

Groton / New London Laboratories  
Pfizer Inc  
Eastern Point Road  
Groton, CT 06340



**Pfizer Global Research & Development**

November 7, 2005

Division of Dockets Management  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, Maryland 20852

Re: Amorphous Atorvastatin

Dear Sir or Madam:

CITIZEN PETITION

On July 28, 2005, we wrote to Gary Buehler to provide background information on amorphous versions of atorvastatin that we believe may be relevant to FDA's consideration of generic drugs that contain such polymorphs. That letter is attached as Exhibit A. In a letter dated August 30, 2005, attached as Exhibit B, Mr. Buehler requested that we file a petition containing the same information. He noted that the citizen petition process would permit others an opportunity to comment on the points we raise and also permit Pfizer the opportunity to comment on the views and opinions of others that may be submitted in the citizen petition file. We submit this petition in response to Mr. Buehler's request.

A. Action Requested

Pfizer asks that FDA consider the information provided in the July 28 letter, together with any additional information that may be submitted to the petition file by Pfizer or others, in FDA's decisions concerning approvals of generic versions of atorvastatin.<sup>1</sup>

B. Statement of Grounds

We incorporate the July 28 letter (Exhibit A) as our statement of grounds for this petition. In addition, we add further scientific evidence which supports the contention that multiple "amorphous" forms of atorvastatin calcium exist (Exhibit B). These data consist of small angle x-ray scattering (SAXS) profiles obtained using synchrotron radiation, and demonstrate that "amorphous" Forms 23 and 27 are structurally different, with Form 23 being more ordered than Form 27, as also demonstrated by powder x-ray diffraction in Attachment 1 of Exhibit A.

<sup>1</sup> Mr. Buehler's letter notes that the issues raised in the July 28 letter may be of significant interest to others. We respectfully suggest that FDA consider scheduling a public meeting on these issues. At that meeting we, as well as experts put forward by other interested parties, could explain the data on amorphous atorvastatin and our views on its potential implications and respond to any questions from FDA experts.

2005P-0452

CP1

Division of Dockets Management  
November 7, 2005  
Page 2

C. Environmental Impact

The relief requested by this petition would result in an informed FDA evaluation of any ANDAs for atorvastatin. Because the grant of this petition would not have an effect on the environment, no environmental assessment is required. 21 C.F.R. § 25.31(a).

D. Economic Impact

Information on the economic impact of the action requested by this petition will be submitted if requested by the Commissioner.

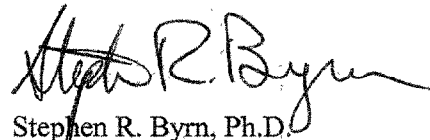
E. Certification

The undersigned certify that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners, which are unfavorable to the petition.

Respectfully submitted,



William J. Curatolo, Ph. D.  
Senior Research Fellow  
Pharmaceutical Sciences Division  
Pfizer Global Research and Development  
MS-4124  
Groton, CT 06340



Stephen R. Byrn, Ph.D.  
Study Director  
SSCI, Inc.  
3065 Kent Avenue  
West Lafayette, IN 47906

cc: Gary Buehler, Office of Generic Drugs, FDA

## EXHIBIT A

Groton/ New London Laboratories  
Pfizer Inc  
Eastern Point Road  
Groton, CT 06340



### Pfizer Global Research & Development

July 28, 2005

Gary J. Buehler  
Director, Office of Generic Drugs  
Food and Drug Administration  
Center for Drug Evaluation and Research  
HFD-600, Room 286  
Metro Park North 2  
7500 Standish Place  
Rockville, MD 20855

Re: Generic Versions of Atorvastatin

Dear Mr. Buehler:

Pfizer Inc. is the manufacturer of Lipitor® (atorvastatin). We are writing to you because we are concerned that ANDA applicants are seeking approval of polymorphs of atorvastatin that are different from, and may be inferior in quality to, Lipitor. We believe that ANDA applicants are likely to use physical forms of atorvastatin that may be susceptible to higher levels of impurities than are found in Lipitor and that may degrade more quickly and thus have inferior stability compared to Lipitor. We ask that such potential differences in quality be carefully scrutinized before the atorvastatin variants are approved under ANDAs.

#### Background

Atorvastatin is an unusual molecule in the sense that it exists in a very large number of different polymorphs. Significantly, there are variations among the potential "amorphous" forms of this molecule and those variations may have somewhat different properties. In addition, since pure, amorphous atorvastatin is chemically unstable, the need to add stabilizers to dosage forms containing amorphous atorvastatin may help alleviate the stability issue, but opens a range of other technical issues and may result in a product which may exhibit very different behavior than Lipitor. Several publications have appeared in the last few years describing amorphous forms of atorvastatin, and the early development work on Lipitor was done with an amorphous form. It is our understanding that there is a pending application for a generic version of this product that is in an amorphous form.

Pfizer, of course, has substantial experience with atorvastatin and has developed information concerning the solid forms of this molecule. We also have acquired samples of generic versions of this drug marketed in other countries of the world and have subjected them to analysis. We believe, based on the information that we have obtained, that a generic version of atorvastatin utilizing an amorphous form would have different properties than Lipitor and would present a risk of different and/or higher levels of impurities than are found in Lipitor. That risk would exist both at the time of initial manufacture of the generic product and, perhaps most important, through degradation during its shelf life. We, of course, have very limited information about any generic atorvastatin product that has been, or will in the future be, submitted to FDA for review. In these circumstances, however, we thought it appropriate to provide to you background information that we have developed concerning atorvastatin in its amorphous form. As noted, we believe that this information may raise questions about the approval of some such applications or, at a minimum, suggests that such applications should contain safeguards against inconsistent or inferior quality.

#### Atorvastatin Appears in Many Polymorphic Forms

Our work with atorvastatin reveals that it can exist both in amorphous forms and in a significant number of different crystalline forms. The marketed atorvastatin product exists in a crystalline form that was discovered during the development process for atorvastatin and is the subject of a Pfizer patent. We are aware of over twenty other crystalline forms of atorvastatin.

#### There are a Variety of "Amorphous" Forms of Atorvastatin

The term "amorphous," at least with respect to this molecule, can cover disordered forms that are, on careful examination, quite different from each other. The most common amorphous form has been designated "Form 27" by us. A somewhat less common amorphous form has been identified as "Form 23". Attachment 1 to this letter demonstrates that these two "amorphous" forms exhibit different powder x-ray diffraction patterns.

#### Use of Different Polymorphs in Drug Development

The original atorvastatin utilized by Pfizer in the early development of this drug was Form 23 (in some documents referred to as amorphous B). During development, after some but not all clinical trials were completed, Pfizer developed a crystalline form, which is the form in which Lipitor is marketed. While bioequivalence testing showed a difference in the rate of absorption for crystalline tablets as opposed to tablets prepared with Form 23, the extent of absorption was equivalent for the two forms. After review of

clinical data relating to the two forms, FDA concluded that approval of the crystalline form was appropriate.

