Salix
PHARMACEUTICALS, INC.

2013 APR 18 A 9:29 March 7, 2013

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, Maryland 20852

CITIZEN PETITION

This Citizen Petition is submitted on behalf of Salix Pharmaceuticals, Inc. ("Salix") under sections 505(j) and 505(q) of the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 355(j) and 355(q), and 21 C.F.R. §§ 10.30, 314.94, and 320.21, to request that the Commissioner of Food and Drugs amend the Food and Drug Administration's (FDA's) existing criteria for how to demonstrate bioequivalence for mesalamine extended release capsules and apply such criteria to any abbreviated new drug application (ANDA) that relies upon the new drug application (NDA) for Apriso® (mesalamine) extended release capsules as the reference listed drug (RLD).

I. Action Requested

On September 21, 2012, FDA issued a Draft Guidance on Mesalamine describing FDA's approach to establishing bioequivalence for extended-release mesalamine products ("Draft Guidance"). As set forth below, the bioequivalence criteria established by FDA fail to consider all of the properties that make the Apriso® formulation unique and is insufficient to establish bioequivalence of a generic mesalamine product to Apriso®.

Salix therefore requests that, to establish bioequivalence for any ANDA that lists Apriso® as the reference listed drug, FDA:

- require bioequivalence to be established under fasted and fed conditions in patients with ulcerative colitis in remission;
- require pharmacokinetic (PK) parameters to be computed using the plasma analytes mesalamine (5-ASA) and its metabolite N-acetyl 5-aminosalicylic acid (N-Ac-5-ASA);
- require bioequivalence to be established on plasma PK parameters computed on plasma analytes 5-ASA and N-Ac-5-ASA for the parameters: maximum plasma drug concentration (C_{max}), area under the plasma concentration vs. time curve (AUC) from the time of dosing to 3 hours after dosing (AUC_{0-3}), AUC from 3 hours after dosing to the last measurable concentration (AUC_{3-t}), AUC from 8 hours after dosing to the last

FDA-2013-P-0470

2013-2875

CP

measurable concentration (AUC_{8-t}), AUC at the last measurable concentration (AUC_t) and time to the occurrence of C_{max} (T_{max}); and

- require a determination of the rate of N-Ac-5-ASA formation detected in the soluble fraction of fecal samples derived from subjects participating in the above pharmacokinetic studies.

We further request that the agency not approve any ANDAs for mesalamine without resolving the issues raised in this Citizen Petition.

II. Statement of Grounds

A. Background

1. Introduction

There are five different approved oral extended-release mesalamine formulations available to physicians treating patients with ulcerative colitis in remission. None of these is bioequivalent to the others. The selection of the type of formulation used for a given patient is based empirically on the therapeutic result obtained during initial treatment. Because Apriso® is presently not indicated for the treatment of acute symptoms, the cohort of patients currently receiving Apriso® maintenance treatment is the result of such empiric trial by the physician and patient after remission has been attained. This means patients successfully maintained on Apriso® have been therapeutically selected as a population whose disease characteristics are uniquely matched with, and respond to, the pharmacokinetic and pharmacodynamic properties of the Apriso® formulation. It is therefore imperative that any generic formulation of Apriso® reproduce a bioequivalent colonic delivery and metabolism of mesalamine specific to this preselected Apriso®-responsive patient population.

2. Draft Guidance for Modified Release Mesalamine Products

Table I below lists the *in vitro* and *in vivo* requirements outlined in the Draft Guidance requirements for mesalamine modified release dosage forms. Guidance on establishing bioequivalence to the azo-bonded products, Colazal®, Dipentum® and Azulfadine® has previously been issued. The bioequivalence requirements are essentially the same for all products, but vary according to the specific pharmacokinetics of each formulation. All require extensive *in vitro* dissolution testing in various pH media as well as *in vivo* fed/fasted pharmacokinetic studies. The bioequivalence measures for the PK studies all require equivalence of C_{max}, T_{max} and AUC determinations between the Test and RLD formulations. In issuing the Draft Guidance, FDA has clearly stated their opinion that the PK profiles of these formulations are sufficient to describe and profile the delivery of active drug to the target organ of pharmacological activity, which in the case of Apriso® is the colon. Apriso® is designed to exert optimum pharmacological action in the colon and ileo-cecal region of the gastrointestinal (GI) tract. Importantly, the local pharmacological effect of Apriso® has not been shown to correlate with the systemic pharmacokinetics of 5-ASA, and therefore clinical endpoints should be

Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

required to establish clinical bioequivalence. In the absence of such a requirement, Salix recommends the requirement of pharmacokinetic bioequivalence consistent with its release profile as described in this document.

Table I: FDA Recommendations on Bioequivalence for Mesalamine modified release dosage forms.

