silde. min MB. OELKE: Your Honor, I have some silde. min MB. OELKE: Your Honor, I have some silde. min MB. OELKE: Your Honor, I have some silde. min MB. OELKE: Your Honor, I have some silde. min MB. OELKE: Your Honor, I have some silde. min you. min min min MB. OELKE: Your Honor, the investore in thic case are set of the compound. min you. min MB. OELKE: Your Honor, the investore in thic case are set of the compound. min are going to ask you to see what you can define and the set of the compound. min you. trails in thic case are set and the set the set and the set of the compound.	09:03:21	6 defendants. With me today are William Hale and Gabriela	09:06:35	6	Now, some of these claims do encompass more than
10013 9 1 think that's it. Right? 20019 Feasterrodim, that is the structure of the 10013 9 1 think that's it. Right? 20019 6 Compound with the saft, the tumarste saft. We have 10013 9 Feasterrodim, that is the structure of the 2011 Compound with the saft, the tumarste saft. We have 10013 9 Feasterrodim, that is the structure of the 2011 Compound with the saft, the tumarste saft. We have 10013 9 Feasterrodim, that is the structure of the 2011 Compound with the saft, the tumarste saft. We have 10013 9 Feasterrodim, that is the structure of the 2011 Compound with the saft, the tumarste saft. We have 10014 Feasterrodim, that is the structure of the 2011 Compound with the saft, the fumarste saft. We have 10015 Feasterrodim, that is the structure of the 2011 Compound with the saft, the fumarste saft. We have 10016 Feasterrodim, that is the saft of the institute 10 2011 Compound we set the saft of the institute 10016 Feasterrodim, that is the saft of the institute 10 10 10 10 10016 Feasterrodim, that is thestute 10 10 <th>09:03:27</th> <th>7 Materassi. Also from Amerigen, Jonathan Nichol.</th> <th>09:06:41</th> <th>7</th> <th>just fesoterodine. The issue here will be about this</th>	09:03:27	7 Materassi. Also from Amerigen, Jonathan Nichol.	09:06:41	7	just fesoterodine. The issue here will be about this
Image: 10 Counsel, are there any housekeeping matters we matter is any house how were any housekeeping matters we matter is any house how were any	09:03:31	8 THE COURT: Good morning.	09:06:46	8	compound, fesoterodine, which is on the screen, Your Honor.
ware 11 need to talk about before we begin? ware 12 WR. OELKE: I don't believe so, Your Honor. ware 13 MR. OELKE: I don't believe so, Your Honor. ware 14 of the portions of the compound we are going to be talking ware 14 MR. OELKE: Your Honor, The Headmath, Your Honor. ware 14 of the portions of the compound we are going to be talking ware 14 MR. OELKE: Your Honor, Thave some side. ware 14 You see the exter group there circled in blue, ware 14 MR. OELKE: Your Honor, Thave some side. ware 14 You see the exter group there circled in blue, ware 14 MR. OELKE: Your Honor, Thave some side. ware 14 of the ing for potential substitution. The alcohol group ware 20 about keeping as close to the mike as you can without being ware 14 is another location of the research talk ware 23 War. Honor, the invention in this case arose ware 24 of the compound wars it benefield the most difficult to trat ware 24 and an active field of pharmaceutical research. And that ware 24 if the would be talking about. ware 24 ware 31 In the late 1990s, a number of different 24 for company. Schwarz Pharma, took a different path. They if the would be talking about. ware 24 ware 31 To orient the pla	09:03:33	9 I think that's it. Right?	09:06:51	9	Fesoterodine, that is the structure of the
amon 12 MR. DELKE: I don't believe so, Your Monor. amon 12 of the portions of the compound we are going to be talking amon 13 MR. DEUXONCYKE. Not form defendants, Your Monor. about in the case. about in the case. amon 14 THE COURT: Let's start with the opening about in the case. about in the case. amon 15 attaments the. about in the case. about in the case. amon 15 attaments the. about in the case. about in the case. amon 16 MR. OELE: Your Monor, Ihave some alides. or at least it's blue on my slide. I an not sure if it's amon 19 I am going to ask you to see what you can ow about the case it's blue on my slide. I an not sure if it's amon 19 about the case it as blue on my slide. about the case it's blue on my slide. about the case it's blue on my slide. amon 19 I am going to ask you to see what you can ow amon 10 or at least it's blue on my slide. about the case it's blue on my slide. amon 14 amon 14 about the case it's blue on my slide. amon 14 at the set if a blue on my slide. amon 14 uncorrelaties on the my the one on the ring for another possibility for at the set if a blue on my slide. at the set if a blue on my slide. amon	09:03:36	0 Counsel, are there any housekeeping matters we	09:06:54	10	compound with the salt, the fumarate salt. We have
