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**UNITED STATES DISTRICT COURT  
SOUTHERN DISTRICT OF CALIFORNIA**

**IN RE: INCRETIN-BASED  
THERAPIES PRODUCTS  
LIABILITY LITIGATION**

**Relates to: ALL CASES**

**MDL No. 13-md-2452-AJB (MDD)**

**MEMORANDUM OF POINTS AND  
AUTHORITIES IN SUPPORT OF  
PLAINTIFFS' MOTION TO  
COMPEL FURTHER RESPONSES  
TO PLAINTIFFS' SET II WRITTEN  
DISCOVERY**

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Defendants predicate their impossibility preemption defense entirely on the unprecedented claim that “FDA *can only* approve a warning as part of the labeling if there is reasonable evidence of a causal association between the medication and a particular risk.” Dkt. 410-1, p. 8 (emphasis added). To investigate and test the factual basis for that argument, Plaintiffs served discovery requesting, e.g., examples of the FDA actually prohibiting *any* warning on that basis.<sup>1</sup> In response, Defendants refused to provide any information about the “reasonable evidence” underlying *even the existing warnings on the drugs in this litigation*. Defendants similarly refused to disclose whether they knew of the FDA actually prohibiting a warning for that reason. Instead, Defendants assert that the only evidence relevant to preemption consists of the materials attached to their motion for summary judgment – a position rendered untenable by the Defendants’ refusal to admit or deny *their own contention* that the FDA will not allow warnings without reasonable evidence of a causal association.<sup>2</sup>

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<sup>1</sup> See, e.g., Interrogatory (ROG) No. 5 and Request for Production (RFP) Nos. 4-5.

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<sup>2</sup> See Request for Admission (RFA) No. 9: “To the best of YOUR knowledge, the FDA has never allowed a branded prescription drug to reference a medical condition for which there is no REASONABLE EVIDENCE OF A CAUSAL ASSOCIATION.” No Defendant admitted or denied the request. Amylin, Lilly, and

1 A party cannot avoid damaging facts – like how the Defendants’ products all  
2 warn about pancreatitis, or how the FDA has apparently never prohibited a  
3 manufacturer from adding a warning about a serious, unlabeled adverse event<sup>3</sup> – by  
4 refusing to engage in discovery on those subjects. For example, it is clearly not  
5 “unduly burdensome” for Defendants to admit or deny if the “serious side effects”  
6 and other medical conditions listed on their drugs satisfy the ‘reasonable evidence’  
7 standard.<sup>4</sup> Defendants’ preference to avoid responding to discovery requests that  
8 undermine their defense, while understandable, has no support under the Rules.

9 Defendants’ refusal to admit or deny Plaintiffs’ requests for admission  
10 needlessly complicates and obfuscates the resolution of their own preemption  
11 defense.<sup>5</sup> Defendants’ refusal to answer Plaintiffs’ requests relating to the “reasonable  
12 evidence” – or lack thereof – underlying the warnings on the drugs in this litigation  
13 prejudices the Plaintiffs and blinds the Court to the way the “reasonable evidence”  
14 standard works in practice at the FDA. Defendants’ refusal to produce documents (or  
15 to admit they have no such documents) showing that the FDA *ever* acts in the way  
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17 Merck refused to state why they could not admit or deny, in violation of Fed.R.Civ.P.  
18 36(a)(4). Novo objected, then stated it “lacks sufficient information to admit or deny  
19 that the FDA has never allowed any prescription drug from any manufacturer to  
20 reference a medical condition for which there is no reasonable evidence of a causal  
21 association,” but, in violation of Rule 36(a)(4), failed to state it made a reasonable  
22 inquiry into the matter.

23 <sup>3</sup> In *Dobbs*, for example, the label and package insert at the time of the decedent’s  
24 suicide both referenced suicide, including it as an “adverse reaction.” *Dobbs v. Wyeth*  
25 *Pharms*, 797 F. Supp. 2d 1264, 1272 (W.D. Okla. 2011). The question was whether  
26 the FDA would have prohibited a strengthened warning, something the FDA had in  
27 fact formally done. Here, pancreatic cancer warnings are non-existent, and the  
28 Defendants admit they have never submitted any proposed warning to the FDA.