Our analysis of various generic products obtained from sources outside the United States suggests that those products that include atorvastatin in the amorphous form are, most commonly, Form 27. Even though both Form 23 and Form 27 appear amorphous by X-ray powder diffraction experiments, analysis of their local structure based on the X-ray powder diffraction data indicates that Form 23 has more compact local packing than Form 27. The difference in such local packing can be expected to lead to a difference in solubility. Indeed, as demonstrated by the enclosed data (Attachment 2), the two forms in fact demonstrate dissolution profiles that differ from each other and from the crystalline form found in Lipitor. In addition, the dissolution profile for Form 27 depends upon its method of manufacture, with different behavior observed for Form 27 prepared by precipitation or by spray-drying (Attachment 2).

By comparison and in general, crystalline compounds can have dissolution behavior which depends upon particle size. The setting of particle size specifications for a crystalline drug is a well-developed regulatory science. In the case of amorphous materials, there is not such a well-developed understanding of the physical properties of different amorphous forms of a drug, or of a single amorphous form manufactured in different ways, as evidenced by our dissolution data for precipitated Form 27, spray-dried Form 27, and Form 23 (prepared by precipitation).

#### Polymorphic Form and Stability

Crystalline forms in general, and the crystalline forms of atorvastatin, are more chemically stable than amorphous forms. Pfizer found, during its own developmental work on atorvastatin, that the bulk amorphous drug substance degraded quickly during accelerated stability studies at 40 °C/75% RH and 80 °C. By comparison, Pfizer's crystalline atorvastatin showed no significant increase in degradation impurities during the accelerated stability studies. See Attachment 3.

#### Potential Differences in Impurity Profiles Among Different Polymorphs

Differences in stability may, particularly over time, result in higher levels of impurities in an amorphous than in a crystalline version of atorvastatin. Because of the disordered physical structure of amorphous atorvastatin, it is predictable that the amorphous form will be more susceptible to degradation than the crystalline product.

Crystallization is usually utilized to achieve the desired chemical purity during the production of active ingredients. The amorphous form has a higher specific surface area, a greater tendency to absorb solvents, and a higher reactivity than the more ordered

crystalline form. Therefore, production of an amorphous form increases the likelihood that increased impurities will be incorporated in the active ingredient during production. In addition to the chemical impurities, higher amounts of solvents may also be incorporated into the amorphous form.

#### Significance for Approval of Generic Versions of Atorvastatin

The generic versions of atorvastatin will differ in physical form from Lipitor solely to support an effort by the generic applicants to avoid the reach of patent protection of the innovator. In the context of FDA's rejection of a Pfizer petition concerning 505(b)(2) applications, FDA suggested that it would consider whether it was appropriate to approve such applications for variations from approved drugs that offer no therapeutic benefit over the innovator. As that letter noted, approval of such variations may 1) undercut incentives for developing new active moieties, 2) lead to proliferation of variations, and 3) divert resources from innovative drug research to the development and patenting of variations simply for competitive purposes relating to the variations. Letter to Katherine Sanzo, et al from Janet Woodcock, M.D. Docket Nos. 2001P-0323, 2002P-0447, 2003P-0408 (Oct. 14, 2003) at 34.<sup>1</sup>

That discussion dealt with differences in salts and esters. The principles articulated apply equally, however, to the development of new physical forms to evade patent protection. FDA properly should look closely at whether any such new forms in fact do result in lower quality products for American consumers. Where, as here, the risk of reduced quality in the generic product is clear, the data submitted to support approval of the generic product should be reviewed with considerable skepticism.<sup>2</sup>

The likelihood that the use of amorphous atorvastatin will result in a risk of higher impurities should be considered as FDA reviews any applications containing this physical form of atorvastatin. Additionally, the use of any stabilizers or stabilizing excipients to improve chemical stability must be viewed very critically. The use of stabilizers of this sort does not have a great deal of precedence in the literature so their impact on the predictability of long-term stability from accelerated conditions is not well known.

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<sup>1</sup> Although Pfizer agrees with these concerns, Pfizer disagrees with the legal interpretation of section 505(b)(2) that is asserted in the petition response.

<sup>2</sup> One way to address these issues would be for FDA to develop, in a public proceeding, a standard of identity for atorvastatin. In somewhat similar circumstances, GlaxoSmithKline has requested that such a standard be developed for one of its products. See Citizen Petition, 2004P-0290 (July 7, 2004), pages 11-12. This reasonable approach should also be applied to atorvastatin.

Gary J. Buehler  
July 28, 2005  
Page 5

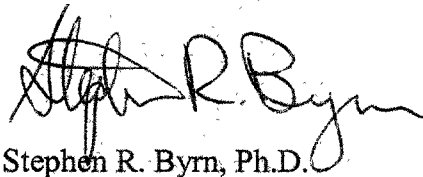
While Pfizer has considerable experience with the various polymorphic forms of atorvastatin, we of course have little or no information about the particular forms that may be incorporated in any potential generic version of atorvastatin for which another company may seek approval. However, the information that we do have about amorphous forms of this molecule suggests that the impurity profiles for such products and, in particular, their stability should be critically evaluated. We enclose a chart (Attachment 4) illustrating the results of our testing of generic versions of amorphous-form atorvastatin marketed abroad and also the data supporting that chart (Attachment 5).

Pfizer would be glad to share with FDA any information in its possession concerning the characteristics of the different polymorphs of atorvastatin that FDA may find useful as it considers any applications for generic versions of atorvastatin that have been or may be submitted. Please feel free to contact us with any questions or requests for information.

Sincerely,



William J. Curatolo, Ph. D.  
Senior Research Fellow  
Pharmaceutical Sciences Division  
Pfizer Global Research and Development  
MS-4124  
Groton, CT 06340  
Tel: 860-441-4890



Stephen R. Byrn, Ph.D.  
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3065 Kent Avenue  
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Tel: 765-714-280