RLD	Formulation	In Vitro Dissolution	In Vivo Fed/Fast PK Plasma 5-ASA			
Apriso®	DR/ER 375mg	0.1N HCL then pH 4.5 6.0, 6.5, 6.8, 7.2, 7.5, to 9hrs	C_{max}	T_{max}	AUC_{0-t}	AUC_{0-3} AUC_{3-t}
Pentasa®	ER250mg (w) and 500mg	pH 4.5, 6.0, 6.5, 6.8, 7.2, 7.5 to 12hr	C_{max}	T_{max}	AUC_{0-t}	AUC_{0-3} AUC_{3-t}
Lialda®	ER 1200 mg	0.1N HCL then pH 6.4, 6.5, 6.8, 7.2, 7.5, to 8hrs	C_{max}	T_{max}	AUC_{0-t}	AUC_{8-48}
Asacol® 400	DR 400mg	0.1N HCL then pH 4.5 6.0, 6.5, 6.8, 7.2, 7.5, to 2.5hrs	C_{max}	T_{max}	AUC_{0-t}	AUC_{8-48}
Asacol® 800	DR 800mg	0.1N HCL then pH 4.5 6.0, 6.5, 6.8, 7.2, 7.5, to 3hrs	C_{max}	T_{max}	AUC_{0-t}	AUC_{8-48}

While the above requirements provide additional dimensions on which bioequivalence must be based, we request that FDA amend the requirements for Apriso® due to the known high variability of mesalamine when measured in plasma, and the specialized manner in which Apriso® was designed to deliver mesalamine to exert a pharmacological action at the ileo-cecal and colonic regions of the GI tract. The current bioequivalence criteria established by the Draft Guidance are not sufficient to establish therapeutic equivalence of generic Apriso® products.

Three distinct properties of the Apriso® formulation make this mesalamine product different from other formulations:

1. A formulation in which the active drug is supplied in granules of approximately 1.0 mm in size that disperse the active drug over a large intestinal surface area before and throughout the drug release process.

2. A pH-sensitive, delayed release of drug from the individual granules, followed by:

3. An extended release of the drug from the individual granules that occurs during a 7-hr. period while the individual granules continue to disperse in the target organ.

These three properties of the formulation result in a plasma PK profile that does not fully characterize the delivery of active drug to the colon. These deficiencies in the Draft Guidance are described below and illuminate the need for additional measures that are required to adequately determine the bioequivalence of formulations similar to the RLD, Apriso®.

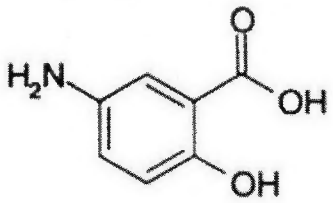
Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

3. Nature of the Apriso® Formulation

The Apriso® package insert clearly states that the Apriso® formulation is a "delayed and extended-release" dosage form as shown in Section 11 of the package insert below:

11 DESCRIPTION

Each APRISO capsule is a delayed- and extended-release dosage form for oral administration. Each capsule contains 0.375 g of mesalamine USP (5-aminosalicylic acid, 5-ASA), an anti-inflammatory drug. The structural formula of mesalamine is:



Molecular Weight: 153.14
Molecular Formula: $C_7H_7NO_3$

Each APRISO capsule contains granules composed of mesalamine in a polymer matrix with an enteric coating that dissolves at pH 6 and above.

The above language in the Apriso® package insert was approved by the reviewing Division after careful consideration of all of the relevant data submitted in the Apriso® NDA. Clearly the Division concluded that the characteristics of this formulation are sufficiently unique from that of other mesalamine formulations to warrant specific language that characterizes the description of the drug.

While the Apriso® formulation is presented in a capsule form, each capsule contains approximately 1,000 granules of individual dosage units. Release of drug substance from each granule is dependent on two distinct steps.

1. An outer pH sensitive coating dissolves when the dissolution media reaches a pH greater than 6.0.

2. Release of mesalamine from the inner polymer matrix is dependent on the properties of the co-polymers constructing the matrix core.

The kinetics of dissolution is therefore an inherent property of the composition and architecture of the individual granules. The Apriso® formulation therefore differs significantly from the delayed-release-only mesalamine formulations that require only a one-step pH dependent dissolution of the tablet coating. This difference can be readily seen in the comparative dissolution test shown below in Figure 1.

Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

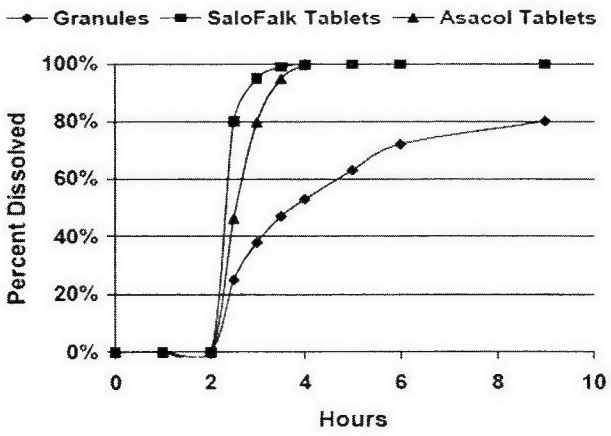


Figure 1: Typical Dissolution Profile of Granulated Mesalamine Capsules Compared to Delayed Release Mesalamine SaloFalk and Asacol Tablets. Dissolution medium was 0.1N HCL for 0-2 hr, followed by pH 6.8 (SaloFalk and Granules) or pH 7.2 (Asacol). 2-9 hrours.