<sup>4</sup> See Request for Admission (RFA) Nos. 1–8.

<sup>5</sup> See *All Star Seed v. Nationwide Agribusiness Ins. Co.*, 2012 U.S. Dist. LEXIS  
151008 \*4-7, 2012 WL 5197669 (S.D. Cal. Oct. 19, 2012)(outlining standard for  
compelling responses to requests for admission).

1 Defendants suggest the FDA must *always* act is disingenuous. Defendants know the  
2 FDA does not act as they represented in their preemption motion. They should not be  
3 allowed to hide that fact by refusing to respond to this discovery.

4 **A. BRIEF SUMMARY OF MEET AND CONFER EFFORTS**

5 Plaintiffs hosted separate teleconferences with each Defendant on September 8,  
6 2014, raising each of the categorical issues in this motion. Plaintiffs agreed to limit  
7 interrogatories 7, 8, and 9 to the policies and practices relevant to the drugs in this  
8 litigation. Defendants maintained all of the objections in their written answers and  
9 confirmed that, for many requests, they had not performed a reasonable investigation  
10 and would not do so until the Court ordered otherwise.

11 **B-C. DESCRIPTION OF THE DISCOVERY SOUGHT TO BE COMPELLED**

12 The discovery relates primarily to preemption. Plaintiffs respectfully request an  
13 order overruling objections to, and compelling a response to, the following:

- 14 • RFA Nos. 1–11 (admit or deny facts relating to the ‘reasonable  
15 evidence’ standard)
- 16 • RFA Nos. 30–37 (admit or deny discussions with regulatory authorities  
17 regarding cancer warnings)
- 18 • ROG Nos. 2–5 (describe ‘reasonable evidence’ for the side effects  
19 warned about for the drugs in this case; identify instances where you  
20 proposed warning for side effects that did not meet the ‘reasonable  
21 evidence’ standard; identify examples of FDA allowing or not allowing  
22 warnings that did not meet the ‘reasonable evidence’ standard)
- 23 • ROG No. 6 (identify instances, if any, of regulatory bodies asking you  
24 to add or strengthen warnings for these drugs relating to pancreatitis,  
25 pancreatic cancer, or pancreatitis)
- 26 • RFP Nos. 4–8 (FDA communications, if any, rejecting a warning  
27 because it did not meet the ‘reasonable evidence’ standard, or rejecting  
28 a warning relating to these drugs)

1 Some of the discovery requests at issue here relate to both preemption and  
2 general causation:

- 3 • ROG Nos. 7–9 (identify pending governmental, qui tam, and corporate  
4 integrity investigations or actions that relate to the drugs in this  
5 litigation or relate to the corporate policies and practices applicable to  
6 the study of these drugs)
- 7 • RFP No. 10 (internal documents in which employees or consultants  
8 recommend including a reference to pancreatic cancer in the  
9 Prescribing Information or Medication Guide for these drugs)

10 The discovery requests were tailored to each Defendant’s medication. A copy  
11 of the requests alone is attached as Exhibit A, and a copy of the requests with the  
12 Defendants’ respective answers is attached as Exhibit B.

13 **D. RELEVANCE AND NECESSITY OF THE REQUESTED DISCOVERY**

14 **1. “Reasonable Evidence of a Causal Association” Discovery: RFA  
15 Nos. 1–11, ROG Nos. 2–5, and RFP Nos. 4–8.**

16 Defendants themselves draw the ‘reasonable evidence’ standard as a line in the  
17 sand. They contend the FDA *cannot*<sup>6</sup> and *will not*<sup>7</sup> approve a warning until the  
18 ‘reasonable evidence’ threshold is crossed, and that the “ultimate inquiry” for  
19 preemption depends upon this “requirement.” Dkt. 410-1, p. 15. Neither the FDA nor  
20 any court has ever accepted that position,<sup>8</sup> but those legal questions will be decided

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21 <sup>6</sup> See Defendants’ motion for summary judgment: “FDA *can only* approve a warning  
22 as part of the labeling if there is reasonable evidence of a causal association ...” Dkt.  
23 410-1, p. 8 (emphasis added).