user 13 MR. DZWONCZYE: Not from defendants, Your Honor. user 13 about In the case. user 14 THE COURT: Let's start with the oponing the case. user 15 mr. DELWE: Your Honor, I have some sildes. off if i	09:03:40	1 need to talk about before we begin?	09:06:57	11	highlighted a few things here just to give a short preview
14 THE COURT: Let's start with the opening 2007 14 You see the ester group there circled in blue, 2007 15 statements them. 2007 16 MR. OELKE: Your Honor, I have some slides. 2007 16 MR. OELKE: Your Honor, That estere sroup is one location 2007 10 or at least it's blue on my slide. I am not sure if it's 2007 19 I am going to ask you to see what you cand 2007 11 or at least it's blue on my slide. I am not sure if it's 2007 10 incomfortable so that everyone can hear. 2007 10 is another location on the ring for another possibility for 2007 10 more inferior the investion in this case are one 2007 21 This Compound arcse out of that research that 2007 21 was an active field to look for a better treatment for 2007 24 24 Compound was it benefited the most difficult-to-treat 2007 2 Year and the invention here 26 27 1 14 that we will be talking about. 2007 2 10 refered to in this case as overactive bladeer on OAB. 2007 1 1 1 1 1 1 1 <	09:03:43	2 MR. OELKE: I don't believe so, Your Honor.	09:07:02	12	of the portions of the compound we are going to be talking
15 statements then. 0007 15 or at least it's blue on my slide. I am not sure if it's 2005 17 THE COURT: Mr. Buckson will take those from 0007 16 0007 17 on the ring for potential substitution. The alcohol group 2005 19 I am going to ask you to see what you can do 0007 19 is another location on the ring for another possibility for 2006 21 monofrotable is of that everyone can bear. 0007 10 other ing for another possibility for 2007 22 MR. OELKE: Good morning, Your Honor. 0007 20 10 other ompound. 2007 23 MR OELKE: Good morning, Your Honor. 0007 22 This compound arose out of that research that 2008 22 MR. OELKE: Good morning, Your Honor. 0007 22 This compound arose out of that research that 2008 23 Your Honor, It at salso going to be 0007 21 This compound arose out of that research arogin at drags 2008 3 In the late 1990s, a number of different 0007 2 11 that we will be talking about. 2006 6 courure bocause a group at a small German pharmaceutical<	09:03:47	3 MR. DZWONCZYK: Not from defendants, Your Honor.	09:07:05	13	about in the case.
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answer 17 THE COURT: Mr. Buckson will take these from answer 17 on the ring for potential substitution. The alcohol group asset 18 you. is another location on the ring for another possibility for asset 19 about keeping as close to the mike as you can without being is another location on the ring for another possibility for asset 22 MR. OELKE: Good morning, Your Honor. amid an active field of pharmaceutical research. And that amid an active field of pharmaceutical research. And that amid an active field of pharmaceutical research. And that amid an active field of pharmaceutical research. And that amid an active field of pharmaceutical research. And that amid an active field of pharmaceutical research. And that amid an active field of pharmaceutical research. And that amid an active field of pharmaceutical research. And that amid an active field of pharmaceutical research. And that amid 1 that we will be talking about. amid 1 that we and amid 1 that the pharmaceutical amid 1	09:03:51	5 statements then.	09:07:10	15	or at least it's blue on my slide. I am not sure if it's
2020 18 you. bit an going to ask you to see what you can do 2020 13 you. bit an going to ask you to see what you can do 2020 14 you teeping as close to the mike as you can without being substitution, which we will be talking about more during the 2020 2 MR. OELKE: Good moming, Your Honor. trait. Finally, in yellow is the fumarte, the salt portion 2020 2 MR. OELKE: Good moming, Your Honor. this case arose 2020 2 MR. OELKE: Good moming, Your Honor. this case arose 2020 2 MR. OELKE: Good moming, Your Honor. this case arose 2020 2 MR. OELKE: Good moming, Your Honor, It the Schwarz scientists conducted. And the result of that 2020 2 an active field to look for a better treatment for that we will be talking about. 2021 2 If we could go to the next side. that we will be talking about. 2021 2 If we could go to the next side. that we will be talking about. 2025 4 affected, at the time frame, as I said, 1998-1999, it that we will be talking about. 2025 6 cocurred because a group at a small German pharmaceutical fif t	09:03:56	6 MR. OELKE: Your Honor, I have some slides.	09:07:14	16	blue for you, Your Honor. That ester group is one location