The dissolution of the Apriso® formulation is clearly distinct from that of the delayed-release only formulations. The two components of the release characteristics can be clearly seen in this comparison. Both types of formulations are resistant to dissolution at acid pH for 2 hr, but once placed in pH 6.8 media, begin to release mesalamine. Complete release of mesalamine from the delayed release-only tablet formulation is accomplished in 90 min (Phase I), while the delayed and extended release properties of the Apriso® granules requires 9 hrs. to achieve 100% release (Phase II).

B. Discussion

1. Relationship Between *In Vitro* and *In Vivo* Dissolution for the RLD

a) Plasma Sampling Only Measures the Initial Release Rate of the RLD and Does not Adequately Measure the Extended Release of the RLD

The relationship between the dissolution process and the pharmacokinetic profile is illustrated using an *in vivo* study (Source: SAG-19/BIO; Apriso® NDA 22-301, Module 5, Volume 15), which was conducted on three mesalamine, delayed and extended release formulation batches that differed in their *in vitro* dissolution profiles. The dissolution kinetics for the 3 batches are shown below in Figure 2. While the ultimate percent dissolution is only marginally different (85%-100%) over a 7 hr. period, the initial rates of mesalamine release are significantly different as shown in Table II.

Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

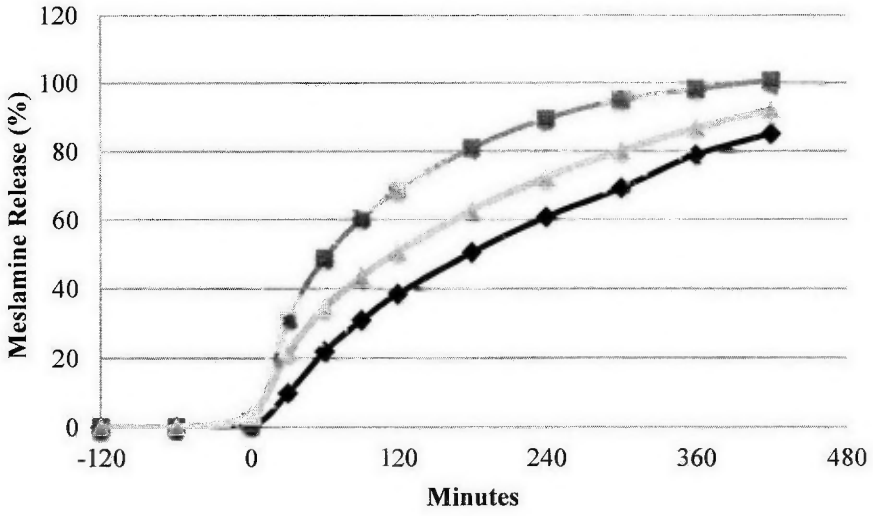


Figure 2. Release kinetics of 5-ASA from three different RLD formulation batches. Dissolution medium was 0.1N HCL (-120 min-0 min) followed by pH 6.8 for 0-420 min. Reference batch is R (Δ), Test(C) (■), Test(D) (◆).

The initial rate (Phase I, 0-60 min) of mesalamine release of each of the batches varies from a low of 0.36 %/min to a high of 0.79 %/min. However, the extended release rate (Phase II, 60-420 min) is not different between the three batches (0.15 %/min).

The plasma PK analysis of 5-ASA in general confirms the relative dissolution profiles of the three batches (Table II). For this analysis, a variety of partial AUC calculations are provided. While there is no difference in the T_{max} of the two Test batches relative to the Reference batch, the C_{max} and most of the partial AUC measurements confirm the Test(C) batch to yield about 60% greater 5-ASA in plasma and the Test(D) batch to yield about 20% less 5-ASA in plasma than the Reference batch. The single exception is the partial AUC8-24 which fails to detect these differences.

Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

Table II: In-vitro Dissolution Parameters of Apriso® RLD and Pharmacokinetics of Two Dissimilar Formulations*

	Reference (R)	Test(C)	Test(D)
In Vitro Dissolution			
Initial phase rate (0-60 min) (%/min)	0.57±0.03	0.79±0.14	0.36±0.02
Extended phase rate (60-420 min) (%/min)	0.15±0.01	0.15±0.02	0.15±0.01
Plasma PK	5-ASA		
K_a (hr^{-1})	0.53±0.13	0.56±13.24	1.5±0.64
T_{max} (hr)	4.29±0.98	4.33±1.43	4.87±1.21
C_{max} (ng/mL)	349.49±152.57	556.50±156.34	266.78±176.35
AUC_{0-3} (ng*h/mL)	113.22±89.90	207.73±149.3	36.8±39.42
AUC_{3-t} (ng*h/mL)	809.22±403.68	1231.05±639.14	687.99±439.82
AUC_{8-24} (ng*h/mL)	145.10±102.64	153.19±121.43	154.258±110.05
$AUC_{0-\infty}$ (ng*h/mL)	1006.49±441.24	1484.09±641.63	760.33±464.43

*N=24 for Reference formulation and N=12 for formulations C and D

b) Plasma 5-ASA Concentrations Alone are not Indicative of RLD Formulation Performance

Mesalalmine (5-ASA) is metabolized to N-acetyl 5-aminosalicylic acid (N-Ac-5-ASA) by acetylation pathways in intestinal mucosal epithelial cells and some of the N-Ac-5-ASA may convert back into 5-ASA by deacetylation. Since Apriso® is designed to specifically deliver 5-ASA to the colon, 5-ASA and N-Ac-5-ASA exist in an equilibrium in the gut and this equilibrium is distinct from the systemic 5-ASA and N-Ac-5-ASA equilibrium. It is the concentrations of 5-ASA and N-Ac-5-ASA in equilibrium in the ileo-cecal junction and colon that is responsible for the therapeutic effect of Apriso® in ulcerative colitis as the systemic 5-ASA concentrations alone are not representative of therapeutic concentrations at the primary site of pharmacological action in the colon. While N-Ac-5-ASA is not considered to have significant pharmacologic activity, formation of N-Ac-5-ASA –and by extension, its plasma pharmacokinetics, are representative of the interaction between the Apriso® formulation granules and the colonic epithelial cells, and therefore provide an essential indicator of the extended phase of mesalamine release after initial activation at pH 6.0. It is therefore, important to consider the pharmacokinetic parameters of N-Ac-ASA as well as 5-ASA, as markers for establishing bioequivalence of this formulation. Table III, below shows the comparative results obtained for three formulations.

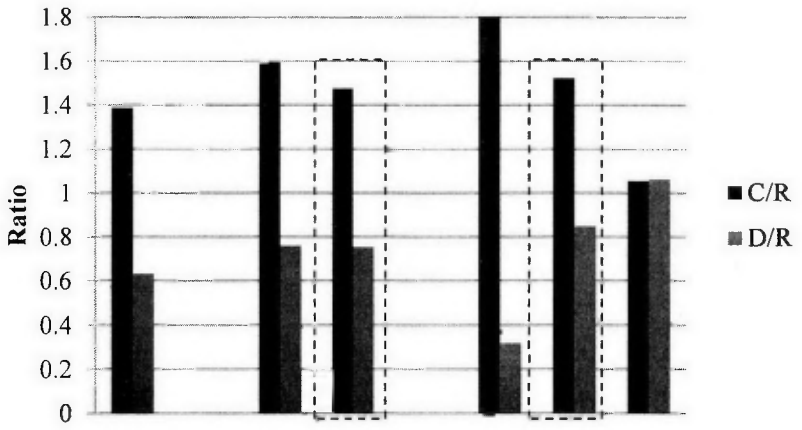
Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

Table III: Pharmacokinetics of N-Ac-5-ASA and Total Drug+metabolite*

	Reference ®	Test(C)	Test(D)
Plasma PK	**N-Ac-5-ASA**		
K_a (hr^{-1})	0.5252±0.13	0.500±0.14	0.58±0.0.14
T_{max} (hr)	8.19±2.38	5.083±1.13	6.33±1.66
C_{max} (ng/mL)	701.02±218.39	940.49±227.48	605.28±305.37
AUC_{0-3} (ng*h/mL)	267.07±174.04	354.42±178.67	88.16±86.80
AUC_{3-t} (ng*h/mL)	5755.75±1491.24	6619.27±1702.49	5048.10±1939.16
AUC_{8-24} (ng*h/mL)	3282.18±941.22	3400.82±1041.66	3062.57±1180.46
$AUC_{0-\infty}$ (ng*h/mL)	8798.71±2669.03	8261.87±2135.13	7460.77±2650.52
Plasma PK	**5-ASA + N-Ac-5-ASA**		
AUC_{0-3} (ng*h/mL)	380.19±263.94	562.15±327.97	124.96±126.22
AUC_{3-t} (ng*h/mL)	6564.98±1730.20	7850.32±2222.36	5736.09±2322.23
AUC_{8-24} (ng*h/mL)	4252.59±1043.86	3554.01±1163.10	3216.83±1290.51
$AUC_{0-\infty}$ (ng*h/mL)	9805.20±3110.27	9745.96±2776.76	8221.10±3114.95

*N=24 for Reference formulation and N=12 for formulations C and D

The point estimates for the comparison of the Test batches to the Reference batch are shown graphically below in Figure 3 and reflect the impressions gained from the pharmacokinetic metrics. It is apparent that the AUC_{0-3} detects the greatest differences between the test and reference formulations. However, the AUC_{3-t} and $AUC_{0-\infty}$ yield contradictory results for the metabolite N-Ac-5-ASA compared with its parent 5-ASA.