24 <sup>7</sup> See, e.g., Defendant Amylin’s response to RFP No. 2: “FDA *will not* approve a  
25 warning unless ‘reasonable evidence of a causal association’ between the disease and  
26 medication supports the warning.” (Emphasis added.)

27 <sup>8</sup> Instead, courts have recognized that a manufacturer is *required* to add a warning  
28 once it has “reasonable evidence of a causal association.” See, e.g., *In re Chantix*, 889  
F. Supp. 2d 1272, 1293 (N.D. Ala. 2012); see also *Newman v. McNeil Consumer  
Healthcare*, 2012 U.S. Dist. LEXIS 2153 \*33–37, 2012 WL 39793 (N.D. Ill. Jan. 9,  
2012) (describing how the FDA relies on adverse event reports and case reports to

1 later. In discovery, as a *factual* matter, and as *law applies to fact*,<sup>9</sup> the “reasonable  
2 evidence” standard is free-form and fact-intensive.<sup>10</sup>

3 Plaintiffs sought the facts underlying Defendants’ unprecedented arguments,  
4 and Defendants’ contentions about the application of law to facts, by way of:

- 5 1. Requests seeking Defendants’ own characterization of this standard;
- 6 2. Requests seeking information about whether and how the adverse  
7 effects warned about for the drugs in this litigation meet the “reasonable  
8 evidence” standard; and,
- 9 3. Requests for examples, if any exist, of the FDA actually interpreting the  
10 “reasonable evidence” standard this way and preventing a manufacturer  
from adding a warning to a medication.

11 Regarding the first category, Defendants responded with circular references to  
12 the regulation itself and the identification of documents that generally outline its  
13 policies. Plaintiffs understand Defendants have conducted a reasonable investigation  
14 and have produced all responsive documents.<sup>11</sup> Thus, those requests are not part of  
15 this motion to compel.

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18 assess when there is “reasonable evidence of a causal association” triggering the  
warning requirement).

19 <sup>9</sup> See, e.g., Fed.R.Civ.P. 36(a)(1)(requests may address “the application of law to  
20 fact”); *Playboy Enters., Inc. v. Welles*, 60 F. Supp. 2d 1050, 1057 (S.D. Cal. 1999)  
(holding that RFAs may properly relate to “the application of law to fact”).

21 <sup>10</sup> As Merck’s own regulatory expert testified last year in the Fosamax litigation,  
22 “reasonable evidence of causal association is not defined in the regulations,” but  
23 rather “has to be discussed and thought about in context,” including “the product  
24 you’re looking at” and “clinical judgment.” See *Merck’s Memorandum in Support of*  
25 *Motion for Judgment As A Matter Of Law* in the Fosamax litigation, available at the  
District of New Jersey, Case 3:11-cv-05304-JAP-LHG, Dkt. 209-1, filed 04/26/13,  
page 16 of 27.

26 <sup>11</sup> See, e.g., this Court’s hearing on September 10, 2014, page 22: “My assumption is  
27 that under Rule 26(g), all of the interrogatory responses or document requests were  
28 verified or signed off on by counsel or the party as to the reasonable inquiry and the  
completeness.”

1           Regarding the second category, the Defendants refused to respond. For  
2 example, Defendants will not admit or deny whether there exists “reasonable  
3 evidence” to support the pancreatitis warnings found on all of their medications,<sup>12</sup> nor  
4 will they search for and produce responsive documents. The relevance of this inquiry  
5 is obvious and was previously raised by the Court in the Onglyza proceedings.<sup>13</sup>  
6 Defendants confirmed during the phone conferences that they were aware of this  
7 Court’s order in the Onglyza proceedings, but they nonetheless refused to respond to  
8 any requests regarding pancreatitis. Defendants similarly refused to respond to any  
9 request regarding the side effects and adverse reactions listed on their drug’s  
10 prescribing information inserts and medication guides.<sup>14</sup>

11           Regarding the third category, even in the novel way that Defendants frame  
12 preemption, they bear the burden of proving a hypothetical course of action by the  
13 FDA, i.e., that the FDA “would have” prohibited them from any mention of  
14 pancreatic cancer. Plaintiffs thus asked Defendants to provide examples, if any exist,  
15 of the FDA actually prohibiting a warning because, in the FDA’s view, there was no  
16 “reasonable evidence of a causal association.” Defendants refused to respond, and in  
17 the meet and confer confirmed they had not performed any investigation into this  
18 issue and would not produce any documents because they believed the FDA’s *actual*  
19 *practices* were irrelevant to their preemption defense.