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22 MR. OELKE: God morning, Your Honor. 000737 22 This compound arose out of that research that 000737 23 Your Honor, the invention in this case arose 000737 22 This compound arose out of that research that 000737 25 was an active field of pharmaceutical research. And that 00779 24 the Schwarz scientists conducted. And the result of that 000747 2 referred to in this case as overactive bladder or OAB. 00779 1 that we will be talking about. 000747 2 research organizations were looking into developing a better 000764 1 that we will be talking about. 000748 4 research organizations were looking into developing a better 000764 1 that we will be talking about. 000748 4 research organizations were looking into developing a better 000764 1 that we will be talking about. 000749 8 darled the invention here 000764 1 that we will be talking about. 000749 8 tarted in 1997. And they tried to develop an OAB drug 000777 1 that time. Over 500 million worldwide. And it was an 000710 taking a different path than all these other research </th <th></th> <th></th> <th></th> <th></th> <th>trial. Finally, in yellow is the fumarate, the salt portion</th>					trial. Finally, in yellow is the fumarate, the salt portion
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					muscarinic receptors that reside in the bladder. So here
09:06:08 24 claims all concern fesoterodine, the drug at issue. 09:09:13 24 The problem with a muscarinic receptor is it's					are three of the drugs that existed at that time in 1998.
	09:06:08	4 claims all concern fesoterodine, the drug at issue.	09:09:13	24	The problem with a muscarinic receptor is it's

	9		11
09:09:20 1	in the brain. It's also in the salivary glands.	09:12:01 1	to work on the same compounds as these other companies.
09:09:24 2	So these drugs all had deficiencies with each of	09:12:05 2	They worked on tolterodine. They started with tolterodine.
09:09:29 3	them.	09:12:08 3	One of the inventors of fesoterodine that came to work with
09:09:29 4	Oxybutynin, for instance, had a severe dry mouth	09:12:13 4	Schwarz had been an inventor on tolterodine. And they
09:09:34 5	problem. Most people that took oxybutynin, up to 70 percent	09:12:17 5	started with tolterodine, and then they decided, well, let's
09:09:38 6	of people that took it had a dry mouth issue. In some it	09:12:21 6	focus on the metabolite of tolterodine. Then, not only
09:09:42 7	was so severe they couldn't take the drug. They had to go	09:12:24 7	that, they decided, let's make a prodrug.
09:09:45 8	off of it.	09:12:27 8	A prodrug, no one had made a prodrug in this
09:09:46 9	Propantheline was another antimuscarinic. It	09:12:30 9	area. No one had made a prodrug with antimuscarinic. And
09:09:51 10	had a wide variety of absorption. Some patients needed a	09:12:35 10	no one had made a drug with an OAB drug at that point. So
09:09:54 11	huge amount. Some patients didn't need as much. And	09:12:38 11	they were working on a blank slate in this area. No one had
09:09:56 12	doctors really didn't know how to dose it.	09:12:41 12	made an antimuscarinic prodrug.
09:10:00 13	Tolterodine was the new drug on the market. In	09:12:43 13	Just to give you a concept quickly, Your Honor,
09:10:03 14	March of 1998, tolterodine was introduced. And the trade	09:12:45 14	of what a prodrug is, this is kind of our crude
09:10:07 15	name for that was Detrol. That drug came on the market in	09:12:50 15	representation of how it works. The idea is that if you
09:10:11 16	1998. And it solved some of these issues. But it had a	09:12:52 16	have an existing drug and it has a problem associated with
09:10:15 17	problem with it as well. That was a dose ceiling. You	09:12:55 17	it, for instance, you can't get it through a membrane. If
09:10:19 18	could only give four milligrams a day of tolterodine. The	09:13:00 18	you have an oral dosage form, it can't get through the gut
09:10:21 19	reason for that was because of a condition called urinary	09:13:03 19	wall. So it just passes through the body. You see here, it
09:10:26 20	retention. Basically, in some patients, if you went above	09:13:07 20	just can't make it through the gut wall.