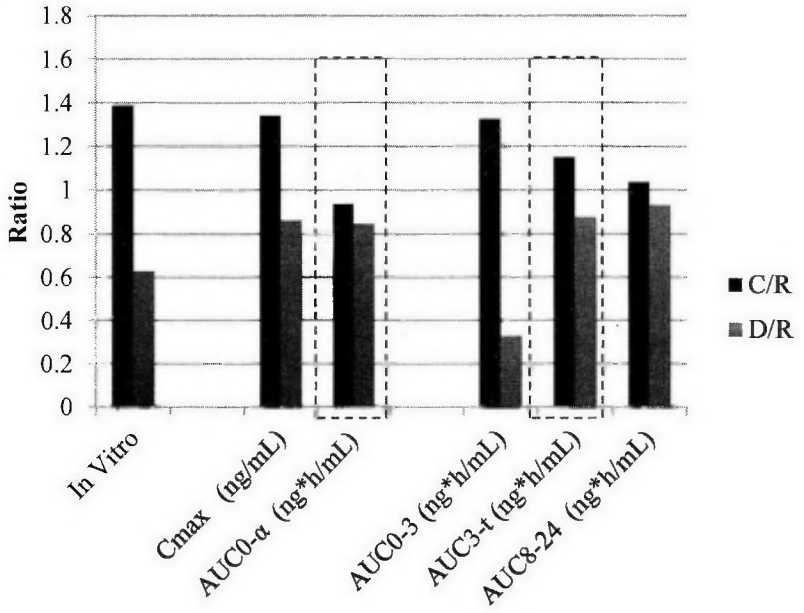


Figure 3: Point estimates for comparison of three Apriso® formulation batches. Top panel 5-ASA, bottom panel, N-Ac-5-ASA. Batch labels are as in Table I & II. Reference R, Test (C), Test (D). Boxes highlight those measurements where 5-ASA and N-Ac-5-ASA differ.

Because the generation of N-Ac-ASA is a function of both the rate of 5-ASA release and the more extended distribution of the formulation granules, it is not surprising that this measure does not reflect the initial rate of mesalamine release. Consistent with this finding is the observation that the AUC_{8-24} for both 5-ASA and N-Ac-5-ASA are also similar among all three formulations.

It has been previously argued by FDA (see Citizen Petition Response to Shire and Warner-Chilcott Aug 20, 2010) that it is not necessary to measure plasma N-Ac-5-ASA. In fact on page 13, paragraph 3 of that citizen petition response FDA states:

> Furthermore, because N-acetyl-mesalamine concentrations are highly correlated with mesalamine concentrations (see Colazal Petition Response at 24), there is no need to separately measure and report N-acetyl-mesalamine concentrations.

Salix agrees that this conclusion may be applicable to Colazal and some other mesalamine formulations, but it is clear from the data presented in Tables II, III and Figure 3 that this correlation is not equally applicable to the case of Apriso®.

The above data suggest that plasma PK is sensitive to, and does reflect, the initial dissolution kinetics of the RLD. However, the data reveal very little about the relative kinetics of the extended release phase of the Apriso® formulation.

Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

2. The Anatomical Site of Mesalamine Release in the GI Tract is a Critical Determinant of Efficacy

The anatomical site of mesalamine release in the GI tract is an important determinant of the efficacy of the drug. While all mesalamine products deliver the same active ingredient (5-ASA) to the GI tract, they are used in differing doses and dose regimens. This is because:

1. The mesalamine formulations differ in the anatomical site to which they deliver 5-ASA and;

2. The prescribing physician settles on a particular mesalamine formulation that empirically treats the disease specific to a given patient.

It is therefore imperative that two formulations, which are expected to be bioequivalent, deliver the same concentration of active drug at the same rate, and to the same location within the colon. To understand this variable, it is important to know the relationship between the plasma mesalamine profile of a given formulation and the location of release of mesalamine from the formulation in the GI tract. This relationship was studied in a combined pharmacokinetic and scintigraphic study using two different mesalamine formulations (SAG-16/BIO: Apriso® NDA 22-301 Module 5, Volume 35). In this study the RLD formulation was compared to a delayed-release only mesalamine tablet formulation (Brunner M *et al* 2003b).

Salofalk granules (500 mg) (European brand of the RLD Apriso) and mesalamine delayed-release tablets (Salofalk® Tablets 500 mg) were radiolabelled with ^{153}Sm and studied in a single dose, 2-way crossover study in 14 volunteer subjects. After ingestion, the anatomical position of the doses was monitored by scintigraphy and compared to the plasma pharmacokinetic profile.