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22 <sup>12</sup> RFA Nos. 10 and 11.

23 <sup>13</sup> *Seufert v. Merck et al.*, July 22, 2014, Dkt. 44, page 2-3: “If the FDA and EMA  
24 position is that the ‘recent assertions of causal association between incretin-based  
25 drugs and pancreatitis and pancreatic cancer, as expressed in the scientific literature  
26 and media, is inconsistent,’ then why is there a warning on the risk of pancreatitis?”

27 <sup>14</sup> One defendant claimed that the Court had *already* precluded this discovery by way  
28 of its February 18, 2014 order limiting discovery to general causation. Plaintiffs noted  
that Defendants’ preemption motion was filed two months *after* that Order, thereby  
making preemption-related issues relevant. Defendants responded that no information  
could be relevant to their motion except for the exhibits they attached.

1 The discovery at issue here is the only way the Court can have any *factual*  
2 basis on which to speculate about what the FDA might have done with a hypothetical  
3 warning. If, for example, the FDA has *ever* allowed a warning despite the absence of  
4 “reasonable evidence,” then the Defendants’ entire argument – ie., “FDA can only  
5 approve a warning as part of the labeling if there is reasonable evidence of a causal  
6 association ...” Dkt. 410-1, p. 8 – has been proven meritless.

7 Moreover, even if Defendants temper their argument and admit the FDA can  
8 and does allow warnings *regardless of the “reasonable evidence” standard*, then,  
9 again, the requested discovery is essential to this Court’s review, because it provides  
10 concrete evidence of how the FDA *actually* acts in these circumstances. This  
11 discovery is the *only* way this Court can begin answering basic questions like: *Why*  
12 *do the Defendants’ products continue to warn about pancreatitis?* and *What*  
13 *“reasonable evidence” underlies the adverse effects listed on the drugs in this*  
14 *litigation?* and *Has the FDA ever prohibited a manufacturer from adding a warning*  
15 *for a serious, unlabeled side effect?*

16 **2. Fraud, Qui Tam, and Corporate Integrity Discovery:**  
17 **ROG Nos. 7, 8, and 9**

18 Defendants’ general causation and preemption arguments both depend heavily  
19 on their own nonclinical studies, clinical studies, and adverse event reporting. Thus,  
20 Plaintiffs inquired into whether Defendants or their employees were the subject of  
21 governmental investigations, False Claims Act investigations, or Corporate Integrity  
22 Agreement negotiations relating to the potential manipulation of scientific data. A  
23 simple “no” would resolve the concern; instead, all Defendants refused to respond. At  
24 the meet and confer, Plaintiffs recognized Defendants’ objection that the request  
25 could be interpreted to extend to situations having no bearing on the drugs at issue in  
26 this case. So, Plaintiffs agreed to limit their request to policies and practices  
27 applicable to these drugs – but the Defendants still refused to respond.

1 Plainly, if this Court is going to rely on Defendants’ scientific evidence to  
2 decide *Daubert* or sit as a mock FDA judging “reasonable evidence,” it should know  
3 if Defendants are being investigated by another governmental entity with regard to  
4 that very same scientific evidence. These interrogatories are clearly relevant and not  
5 burdensome or harassing in the least; how many simultaneous scientific fraud  
6 investigations could Defendants truly be facing? These questions should be answered.

7 **3. Internal Warning Recommendations: RFP No. 10**

8 Plaintiffs’ Request for Production No. 10 sought the following information  
9 from each Defendant:

10 Every DOCUMENT in which an employee of, or consultant to, YOUR  
11 company recommends including a reference to pancreatic cancer in the  
12 BYETTA Prescribing Information or Medication Guide.