09:10:29 21	four milligrams a day, it froze their bladder. So then they	09:13:10 21	So the possibility with a prodrug is, ideally,
09:10:33 22	couldn't urinate at all. And that is called a backup. That	09:13:12 22	if it would work, is that it would deliver that drug across
09:10:37 23	wasn't just an uncomfortable side effect, that could be a	09:13:17 23	the gut wall, and then when it gets to the intended site of
09:10:40 24	serious side effect. It could actually lead to kidney	09:13:22 24	action, an enzyme cleaves off the prodrug group, leaving the
09:10:42 25	failure.	09:13:27 25	intended drug at the appropriate site.
	10		12
09:10:43 1		09:13:30 1	
	10		12
09:10:43 1	10 So doctors just would not go above that ceiling	09:13:30 1	12 But there is a reason no one was looking at
09:10:43 1 09:10:45 2	10 So doctors just would not go above that ceiling of four milligrams a day with tolterodine.	09:13:30 1 09:13:33 2	12 But there is a reason no one was looking at prodrugs at that time, because prodrugs are a very difficult
09:10:43 1 09:10:45 2 09:10:48 3	10 So doctors just would not go above that ceiling of four milligrams a day with tolterodine. These were the options that existed.	09:13:30 1 09:13:33 2 09:13:38 3	12 But there is a reason no one was looking at prodrugs at that time, because prodrugs are a very difficult set of compounds to try to develop because you are
09:10:43 1 09:10:45 2 09:10:48 3 09:10:50 4	10 So doctors just would not go above that ceiling of four milligrams a day with tolterodine. These were the options that existed. So there were a large number of research groups	09:13:30 1 09:13:33 2 09:13:38 3 09:13:41 4	12 But there is a reason no one was looking at prodrugs at that time, because prodrugs are a very difficult set of compounds to try to develop because you are essentially trying to thread a series of needles to get a
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	13		15
09:14:46 1	the grain when they decided let's try to make a prodrug in	09:17:49	on 5-HMT, but the defendants will give two reasons why you
09:14:49 2	this field. No one had ever done it before.	09:17:52 2	
09:14:51 3	Now, the issue of obviousness, where we're going	09:17:55	you are looking at tolterodine, then you would look over to
09:14:56 4	to start, there are four issues, Your Honor, that remain in	09:17:58	the metabolite.
09:15:01 5	the case: obviousness, anticipation, indefiniteness I	09:17:58	They'll say, well, variability of metabolism was
09:15:07 6	believe, and then one small issue of infringement as to	09:18:01	an issue with tolterodine.
09:15:10 7	Sandoz on two of the 12 claims. But obviousness is the	09:18:03 7	There were two groups of patients, Your Honor.
09:15:13 8	issue that touches on all of the claims. I'm going to spend	09:18:08	One would be extensive metabolizers and the other would be
09:15:18 9	my time speaking about that issue first.	09:18:12	poor metabolizers. The reason for this is the enzyme in the
09:15:21 10	The issue of obviousness is addressed from the	09:18:16 10	body that works on tolterodine to convert it into the
09:15:26 11	person from the standpoint of a person of ordinary skill	09:18:20 11	metabolite, what is called CYP2D6, you will hear that, that
09:15:29 12	and what that person of ordinary skill would have been	09:18:26 12	enzyme some people just don't have it or they don't have
09:15:33 13	confronted with at this point in 1998, a series of	09:18:28 13	much of it in their body. So those patients don't convert
09:15:39 14	questions. And these series of questions all have to be	09:18:31 14	to the metabolite or very little. They're called poor
09:15:42 15	answered in a particular way in the defendants' favor for	09:18:35 15	metabolizers.
09:15:44 16	them to carry their prima facie burden.	09:18:36 16	But what the prior art shows is it doesn't
09:15:48 17	Now, the first question is what is the classic	09:18:38 17	matter, because both tolterodine and its metabolite are
09:15:53 18	compound you are going to look at. As we saw, there are	09:18:42 18	active at the bladder. And so the label for Detrol actually
09:15:55 19	more than just antimuscarinics that were possibilities. The	09:18:47 19	states the net activity of Detrol tablets is expected to be
09:15:56 20	defendants say you just focus on antimuscarinics.	09:18:51 20	similar in extensive and poor metabolizers.