The data show that progress of tablets and granules was similar through the upper GI tract. Both dosage forms disappeared from the small intestine and arrived at the ileo-cecal junction within the same time periods. These data are shown in Table IV.

Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

Table IV: GI Segmental Transit and Absorption Characteristics of Mesalamine Granules and Tablets

	GRANULES			TABLETS		
	Mean ± SD	**Min**	**Max**	**Mean ± SD**	**Min**	**Max**
Transit Times (hr)						
Gastric emptying	0.94 ± 0.70	0.05	2.00	0.56 ± 0.71	0.05	2.33
Location in SI	0.65 ± 0.40	0.05	1.67	0.79 ± 0.71	0.05	2.33
Disappearance from SI	3.71 ± 1.08	2.33	5.33	3.79 ± 1.17	2.00	5.67
Arrival at IC	3.31 ± 1.03	1.33	5.00	3.83 ± 0.893	2.33	5.00
Duration in IC	2.85 ± 2.21	0.33	8.33	1.72 ± 0.33	1.72	3.83
Duration in AC	9.49 ± 5.39	5.33	21.67	6.14 ± 1.89	3.67	9.33
5-ASA Pharmacokinetic Parameters						
C_{max} (ng/mL)	428.89 ± 261.93	130.27	1035.08	1241 ± 1304.7	151.83	3863.6
T_{max} (hr)	4.11 ± 0.96	1.5	5	5.14 ± 1.23	3	8
T_0 (hr)	2.54 ± 0.89	1	4	3.14 ± 0.86	2	5
AUC (ng*h/mL)	968.32 ± 628.84	295.07	2476.06	2205.8 ± 1766.52	355.61	5772.54

Dissolution of both dosage forms is activated in the ileo-cecal segment where a pH of >6.0 is achieved. The pharmacokinetic parameters (Table IV) show that systemic exposure to mesalamine is greater from the tablets than the granules. The C_{max} reached by the granules is only about 34% of that reached by the tablets and the AUC is approximately 44% of the tablet AUC.

These results are in contrast to those of a similar study using a tablet formulation with the same delayed-release-only characteristics as the mesalamine tablet used here (Claversal®) and a delayed-release-only, micropellet formulation with an identical pH-dependent coating. In that study, the pharmacokinetic parameters, C_{max} and AUC, were found to be similar between the two formulations (Wilding I *et al* 2003). This suggests that the extended release characteristics of the RLD formulation are primarily responsible for the lower bioavailability of 5-ASA relative to that of the tablet formulation.

As was previously discussed (Figure 1), release of mesalamine from the delayed–release tablets occurs over the course of about 60 min. It is therefore expected that the entire dose of mesalamine is released from the tablets during the 1.72 hr (103 min) that they were observed to reside in the ileo-cecal region. This expectation is confirmed by the relative kinetic profiles shown in Figure 4. The T_{max} for the plasma mesalamine profile occurs at 5.14±1.23 hr (or 308 min), which is virtually coincident with the time of complete dissolution of the tablets.

Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

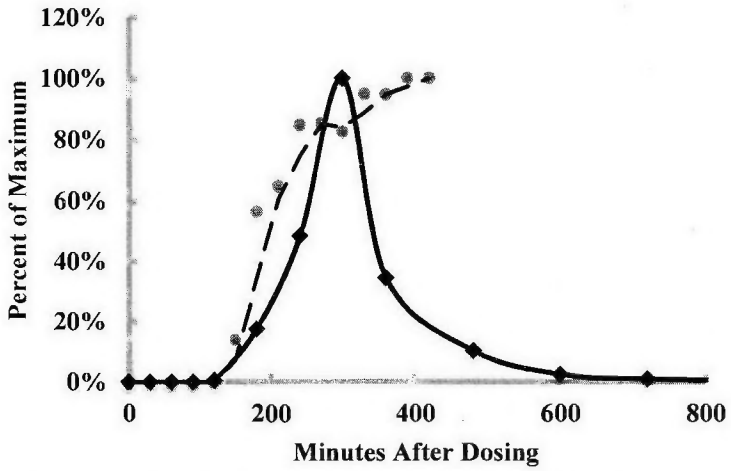


Figure 4: Plasma profile of 5-ASA released from 500 mg delayed-release tablets in relation to the tablet dissolution kinetics. Plasma values are shown as the mean of 14 subjects and are displayed as percentage of C_{max} (◆). The plasma T_0 time point for each subject was used as the dissolution activation time point. The mean theoretical % dissolution (■) is shown relative to the mean plasma mesalamine concentration.

In contrast to the dissolution and pharmacokinetic profile observed for the delayed-release tablets, *in vitro* dissolution of the granules occurs over the course of 8-10 hr. The surprising observation from the results of this study is that the mesalamine plasma profile does not reflect the release kinetics of the granules during the extended (Phase II) phase of their dissolution. The T_{max} for the plasma profile occurs at 4.11±0.96 hr or 246 min, which corresponds to a mean of about 52% of the dose of mesalamine released from the granule formulation (Figure 5).

Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

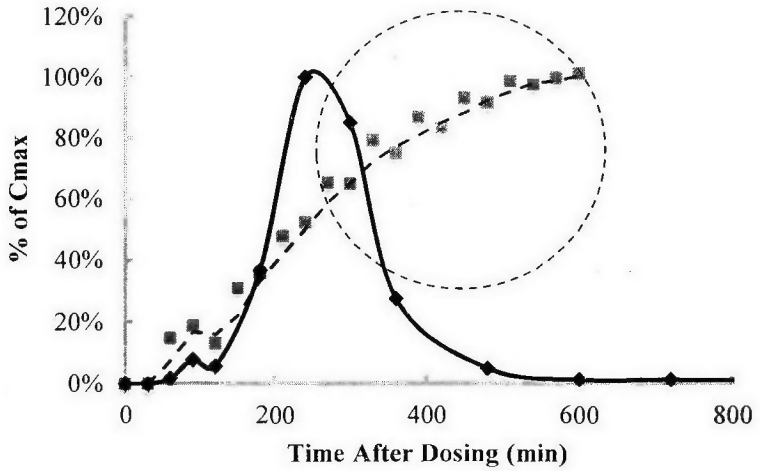


Figure 5: Plasma profile of 5-ASA released from 500 mg delayed and extended release granules in relation to the granule dissolution kinetics. Plasma values are shown as the mean of 14 subjects and are displayed as percentage of C_{max} (◆). The plasma T_0 time point for each subject was used as the dissolution activation time point. The mean theoretical % dissolution (■) is shown relative to the mean plasma mesalamine concentration. Circle denotes the portion of the dose remaining unreleased after the C_{max} is reached.

A comparison of the two plasma pharmacokinetic profiles of the granules and tablets also shows that the mesalamine elimination kinetics are not dramatically different between the two formulations as shown in Figure 6 below. This further suggests that the terminal extended release phase of the granule formulation contributes very little to the mesalamine plasma pharmacokinetic profile. The N-Ac-5-ASA concentration-time profiles for the two formulations also confirm a similar elimination rate between the two formulations for this metabolite (Figure 7).

Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

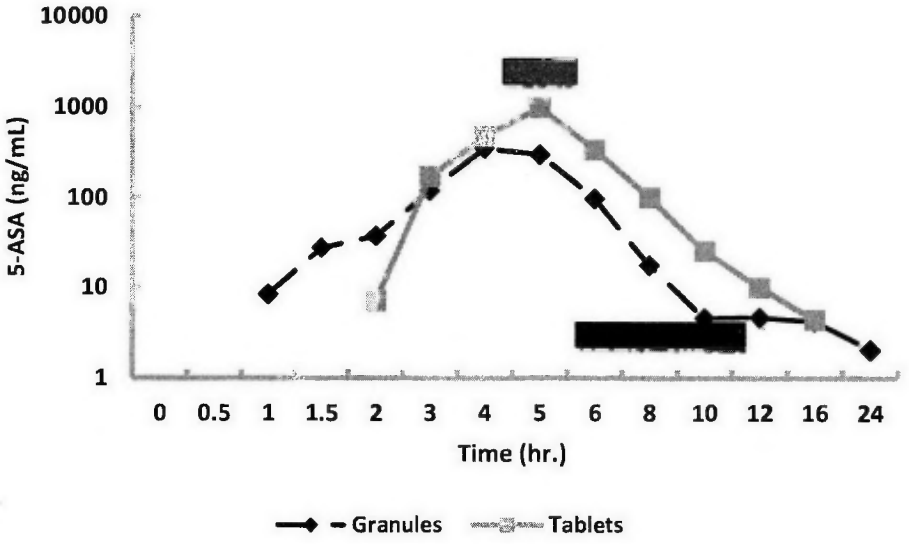


Figure 6: Plasma 5-ASA – time profile of 500 mg delayed-release tablets ( ) and 500 mg delayed and extended release granules (-----). Boxes show the median interval during which the remaining 50% of the mesalamine dose is released from each formulation.