13 Defendant Amylin’s answer to this question, after its generalized objections, is  
14 revealing:

15 Subject to and without waiving the foregoing objections, Amylin responds  
16 as follows: To the extent such information exists in the files of the  
17 custodians agreed upon by the parties, Amylin refers Plaintiffs to  
18 documents previously produced in this litigation. Specifically, Amylin  
19 refers Plaintiffs to Exhibit D to Amylin’s Responses and Objections to  
20 Plaintiffs’ General Causation Interrogatories, which lists the custodians  
21 whose files have been produced, the custodians’ job titles, and the Bates  
22 numbers at which documents from their files may be found. Plaintiffs can  
23 locate and identify documents responsive to this Request within these  
24 productions as readily as Amylin could.

25 Amylin thus admits it has *not* performed a Rule 26 investigation into this  
26 matter. Instead, it simply affirms it has not removed such files from the custodial  
27 productions. That is insufficient.<sup>15</sup> If Defendants know of such documents, they must  
28 be produced.

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27 <sup>15</sup> See, e.g., *3M Innovative Prods. Co. v. Tomar Elecs.*, 2006 U.S. Dist. LEXIS 80571,  
28 \*17 (D. Minn. July 21, 2006)(“Accordingly, a reasonable investigation by a company  
would include an inquiry of a company’s employees for relevant information. A

1           **4. Remaining Regulatory Discussions: RFA Nos. 30–37, ROG No. 6**

2           These requests are related to, but not overlapping of, the requests at issue in the  
3 Motion to Compel Against All Defendants for Their Communications With or  
4 Related to Certain Foreign Regulatory Agencies. Dkt. 630. That motion addresses  
5 requests for production of documents from Plaintiffs’ first set of “general causation”  
6 discovery. At issue here are:

- 7           • An interrogatory on whether any regulatory body has requested or  
8 required Defendants to change their labels relating to pancreatitis,  
9 pancreatic cancer, or other cancers; and,  
10           • Seven requests for admission about whether the Defendants are, or are  
11 not, in discussions with the FDA (requests 30 & 31)<sup>16</sup>, EMA (requests  
12 32 & 33), or other regulatory bodies (requests 34, 35, 36, 37) about  
adding warnings for pancreatic cancers or all cancers.

13           All of these requests are likely to produce relevant information that will  
14 streamline the proceedings. For example, Amylin refused to admit or deny if it was in  
15 discussions with the FDA about adding a warning for all cancers. If it actually is  
16 engaged such discussions, that raises a number of issues about how, and why, such  
17 discussions are occurring; and it would call into question Defendants’ contentions  
18 about the “reasonable evidence” standard. The other requests similarly are not  
19 burdensome, but can provide a wealth of relevant information. For example, if any of  
20 the Defendants are in discussions with any regulatory authorities about adding  
21 pancreatic cancer warnings, it would raise serious questions about the information  
22 *those* authorities were given that the FDA was *not* given.  
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25 company need not question all employees, but must question those that would  
26 reasonably have relevant information.”); *Brown v. Tellerate Holdings Ltd.*, 2014  
27 U.S. Dist. LEXIS 90123, \*43 (S.D. Ohio July 1, 2014)(sanctioning counsel for  
interposing objections instead of speaking with client’s employees and agents).

28 <sup>16</sup> Lilly properly answered these two as “Admitted” and “Denied,” because it is no longer involved in the sale of Byetta.

1 **CONCLUSION**

2 For the reasons set forth above, Plaintiffs respectfully request an Order  
3 compelling meaningful and complete responses to Plaintiffs’ Set II written discovery:  
4 ROG Nos. 2-9; RFP Nos. 4-8 and 10; and RFA Nos. 1-11 and 30-37.

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6 DATED: September 16, 2014

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1 **CERTIFICATE OF SERVICE**

2 I hereby certify that on September 16, 2014, I caused the above document to be  
3 filed via the CM/ECF system for the Southern District of California, and the CM/ECF  
4 system served the same upon all registered users at their registered email addresses.

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