09:16:00 21	But even if a person of ordinary skill decides,	09:18:54 21	So there really was not an issue here. When a
09:16:02 22	okay, well, I'll focus on antimuscarinics, you go to the	09:18:57 22	patient came into the doctor's of office, the doctor didn't
09:16:06 23	next step. You go to the second step. And there you have a	09:19:00 23	try to figure out is the patient a extensive metabolizer or
09:16:14 24	number of possibilities. These are all compounds that were	09:19:04 24	a poor metabolizer because the label said it doesn't make a
09:16:16 25	either, that were either antimuscarinics or in development	09:19:07 25	difference. Both get the same effect.
	14		16
09:16:21 1	14 or some companies were looking at it and Dr. Maag, who was a	09:19:09	16 The second reason they're going to give is
09:16:21 1 09:16:27 2		09:19:09 1 09:19:11 2	The second reason they're going to give is
	or some companies were looking at it and Dr. Maag, who was a		The second reason they're going to give is they're going to say, well, it's known that 5-HMT, the
09:16:27 2 09:16:32 3 09:16:33 4	or some companies were looking at it and Dr. Maag, who was a prodrug specialist and a medicinal chemist who worked at	09:19:11 2	The second reason they're going to give is they're going to say, well, it's known that 5-HMT, the metabolite, is more potent than tolterodine, but the
09:16:27 2 09:16:32 3 09:16:33 4 09:16:35 5	or some companies were looking at it and Dr. Maag, who was a prodrug specialist and a medicinal chemist who worked at Roche at this time will testify about these possibilities.	09:19:11 2 09:19:14 3 09:19:19 4 09:19:23 5	The second reason they're going to give is they're going to say, well, it's known that 5-HMT, the metabolite, is more potent than tolterodine, but the information they cite to for that is early clinic, pre-clinical work in cats.
09:16:27 2 09:16:32 3 09:16:33 4 09:16:35 5 09:16:38 6	or some companies were looking at it and Dr. Maag, who was a prodrug specialist and a medicinal chemist who worked at Roche at this time will testify about these possibilities. He was working in the field at the time. The defendants will say you focused on tolterodine because it was the hot new drug that had just	09:19:11 2 09:19:14 3 09:19:19 4 09:19:23 5 09:19:25 6	The second reason they're going to give is they're going to say, well, it's known that 5-HMT, the metabolite, is more potent than tolterodine, but the information they cite to for that is early clinic, pre-clinical work in cats. That did not prove to be the case in humans. In
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09:16:27 2 09:16:32 3 09:16:33 4 09:16:35 5 09:16:36 6 09:16:42 7 09:16:45 8 09:16:53 10 09:16:56 11 09:16:56 13 09:17:00 12 09:17:03 13 09:17:07 14	or some companies were looking at it and Dr. Maag, who was a prodrug specialist and a medicinal chemist who worked at Roche at this time will testify about these possibilities. He was working in the field at the time. The defendants will say you focused on tolterodine because it was the hot new drug that had just come out. But these were all possibilities here. And once defendants say, well, lets focus on tolterodine, then they actually want you to switch. They want to say, well, follow what the inventors did and look over at the metabolite. But there is reasons why you wouldn't look at that metabolite, and the metabolite is 5-HMT, just so when you see that name, that is referring to the metabolite. That's the compound we have up there.	09:19:11 2 09:19:14 3 09:19:19 4 09:19:23 5 09:19:25 6 09:19:25 7 09:19:26 7 09:19:36 10 09:19:36 10 09:19:39 11 09:19:39 11 09:19:40 12 09:19:49 14	The second reason they're going to give is they're going to say, well, it's known that 5-HMT, the metabolite, is more potent than tolterodine, but the information they cite to for that is early clinic, pre-clinical work in cats. That did not prove to be the case in humans. In humans, they're equipotent. They have the same potency. You shouldn't focus on the cat data once you have the data in humans. So that basis for focusing on 5-HMT also did not hold up. But, Your Honor, even if you decide to focus on 5-HMT, you have a number of options once you start with that as a lead compound. And that is what we have labeled as No.