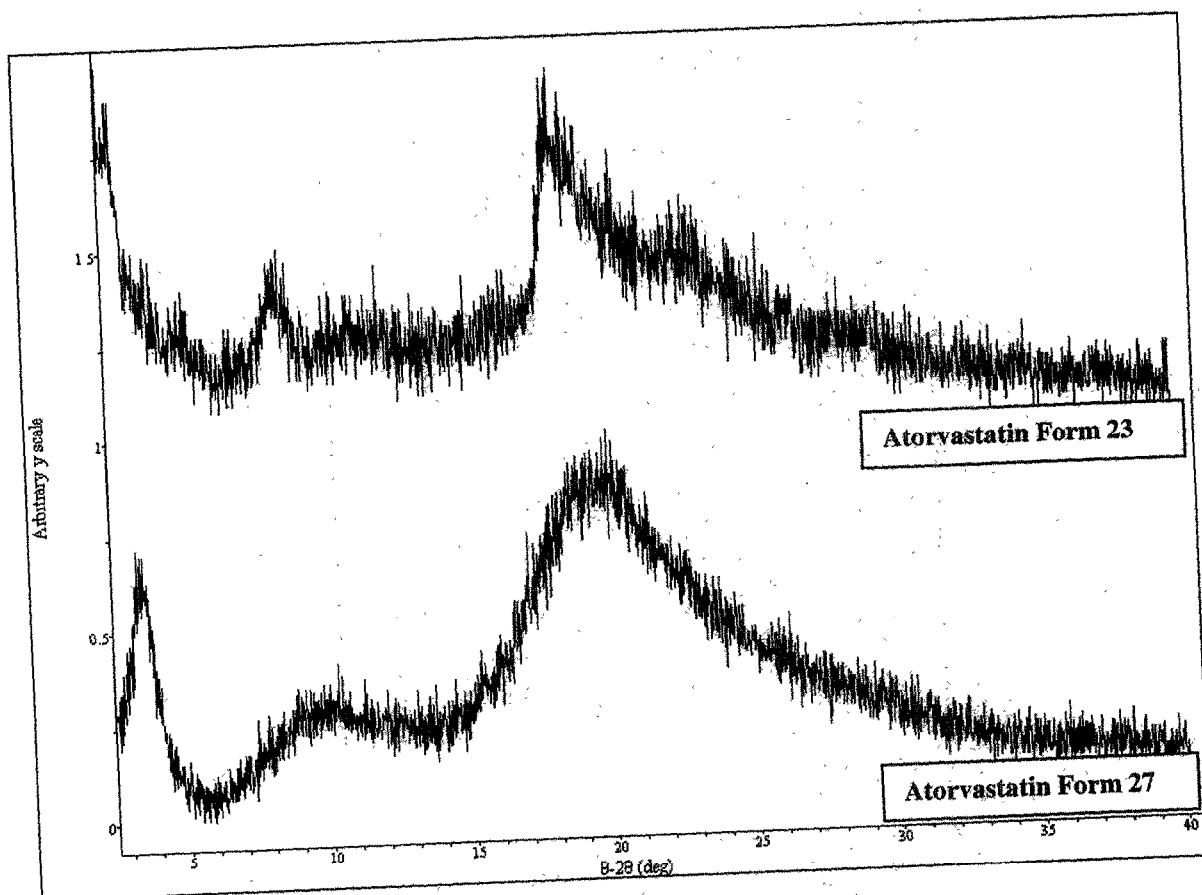
cc: Mr. J. Chasnow, Pfizer Legal  
Mr. J. Blumenstein, Pfizer PGRD Reg CMC

## **Attachments**

- Attachment 1: Powder X-ray diffraction patterns of two "amorphous" atorvastatin calcium forms.
- Attachment 2: Dissolution of atorvastatin calcium forms.
- Attachment 3: Stability of atorvastatin calcium forms.
- Attachment 4: Generic atorvastatin impurity profiles (bar chart).
- Attachment 5: Generic atorvastatin impurity profiles (data table).



**Attachment 1.**



## Attachment 2

Pfizer Global Research & Development  
Groton Laboratories  
Pfizer Inc  
Eastern Point Road  
Groton, CT 06340-5146

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### Analytical Research & Development

**DATE:** July 28, 2005  
**TO:** William Curatolo  
**FROM:** Segufta Kasli and Anthony Campeta  
**SUBJECT:** Solubility Study at 37°C for Crystalline Atorvastatin Calcium Commercial Form and Amorphous Atorvastatin Calcium Forms 23, 27 Spray Dried and 27 Precipitated

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Attached is a summary of the data for the solubility study at 37°C for crystalline atorvastatin calcium commercial form and amorphous atorvastatin calcium Forms 23, 27 spray dried and 27 precipitated. A copy of this report will be available in GDMS.

Please let us know if you have any questions.

A handwritten signature in cursive script, appearing to read "Segufta Kasli".

Segufta Kasli  
July 28, 2005

A handwritten signature in cursive script, appearing to read "Anthony Campeta".

Anthony Campeta  
July 28, 2005

Notebook references: 65813 (AMC) and 64527 (MLR)

cc: W. Curatolo  
M. Snyder  
M. Reynolds  
R. Reddy

**Solubility Study at 37°C for Crystalline Atorvastatin Calcium Commercial Form and Amorphous Atorvastatin Calcium Forms 23, 27 Spray Dried and 27 Precipitated**

<b>Atorvastatin Calcium</b>	<b>Crystalline Commercial Form, Lot 60294</b> <b>Amorphous Form 23, Lot 54910-38-1</b> <b>Amorphous Form 27 Spray Dried, Lot 57141-84 (BRI 2190-169)</b> <b>Amorphous Form 27 Precipitated, Lot 54910-36-1</b>
<b>Solution Media</b>	<b>Simulated Gastric Fluid (SGN), no enzyme</b> <b>Simulated Intestinal Fluid (SIF), no enzyme</b> <b>Water</b>
<b>Time Points</b>	<b>15 minutes</b> <b>30 minutes</b> <b>60 minutes</b> <b>24 hours</b>

**Objective:**

To determine the solubility at 37°C of crystalline atorvastatin calcium commercial form and amorphous atorvastatin calcium Forms 23, 27 spray dried and 27 precipitated in simulated gastric fluid, simulated intestinal fluid and water over 24 hours.

**Tests:**

<b>Test</b>	<b>Methodology</b>	<b>Test Method</b>
Assay	High Performance Liquid Chromatography	Assay and Purity Evaluation of Atorvastatin Blends, Granulations and Tablets by RPLC (adapted from ATP 6170-12)
Purity	High Performance Liquid Chromatography	Assay and Purity Evaluation of Atorvastatin Blends, Granulations and Tablets by RPLC (adapted from ATP 6170-12)

**Assay and Purity Experimental:**

Assay and Purity Evaluation of Atorvastatin Blends, Granulations and Tablets by RPLC (adapted from ATP 6170-12)

**Chromatographic Conditions**

<b>Column</b>	<b>Phenomenex Ultramex C-18, 5µ particle size, 4.6X250mm</b>
<b>Column Temperature</b>	<b>Ambient</b>
<b>Injection Volume</b>	<b>20µL</b>
<b>Flow Rate</b>	<b>1.5mL/min</b>
<b>Autosampler Temperature</b>	<b>15°C</b>
<b>Detection</b>	<b>UV detector at 244nm</b>
<b>Mobile Phase</b>	<b>0.05M Ammonium Citrate (pH 4.0)/Acetonitrile(ACN)/Tetrahydrofuran(THF), 53/27/20, (v/v/v)</b>

**Preparation:**

Crystalline atorvastatin calcium commercial form, Lot 60294, and amorphous atorvastatin calcium Forms 23, Lot 54910-38-1; 27 spray dried, Lot 57141-84 (BRI 2190-169); and 27 precipitated, Lot 54910-36-1 were used in this experiment. The simulated gastric fluid, no enzyme (SGN) and simulated intestinal fluid, no enzyme (SIF) were prepared according to the U.S. Pharmacopoeia 28. Deionized water was obtained through a Nanopure Infinity water filtration system. About 20mg of each API was placed in a 5mL tube, flowed by 4.5mL of the appropriate solubility

medium pre-equilibrated at 37°C. Duplicate tubes were prepared for each API/solvent combination. The tubes were capped and allowed to slowly invert on a rotating tube rack in a 37°C water bath. At the appropriate time points (15, 30, 60 minutes and 24 hours), about 1mL of slurry was removed, filtered (37°C equilibrated syringe and filter), and appropriately diluted with extraction solvent (1:1 pH7.4, 0.05M citrate buffer:ACN). The diluted information is shown in Table 1.