09:16:27 2 09:16:32 3 09:16:33 4 09:16:35 5 09:16:38 6 09:16:42 7 09:16:42 7 09:16:49 9 09:16:56 11 09:17:00 12 09:17:00 13 09:17:07 14 09:17:10 15	or some companies were looking at it and Dr. Maag, who was a prodrug specialist and a medicinal chemist who worked at Roche at this time will testify about these possibilities. He was working in the field at the time. The defendants will say you focused on tolterodine because it was the hot new drug that had just come out. But these were all possibilities here. And once defendants say, well, lets focus on tolterodine, then they actually want you to switch. They want to say, well, follow what the inventors did and look over at the metabolite. But there is reasons why you wouldn't look at that metabolite, and the metabolite is 5-HMT, just so when you see that name, that is referring to the metabolite. That's the compound we have up there. Now, 5-HMT would not have been an attractive	09:19:11 2 09:19:14 3 09:19:19 4 09:19:25 6 09:19:25 7 09:19:26 7 09:19:26 7 09:19:26 10 09:19:36 10 09:19:36 10 09:19:36 11 09:19:40 12 09:19:40 12 09:19:49 14 09:19:49 14	The second reason they're going to give is they're going to say, well, it's known that 5-HMT, the metabolite, is more potent than tolterodine, but the information they cite to for that is early clinic, pre-clinical work in cats. That did not prove to be the case in humans. In humans, they're equipotent. They have the same potency. You shouldn't focus on the cat data once you have the data in humans. So that basis for focusing on 5-HMT also did not hold up. But, Your Honor, even if you decide to focus on 5-HMT, you have a number of options once you start with that as a lead compound. And that is what we have labeled as No. 3 on this slide.
09:16:27 2 09:16:32 3 09:16:33 4 09:16:35 5 09:16:36 6 09:16:42 7 09:16:45 8 09:16:53 10 09:16:56 11 09:17:00 12 09:17:03 13 09:17:10 15 09:17:16 16	or some companies were looking at it and Dr. Maag, who was a prodrug specialist and a medicinal chemist who worked at Roche at this time will testify about these possibilities. He was working in the field at the time. The defendants will say you focused on tolterodine because it was the hot new drug that had just come out. But these were all possibilities here. And once defendants say, well, lets focus on tolterodine, then they actually want you to switch. They want to say, well, follow what the inventors did and look over at the metabolite. But there is reasons why you wouldn't look at that metabolite, and the metabolite is 5-HMT, just so when you see that name, that is referring to the metabolite. That's the compound we have up there. Now, 5-HMT would not have been an attractive lead compound for a number of reasons. One, it has never	09:19:11 2 09:19:14 3 09:19:19 4 09:19:23 5 09:19:25 6 09:19:25 6 09:19:26 7 09:19:27 9 09:19:38 10 09:19:39 11 09:19:39 12 09:19:40 12 09:19:42 14 09:19:52 15 09:19:53 16	The second reason they're going to give is they're going to say, well, it's known that 5-HMT, the metabolite, is more potent than tolterodine, but the information they cite to for that is early clinic, pre-clinical work in cats. That did not prove to be the case in humans. In humans, they're equipotent. They have the same potency. You shouldn't focus on the cat data once you have the data in humans. So that basis for focusing on 5-HMT also did not hold up. But, Your Honor, even if you decide to focus on 5-HMT, you have a number of options once you start with that as a lead compound. And that is what we have labeled as No. 3 on this slide. You can make a structural analog of the
09:16:27 2 09:16:32 3 09:16:33 4 09:16:35 5 09:16:36 6 09:16:37 7 09:16:42 7 09:16:53 10 09:16:56 11 09:16:56 11 09:17:00 12 09:17:07 14 09:17:10 15 09:17:16 16 09:17:19 17	or some companies were looking at it and Dr. Maag, who was a prodrug specialist and a medicinal chemist who worked at Roche at this time will testify about these possibilities. He was working in the field at the time. The defendants will say you focused on tolterodine because it was the hot new drug that had just come out. But these were all possibilities here. And once defendants say, well, lets focus on tolterodine, then they actually want you to switch. They want to say, well, follow what the inventors did and look over at the metabolite. But there is reasons why you wouldn't look at that metabolite, and the metabolite is 5-HMT, just so when you see that name, that is referring to the metabolite. That's the compound we have up there. Now, 5-HMT would not have been an attractive lead compound for a number of reasons. One, it has never been studied as a drug. It had only been studied as a	09:19:11 2 09:19:14 3 09:19:19 4 09:19:23 5 09:19:25 6 09:19:25 7 09:19:25 7 09:19:26 7 09:19:27 9 09:19:38 10 09:19:39 11 09:19:39 12 09:19:39 14 09:19:40 12 09:19:40 12 09:19:41 14 09:19:52 15 09:19:53 16 09:19:53 16 09:19:54 17	The second reason they're going to give is they're going to say, well, it's known that 5-HMT, the metabolite, is more potent than tolterodine, but the information they cite to for that is early clinic, pre-clinical work in cats. That did not prove to be the case in humans. In humans, they're equipotent. They have the same potency. You shouldn't focus on the cat data once you have the data in humans. So that basis for focusing on 5-HMT also did not hold up. But, Your Honor, even if you decide to focus on 5-HMT, you have a number of options once you start with that as a lead compound. And that is what we have labeled as No. 3 on this slide. You can make a structural analog of the compound. You can make a structural analog of tolterodine