**Table 1: Dilution Information for Crystalline Atorvastatin Calcium Commercial Form and Amorphous Atorvastatin Calcium Forms 23, 27 Spray Dried and 27 Precipitated**

Solution Media	Time Point	Sample Volume	Into	Total Volume	Dilution Factor
SGN	All	500µL	HPLC vial	1000µL	2
SIF	15, 30 & 60 minutes	500µL	HPLC vial	1000µL	2
	24 hours	500µL	10mL volumetric flask	10mL	20
Water	15, 30 & 60 minutes	500µL	HPLC vial	1000µL	2
	24 hours	500µL	10mL volumetric flask	10mL	20

Some exceptions to Table 1 occurred due to filtration difficulties of the slurries. Exact sample volumes and total volumes were recorded in the notebook.

After the 24 hour time point, the pH of each solution was tested.

The final diluted samples were tested for atorvastatin concentration and lactone (PD 130694) levels using the HPLC method described above. The results are reported as the average actual concentration of atorvastatin active (µg/mL) and average %area of lactone.

The test results are in the following table.

**General Observation:**

- For all atorvastatin forms, the acidic SGN media shows a lower pH than SIF and water. Due to this low pH, an increase in lactone levels is observed for all forms.
- After 24 hour equilibration, solubility for all forms was greatest in SIF.
- Solubility of the amorphous atorvastatin calcium forms was higher than that of crystalline atorvastatin calcium commercial form at early time points (after 15-60 minutes) in water and SIF.

**Solubility at 37°C of Crystalline Atorvastatin Calcium Commercial Form  
and Amorphous Atorvastatin Calcium Forms 23, 27 Spray-Dried and 27 Precipitated**

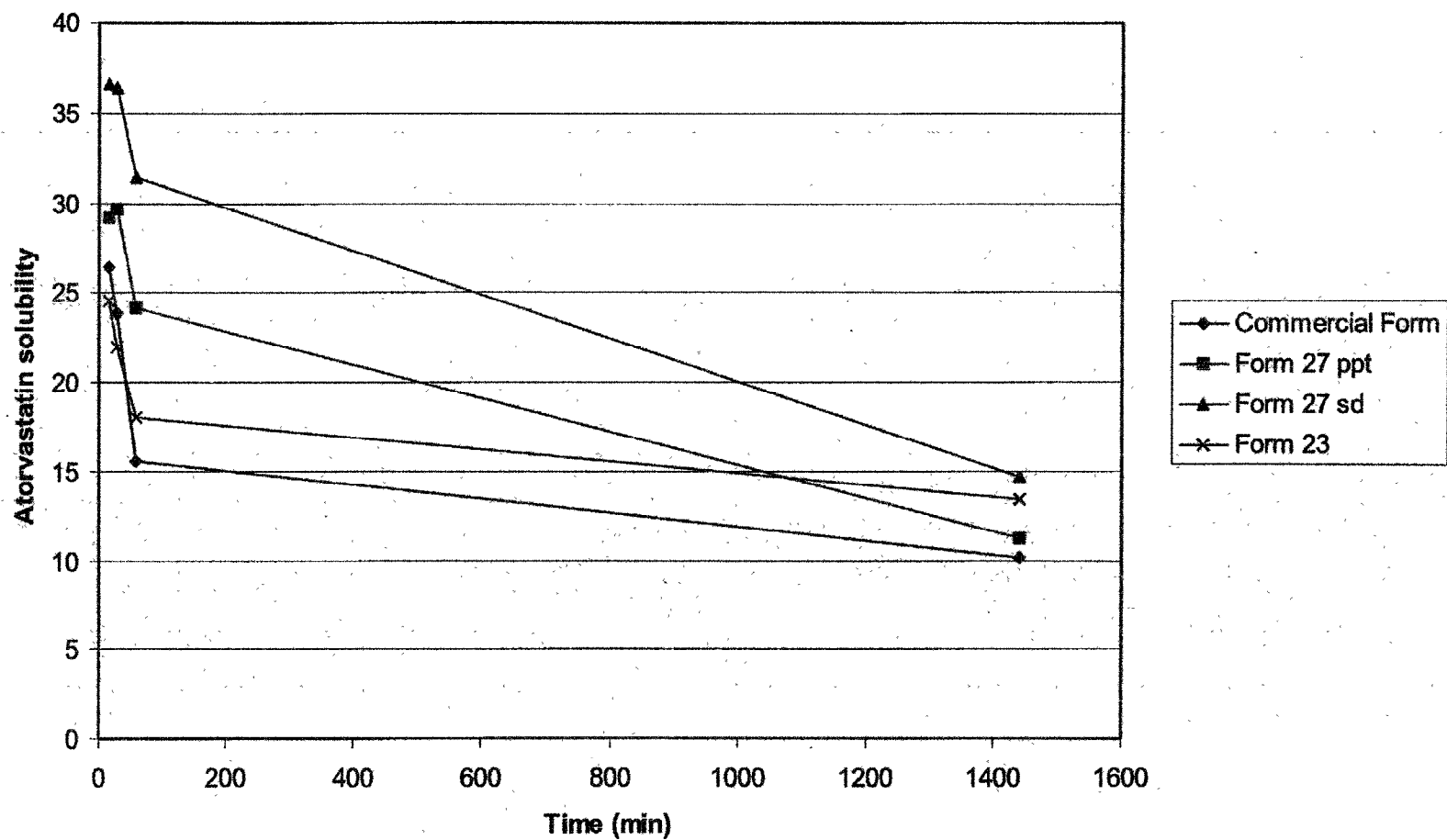
	Solution	Average Atorvastatin Concentration (ugA/mL)				Average Final pH	Average Lactone (% Area)			
		15 min	30 min	60 min	24 hr		15 min	30 min	60 min	24 hr
Commercial Form	SGN	26.4	23.8	15.6	10.1	1.22	8.3	11.0	17.3	39.0
Form 27 ppt	SGN	29.2	29.7	24.1	11.2	1.26	7.3	7.7	12.3	36.2
Form 27 sd	SGN	36.6	36.4	31.4	14.7	1.25	8.8	9.4	11.9	38.8
Form 23	SGN	24.5	22.0	18.0	13.4	1.26	17.8	22.7	27.1	34.2
Commercial Form	SIF	205.1	227.4	229.5	325.3	6.86	nd	nd	nd	nd
Form 27 ppt	SIF	597.2	373.9	402.4	489.6	6.86	nd	nd	nd	nd
Form 27 sd	SIF	616.7	648.0	601.9	542.2	6.84	nd	nd	nd	nd
Form 23	SIF	538.1	629.2	668.3	556.6	6.82	<LOQ	<LOQ	nd	nd
Commercial Form	Water	109.5	113.7	116.6	157.7	6.21	nd	nd	nd	nd
Form 27 ppt	Water	393.4	483.0	407.6	154.3	7.00	nd	nd	nd	nd
Form 27 sd	Water	731.3	626.6	508.6	160.6	6.47	nd	nd	nd	nd
Form 23	Water	357.8	382.1	370.1	160.3	6.39	<LOQ	<LOQ	<LOQ	nd

ppt = precipitated  
sp = spray dried

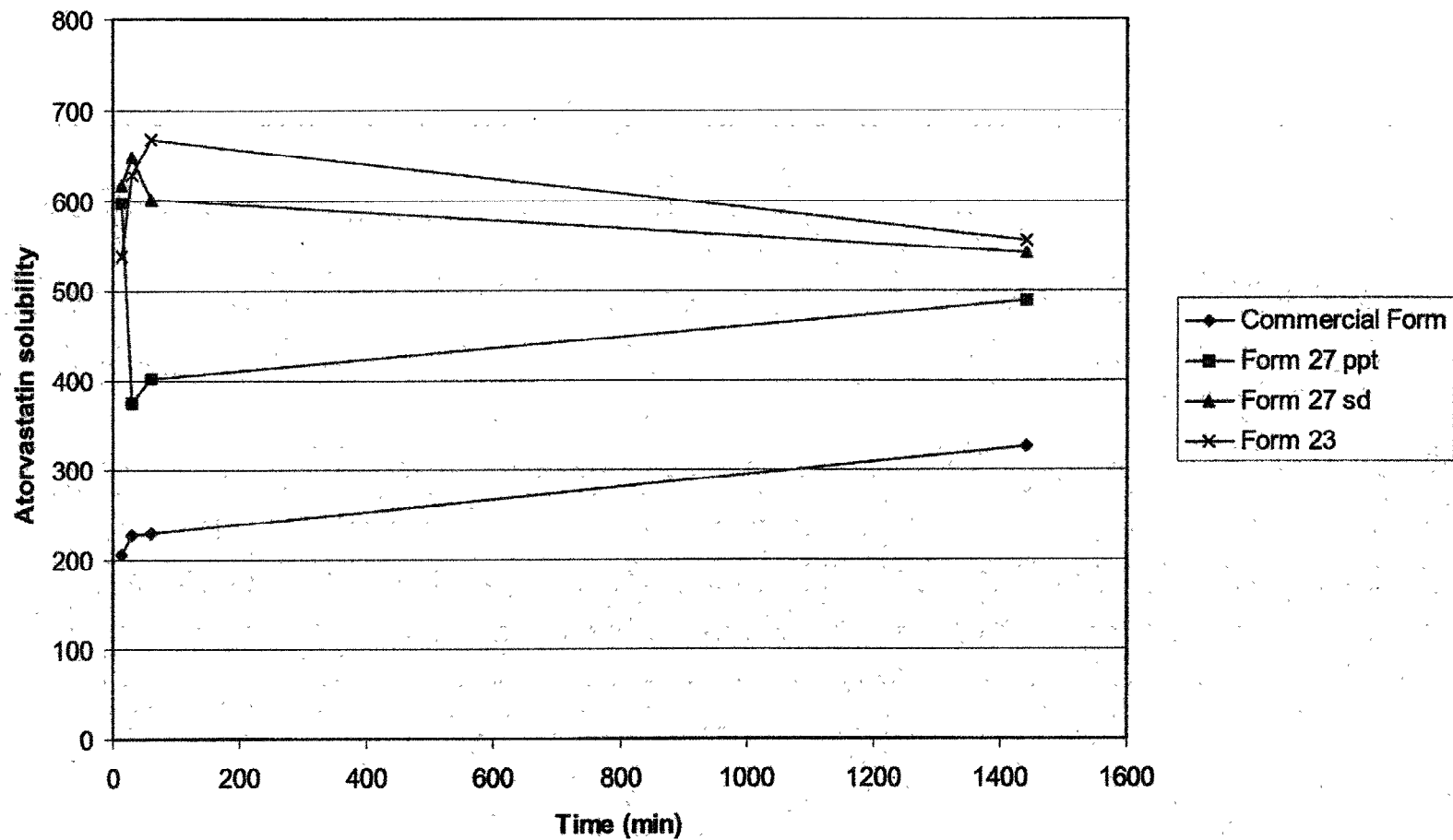
SGN = simulated gastric fluid  
SIF = simulated intestinal fluid

nd = not detected  
LOQ = 0.1%

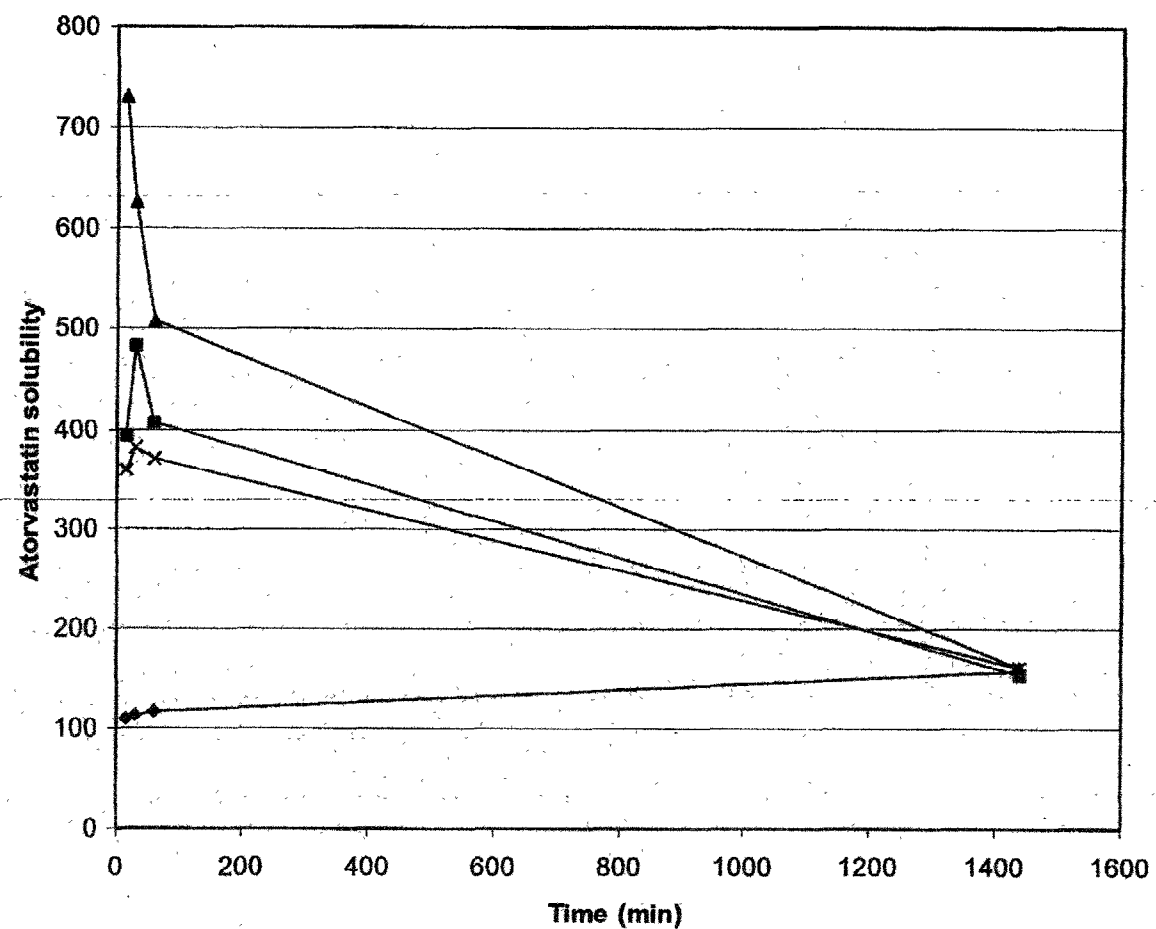
**Solubility at 37C of Crytalline Atorvastatin Calcium Commercial Form and  
Amorphous Atorvastatin Calcium Forms in SGN**