09:16:27 2 09:16:32 3 09:16:33 4 09:16:35 5 09:16:35 5 09:16:36 6 09:16:42 7 09:16:45 8 09:16:53 10 09:16:56 11 09:17:00 12 09:17:01 15 09:17:10 15 09:17:19 17 09:17:23 18	or some companies were looking at it and Dr. Maag, who was a prodrug specialist and a medicinal chemist who worked at Roche at this time will testify about these possibilities. He was working in the field at the time. The defendants will say you focused on tolterodine because it was the hot new drug that had just come out. But these were all possibilities here. And once defendants say, well, lets focus on tolterodine, then they actually want you to switch. They want to say, well, follow what the inventors did and look over at the metabolite. But there is reasons why you wouldn't look at that metabolite, and the metabolite is 5-HMT, just so when you see that name, that is referring to the metabolite. That's the compound we have up there. Now, 5-HMT would not have been an attractive lead compound for a number of reasons. One, it has never been studied as a drug. It had only been studied as a metabolite. It was a metabolite of tolterodine, but no one	09:19:11 2 09:19:14 3 09:19:19 4 09:19:23 5 09:19:25 6 09:19:25 6 09:19:25 7 09:19:26 7 09:19:27 6 09:19:28 7 09:19:36 10 09:19:36 10 09:19:36 10 09:19:37 11 09:19:40 12 09:19:40 12 09:19:40 12 09:19:40 12 09:19:40 12 09:19:52 15 09:19:53 16 09:19:53 16 09:19:56 17 09:20:00 18	The second reason they're going to give is they're going to say, well, it's known that 5-HMT, the metabolite, is more potent than tolterodine, but the information they cite to for that is early clinic, pre-clinical work in cats. That did not prove to be the case in humans. In humans, they're equipotent. They have the same potency. You shouldn't focus on the cat data once you have the data in humans. So that basis for focusing on 5-HMT also did not hold up. But, Your Honor, even if you decide to focus on 5-HMT, you have a number of options once you start with that as a lead compound. And that is what we have labeled as No. 3 on this slide. You can make a structural analog of the compound. You can make a structural analog of tolterodine or you could make a formulation. If there really is an
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09:16:27 2 09:16:32 3 09:16:33 4 09:16:35 5 09:16:36 6 09:16:42 7 09:16:43 8 09:16:44 7 09:16:45 8 09:16:56 11 09:17:00 12 09:17:01 15 09:17:10 15 09:17:16 16 09:17:23 18 09:17:30 20 09:17:30 20 09:17:30 20 09:17:34 21	or some companies were looking at it and Dr. Maag, who was a prodrug specialist and a medicinal chemist who worked at Roche at this time will testify about these possibilities. He was working in the field at the time. The defendants will say you focused on tolterodine because it was the hot new drug that had just come out. But these were all possibilities here. And once defendants say, well, lets focus on tolterodine, then they actually want you to switch. They want to say, well, follow what the inventors did and look over at the metabolite. But there is reasons why you wouldn't look at that metabolite, and the metabolite is 5-HMT, just so when you see that name, that is referring to the metabolite. That's the compound we have up there. Now, 5-HMT would not have been an attractive lead compound for a number of reasons. One, it has never been studied as a drug. It had only been studied as a metabolite. It was a metabolite of tolterodine, but no one had ever dosed it as a drug. So there was no experience with the compound as a drug, only as a metabolite.	09:19:11 2 09:19:14 3 09:19:19 4 09:19:23 5 09:19:24 7 09:19:25 6 09:19:26 7 09:19:27 7 09:19:28 7 09:19:28 7 09:19:35 9 09:19:36 10 09:19:37 11 09:19:38 11 09:19:40 12 09:19:40 12 09:19:51 16 09:19:52 15 09:19:53 16 09:19:54 17 09:20:00 18 09:20:00 18 09:20:03 19 09:20:04 21 09:20:07 20 09:20:07 21	The second reason they're going to give is they're going to say, well, it's known that 5-HMT, the metabolite, is more potent than tolterodine, but the information they cite to for that is early clinic, pre-clinical work in cats. That did not prove to be the case in humans. In humans, they're equipotent. They have the same potency. You shouldn't focus on the cat data once you have the data in humans. So that basis for focusing on 5-HMT also did not hold up. But, Your Honor, even if you decide to focus on 5-HMT, you have a number of options once you start with that as a lead compound. And that is what we have labeled as No. 3 on this slide. You can make a structural analog of the compound. You can make a structural analog of tolterodine or you could make a formulation. If there really is an issue with 5-HMT, then you can make a formulation. The defendants are going to say the reason you have to alter 5-HMT into a prodrug is because there is an absorption problem of 5-HMT, but this goes back to what I talked about before. No one has ever actually tried dosing

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		17		19
09:20:27	1	If you did have an absorption problem, you could	09:23:05 1	If you go to the next slide.