**Solubility at 37C of Crystalline Atorvastatin Calcium Commercial Form and Amorphous Atorvastatin Calcium Forms in SIF**



**Solubility at 37C of Crytalline Atorvastatin Calcium Commercial Form and Amorphous Atorvastatin Calcium Forms in Water**





Butler, Jennie C

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**From:** Curatolo, William J [William.J.Curatolo@pfizer.com]  
**Sent:** Thursday, November 17, 2005 6:26 PM  
**To:** jbutler1@oc.fda.gov  
**Cc:** Chasnow, Jeffrey B; Blumenstein, Jeffrey J  
**Subject:** Pfizer Citizen Petition

Dear Ms. Butler:

In response to your phone contact, the Pfizer Citizen Petition on Amorphous Lipitor (Docket #2005P-0452) does not contain any information (including the attachments) which we wish to keep confidential.

Thank you.

William Curatolo  
Senior Research Fellow  
Groton/New London Labs  
Pfizer PGRD

Tel: 860-441-4890

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**C O N F I D E N T I A L**

**PARKE-DAVIS PHARMACEUTICAL RESEARCH  
DIVISION OF WARNER-LAMBERT COMPANY  
ANN ARBOR, MICHIGAN**

**RESEARCH REPORT NO.:** RR 730-02404

**PD AUTHOR(S):**  
HURLEY T  
COLSON C

**DATE ISSUED:** 10/04/95

**PERIOD(S) COVERED:**

**DEPARTMENT:** CHEMICAL DEVELOPMENT

**NOTEBOOK (OR OTHER REFS):**  
38551X32

**INVESTIGATOR(S):**

**SUGGESTED KEY WORDS:**  
ATORVASTATIN  
BULK DRUG SUBSTANCE  
LONG-TERM STABILITY  
AMORPHOUS VERSUS CRYSTALLINE

**COMPOUND NUMBERS (PD,WL,GOE,CI):**  
CI-981  
PD 134298-38A

**TITLE:** ACCELERATED STABILITY OF ATORVASTATIN (CI-981) BULK DRUG SUBSTANCE:  
AMORPHOUS VERSUS CRYSTALLINE FORMS

Accelerated stability studies were performed on 2 lots of atorvastatin (CI-981) bulk drug substance. One lot (Holland 36580X104X5) was the amorphous form of the compound. The other lot (Holland 36582X142X23) was in the crystalline form. Both lots were exposed to elevated temperature (80°C) and elevated temperature/humidity (40°C/75% RH) conditions for 4 weeks. HPLC analyses were performed on both lots under both conditions at 0, 1, 2, 3, and 4 weeks. The crystalline material was also analyzed after 8 weeks under both accelerated conditions. This report details recoveries and impurity profiles of both the amorphous and crystalline forms of atorvastatin bulk drug substance exposed to accelerated decomposition conditions.

Introductory Material 1 Pages  
Main Report 6 Pages

RR 730-02404

1

## ACCELERATED STABILITY OF ATORVASTATIN (CI-981) BULK DRUG SUBSTANCE: AMORPHOUS VERSUS CRYSTALLINE FORMS

### INTRODUCTION

Accelerated stability studies were performed on 2 lots of atorvastatin (CI-981) bulk drug substance. One lot (Holland 36580X104X5) was the amorphous form of the compound. The other lot (Holland 36582X142X23) was in the crystalline form. Both lots were exposed to elevated temperature (80°C) and elevated temperature/humidity (40°C/75% RH) conditions for 4 weeks. HPLC analyses were performed on both lots under both conditions at 0, 1, 2, 3, and 4 weeks. The crystalline material was also analyzed after 8 weeks under both accelerated conditions. This report details recoveries and impurity profiles of both the amorphous and crystalline forms of atorvastatin bulk drug substance exposed to accelerated decomposition conditions.

### EXPERIMENTAL

#### Atorvastatin Lots Used in Study

Crystalline:	Holland 36582X142X23
Amorphous:	Holland 36580X104X5

#### Storage Conditions

80°C:	Drug substance placed in glass reaction vials sealed with screw-cap lids and placed in heating block set to 80°C
40°C/75% RH:	Stability oven

**Sampling Frequency:** 0, 1, 2, 3, and 4 weeks (both lots). The crystalline compound was sampled at 8 weeks.

**Tests Run:** HPLC assay, Impurity Profiles 1 and 2, all according to SOP 51.121.11; H<sub>2</sub>O analyses (Karl Fischer).

RR 730-02404

2

## RESULTS

Tables 1 and 2 show the details (assay, H<sub>2</sub>O content and individual impurity levels) of the amorphous drug substance under both storage conditions for the 4-week duration of the study. Tables 3 and 4 show the details of the crystalline drug substance under both storage conditions for the first 4 weeks of the study and also the 8-week data.

TABLE 1. Stability of Amorphous Atorvastatin Bulk Drug Substance  
(Lot 36580X104X5) Stored at 80°C

Component Detected <sup>a</sup>	Sampling Time Point				
	Initial	1 Week	2 Week	3 Week	4 Week
% Assay <sup>b</sup>	92.81	89.86	89.06	86.76	81.81
% H <sub>2</sub> O <sup>c</sup>	1.74	1.50	1.40	1.11	1.14
% PD 138151	0.09	0.04	0.05	0.11	0.15
% PD 140728	0.36	0.39	0.39	0.41	0.51
% PD 138703	0.18	0.17	0.12	0.09	0.18
% "Desfloro-B"	<0.01	0.07	<0.01	0.01	0.08
% PD 140086	0.09	0.08	0.08	0.06	0.14
% PD 138723	0.07	0.27	0.13	0.06	0.07
% Others (IP-1)	0.31	0.67	1.08	1.99	2.65
% PD 139687	0.02	0.01	0.02	0.02	0.02
% PD 153824 (AA-6)	0.12	0.67	0.67	0.98	1.46
% PD 148996 (AA-1)	0.25	0.92	1.03	1.30	1.98
% RRT 2.60	0.05	0.31	0.30	0.38	0.39
% RRT 3.60	<0.01	0.06	0.13	0.19	0.30
% PD 139688	0.01	0.01	0.01	0.01	0.01
% PD 130694	0.08	0.24	0.28	0.38	0.55
% PD 139884	0.55	0.65	0.77	0.90	1.08
% PD 133272	<0.01	<0.01	<0.01	<0.01	<0.01
% PD 138144	<0.01	<0.01	<0.01	<0.01	<0.01
% PD 135841	<0.02	<0.02	<0.02	<0.02	<0.02
% Others (IP-2)	1.15	0.82	0.91	1.23	0.80
% Total Impurities (Area)	3.33	5.37	5.97	8.12	10.37

% Others (IP-1) = % unlisted impurities determined by Impurity Profile 1 (area normalization);

RRT = Relative retention time (relative to CI-981 in Impurity Profile 2); % Others (IP-2) = % Unlisted impurities determined by Impurity Profile 2 (area normalization).