09:20:30	2	address it through a formulation or you could address it	09:23:06 2	They will point to two references, Your Honor,
09:20:32	3	through making a structural analog. The prodrug would be	09:23:09 3	prodrug secondary references; and one is called the Drustrup
09:20:37	4	your last approach. The defendants say that is what you	09:23:14	reference. This reference concerns morphine. It has
09:20:38	5	would go to first.	09:23:16 5	nothing to do with antimuscarinic or OAB. The structure as
09:20:39	6	Now, if you do go to a prodrug, Your Honor, even	09:23:20	you can see is very different. It's a very rigid structure
09:20:42	7	then you have the number of options for the types of	09:23:23 7	morphine, and, of course, it is not meant for OAB. It's an
09:20:45	8	prodrugs.	09:23:27 8	analgesic.
09:20:45	9	And we have labeled this as No. 4. You have	09:23:28	And this reference actually discusses how it's a
	10	ethers, you have esters, you have phosphates, carbamates,	09:23:31 10	very slow conversion, which is the last thing you would want
09:20:52		carbonates. These are all possibilities.	09:23:34 11	if you are making a prodrug of 5-HMT.
09:20:55		Defendants are going to say, well, you only	09:23:37 12	The only way you would get to Drustrup is if
09:20:57		focus on esters. Just try ester prodrugs. They say those	09:23:42 13	you needed just for focusing on one of the two locations.
09:21:01		are the old prodrugs that have been around since the '60s or	09:23:45 14	A person of ordinary skill looking at the
09:21:04		'70s so start there.	09:23:47 15	problem that was confronting people in the OAB field is not
09:21:04		But by 1998, the time of the invention, many of	09:23:47 1 0	going to look at a morphine reference, Your Honor.
09:21:05	-	these other types are being used. And one of the reasons is	09:23:50	If you go to the next slide.
09:21:10		because ester prodrugs have an issue with them. They	09:23:52 17 09:23:54 18	Even if you decide where you are going to put
09:21:14			09:23:54 10 09:23:57 19	
09:21:18		convert in the stomach in many cases because the enzyme that	09:23:57	that prodrug group, then you have to decide what group am I
09:21:23		converts ester prodrugs is in the stomach. So you have an	09:24:02 20 09:24:06 21	going to put at that location, or at both locations.
09:21:27		early conversion problem with ester prodrugs in some cases	09:24:06 21 09:24:10 22	And what defendants will say is you would
09:21:30		and it would have been a concern for 5-HMT if you decided to	09:24:10 22 09:24:16 23	naturally go to the isobutyryl group which is in fesoterodine. That is what we show here as the final
09:21:34		make a prodrug of 5-HMT.	09:24:16 23 09:24:17 24	
09:21:36		But even then, Your Honor, if you decide to make	09:24:17 24 09:24:20 25	compound. But, of course, this is just one of many
09:21:39	25	an ester prodrug, you still have to decide where am I going	09:24:20 23	possibilities, as Dr. Roush will testify.
	<u>25</u>	18		20
09:21:42	1	18 to put that ester?	09:24:25 1	20 The defendants will going to point to the Daas
09:21:42	_	18 to put that ester? If you look at the structure again that we put	09:24:25 1 09:24:27 2	20 The defendants will going to point to the Daas reference to say you would focus on the isobutyryl group
09:21:42 09:21:44 09:21:46	1 2	18 to put that ester? If you look at the structure again that we put up earlier, now this structure we're going to put up is	09:24:25 1 09:24:27 2 09:24:31 3	20 The defendants will going to point to the Daas reference to say you would focus on the isobutyryl group but, Daas has nothing to do with antimuscarinics, it has
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