<sup>a</sup> Individual impurities reported as normalized area percentages.

<sup>b</sup> Assayed versus CI-981 analytical reference material Lot 1

<sup>c</sup> Karl Fischer titration

RR 730-02404

3

TABLE 2. Stability of Amorphous Atorvastatin Bulk Drug Substance  
(Lot 36580X104X5) Stored at 40°C/75% RH

Component Detected <sup>a</sup>	Sampling Time Point				
	Initial	1 Week	2 Week	3 Week	4 Week
% Assay <sup>b</sup>	92.81	94.96	95.61	94.53	93.64
% H <sub>2</sub> O <sup>c</sup>	1.74	4.46	4.88	4.87	4.53
% PD 138151	0.09	0.03	0.04	0.07	0.06
% PD 140728	0.36	0.34	0.36	0.38	0.39
% PD 138703	0.18	0.16	0.16	0.17	0.17
% "Desfloro-B"	<0.01	0.02	0.02	0.02	0.02
% PD 140086	0.09	0.08	0.08	0.07	0.07
% PD 138723	0.07	0.15	0.12	0.11	0.10
% Others (IP-1)	0.31	0.35	0.37	0.47	0.52
% PD 139687	0.02	0.02	0.02	0.02	0.02
% PD 153824 (AA-6)	0.12	0.23	0.29	0.32	0.39
% PD 148996 (AA-1)	0.25	0.33	0.38	0.43	0.46
% RRT 2.60	0.05	0.12	0.10	0.13	0.14
% RRT 3.60	<0.01	<0.01	0.01	0.04	0.06
% PD 139688	0.01	0.01	0.01	0.01	0.01
% PD 130694	0.08	0.12	0.22	0.11	0.20
% PD 139884	0.55	0.46	0.55	0.41	0.71
% PD 133272	<0.01	<0.01	<0.01	<0.01	<0.01
% PD 138144	<0.01	<0.01	<0.01	<0.01	<0.01
% PD 135841	<0.02	<0.02	<0.02	<0.02	<0.02
% Others (IP-2)	1.15	0.88	0.97	0.97	1.06
% Total Impurities(Area)	3.33	3.30	3.70	3.73	4.48

% Others (IP-1) = % unlisted impurities determined by Impurity Profile 1 (area normalization);

RRT = Relative retention time (relative to CI-981 in Impurity Profile 2); % Others (IP-2) = % Unlisted impurities determined by Impurity Profile 2 (area normalization).

<sup>a</sup> Individual impurities reported as normalized area percentages.

<sup>b</sup> Assayed versus CI-981 analytical reference material Lot 1

<sup>c</sup> Karl Fischer titration

RR 730-02404

4

TABLE 3. Stability of Crystalline Atorvastatin Bulk Drug Substance  
(Lot 36582X142X23) Stored at 80°C

Component Detected <sup>a</sup>	Sampling Time Point					
	Initial	1 Week	2 Week	3 Week	4 Week	8 Week
% Assay <sup>b</sup>	100.74	99.59	100.13	100.01	99.67	ND
% H <sub>2</sub> O <sup>c</sup>	4.81	4.96	5.09	4.60	4.80	ND
% PD 138151	0.05	0.04	0.04	0.04	0.04	0.03
% PD 140728	0.02	0.01	0.01	0.01	0.01	0.01
% PD 138703	0.15	0.14	0.14	0.14	0.11	0.14
% "Desfloro-B"	0.05	0.06	0.05	0.06	0.05	0.06
% PD 140086	0.10	0.10	0.10	0.09	0.10	0.11
% PD 138723	0.06	0.07	0.06	0.06	0.07	0.09
% Others (IP-1)	0.01	0.01	0.01	0.02	0.02	0.02
% PD 139687	<0.01	<0.01	<0.01	<0.01	0.02	0.01
% PD 153824 (AA-6)	<0.01	0.01	0.02	0.02	0.03	0.04
% PD 148996 (AA-1)	<0.01	0.02	0.02	0.02	0.04	0.04
% RRT 2.60	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
% RRT 3.60	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
% PD 139688	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
% PD 130694	<0.01	<0.01	0.02	0.02	0.03	0.03
% PD 139884	<0.02	<0.02	<0.02	<0.02	<0.02	0.02
% PD 133272	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
% PD 138144	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
% PD 135841	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02
% Others (IP-2)	0.01	0.00	0.00	0.01	0.03	0.00
% Total Impurities (Area)	0.46	0.46	0.47	0.47	0.53	0.60

% Others (IP-1) = % unlisted impurities determined by Impurity Profile 1 (area normalization);

RRT = Relative retention time (relative to CI-981 in Impurity Profile 2); % Others (IP-2) = % Unlisted impurities determined by Impurity Profile 2 (area normalization); ND = Not determined.

<sup>a</sup> Individual impurities reported as normalized area percentages.

<sup>b</sup> Assayed versus CI-981 analytical reference material Lot 1

<sup>c</sup> Karl Fischer titration

RR 730-02404

5

**TABLE 4. Stability of Crystalline Atorvastatin Bulk Drug Substance  
(Lot 36582X142X23) Stored at 40°C/75% RH**

Component Detected <sup>a</sup>	Sampling Time Point					
	Initial	1 Week	2 Week	3 Week	4 Week	Week 8
% Assay <sup>b</sup>	100.74	99.50	100.27	100.28	100.47	ND
% H <sub>2</sub> O <sup>c</sup>	4.81	5.03	5.09	4.74	4.70	ND
% PD 138151	0.05	0.04	0.04	0.05	0.05	0.04
% PD 140728	0.02	0.01	0.01	0.01	0.01	0.01
% PD 138703	0.15	0.10	0.14	0.14	0.14	0.14
% "Desfloro-B"	0.05	0.05	0.05	0.05	0.05	0.05
% PD 140086	0.10	0.10	0.10	0.09	0.10	0.10
% PD 138723	0.06	0.06	0.06	0.06	0.07	0.07
% Others (IP-1)	0.01	0.01	0.01	0.02	0.02	0.02
% PD 139687	<0.01	<0.01	<0.01	0.01	0.01	0.01
% PD 153824 (AA-6)	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
% PD 148996 (AA-1)	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
% RRT 2.60	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
% RRT 3.60	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
% PD 139688	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
% PD 130694	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
% PD 139884	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02
% PD 133272	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
% PD 138144	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
% PD 135841	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02
% Others (IP-2)	0.01	0.00	0.01	0.02	0.04	0.03
% Total Impurities(Area)	0.46	0.37	0.42	0.45	0.49	0.47

% Others (IP-1) = % unlisted impurities determined by Impurity Profile 1 (area normalization);

RRT = Relative retention time (relative to CI-981 in Impurity Profile 2); % Others (IP-2) = % Unlisted impurities determined by Impurity Profile 2 (area normalization); ND = Not determined.

<sup>a</sup> Individual impurities reported as normalized area percentages.

<sup>b</sup> Assayed versus CI-981 analytical reference material Lot 1

<sup>c</sup> Karl Fischer titration

## DISCUSSION

### Stability of Amorphous Atorvastatin

Over the 4-week duration of the study, the amorphous form of atorvastatin bulk drug substance was shown to have decomposed by a 7.0% increase in observed impurities at 80°C and by a 1.2% increase in observed impurities at 40°C/75% RH. The highest increases at 80°C were observed in the levels of PD 148996 (1.7% increase),

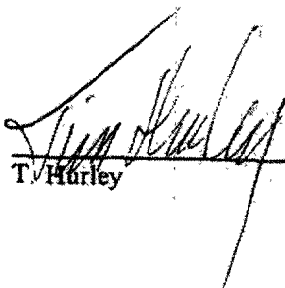
RR 730-02404

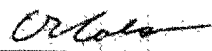
6

PD 153824 (1.3%), and PD 139884 (0.5%). The highest increases at 40°C/75%RH were observed in the levels of PD 153824 (0.27% increase), PD 148996 (0.21%), and PD 139884 (0.16%). At 80°C, a corresponding decrease of 11% was found in the assay. Due to the use of area normalization in these studies, mass balance cannot be demonstrated.

#### Stability of Crystalline Atorvastatin

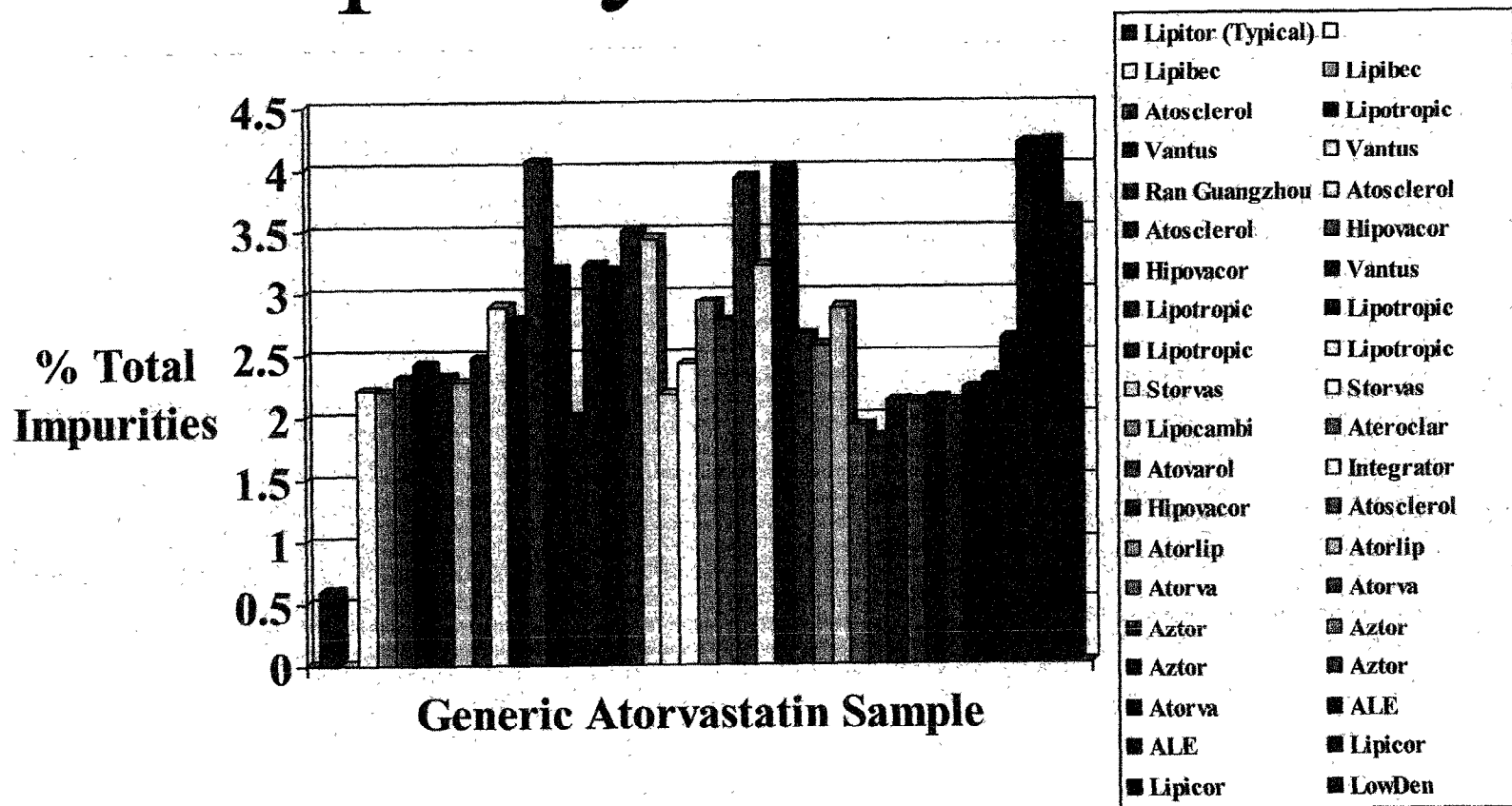
For the 8-week duration of the study, the crystalline form of atorvastatin bulk drug substance remained stable under both storage conditions. There were no observed increases of >0.05% in any impurity at 80°C or at 40°C/75% RH after 8 weeks.

  
T. Hurley

  
C. Colson, PhD



# Generic Atorvastatin Impurity Profiles



## Attachment 5

	<u>% Total Impurities</u>
Lipitor (Typical)	0.6
Generic Atorvastatin Sample:	
Lipibec	2.22
Lipibec	2.2
Atosclerol	2.31
Lipotropic	2.42
Vantus	2.33
Vantus	2.28
Ran Guangzhou	2.47
Atosclerol	2.88
Atosclerol	2.78
Hipovacor	4.05
Hipovacor	3.18
Vantus	1.98
Lipotropic	3.21
Lipotropic	3.17
Lipotropic	3.49
Lipotropic	3.43
Storvas	2.18
Storvas	2.42
Lipocambi	2.92
Ateroclar	2.77
Atovarol	3.92
Integrator	3.21
Hipovacor	4
Atosclerol	2.66
Atorlip	2.57
Atorlip	2.87
Atorva	1.92
Atorva	1.83
Aztor	2.12
Aztor	2.1
Aztor	2.14
Aztor	2.11
Atorva	2.22
ALE	2.3
ALE	2.62
Lipicor	4.19
Lipicor	4.2
LowDen	3.65