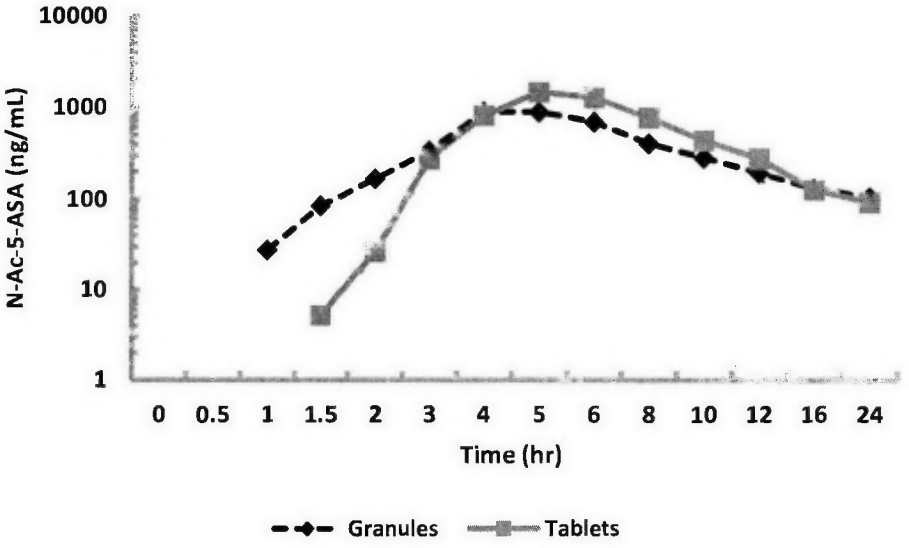


Figure 7: Plasma N-Ac-5-ASA – time profile of 500 mg delayed-release tablets ( ) and 500 mg delayed and extended release granules (-----).

The comparative pharmacokinetic data presented above also support the conclusions of the previous section, that the plasma mesalamine profile of the RLD reflects primarily the initial dissolution rate of the formulation. There is no evidence from the elimination rate that the later time points (5-24hr) are influenced by the extended dissolution of the formulation during this period. The plasma profile does not appear to account for as much as 50% of the dissolution process.

Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

3. Factors Influencing the Plasma Profile During the Extended Release Phase

The observations made in the preceding section raise a number of questions regarding the contribution of the extended-release phase of the RLD formulation to the observed plasma pharmacokinetic profile. For example:

a. Are the absorption characteristics of the ascending colon sufficiently lower than that of the ileo-cecal junction such that the remaining dose of 5-ASA released in the ascending colon is not detected in plasma?

b. Are the *in vivo* dissolution kinetics the same as those observed *in vitro*?

c. Does the spreading of the granules decrease the local concentration of the released 5-ASA to a level that is not detected in plasma?

a) Absorption Characteristics of Ileo-ceacal Segment vs Ascending Colon

Several studies have compared the absorption characteristics of various regions of the gastrointestinal tract including that of mesalamine absorption. The duodenum and jejunum are relatively efficient with respect to 5-ASA absorption compared to the colon (Bondesen S *et al* 1997). Although the mesalamine absorptive properties of the ileo-cecal region versus the ascending colonic segments have not been directly compared, their relative capacity to absorb isosorbide-5-mononitrate differs by only about 20% (Kramer WG 1994). However, rectal absorption of 5-ASA form enema formulations is substantially reduced (by 70%) relative to that of oral delivery (Dilger K *et al* 2007).

Although 5-ASA absorption may decrease in the colon relative to the terminal small intestine, plasma 5-ASA, appearing from mesalamine formulations that release 5-ASA primarily in the colon, can readily be detected. These include azo-bonded formulations (Colazal, Dipentum and Azulfadine), as well as Asacol and Lialda. Of primary interest are the data available for Lialda as this formulation has both delayed and extended release characteristics, although dissolution activation occurs at a higher pH (pH 6.8) than that of the Apriso® granules (pH 6.0). In that formulation, the extended release characteristics can readily be observed in the plasma mesalamine kinetic profile (Brunner M *et al* 2003a).

b) Factors Influencing *In vivo* versus *In Vitro* Dissolution

The volume of fluid in the ascending colon is not large compared to that of the *in vitro* dissolution vessel. A fairly recent study estimated that the free fluid volume of the human ascending colon may be as low as 15 mL (Diakidou A *et al* 2009). This would tend to reduce the rate of dissolution, resulting in a lumenal mesalamine concentration rise that is even less than that predicted from the *in vitro* dissolution data. It is therefore possible that dissolution of the granules as they enter the ascending colon becomes even slower than would be predicted based

Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

on the *in vitro* dissolution kinetics. The extent of dissolution and its relation to the appearance of 5-ASA in plasma suggested in Figure 5 (above) may therefore even be somewhat optimistic.

c) Effect of Dose Dilution by Granule Spreading and Impact on Mesalamine Metabolism

The actual luminal concentration of mesalamine available for absorption from a formulation consisting of granules will be influenced by the dispersion of the granules in the GI tract resulting in an increased volume of distribution. The luminal concentration can therefore be viewed as a function of two processes:

[Lumenal Concentration Rate] = [Rate of Dose Release] x [Rate of Dose Dilution]

The rate of dose dilution due to granule dispersion is not known. Although some predictions might be made for the spreading rate of the granules through the ascending colon based on the radiographic images obtained through scintigraphy (Brunner M *et al* 2003b), little information can be gleaned concerning the spreading rate in the region of initial granule dissolution. At best it can be concluded that the granules are distributed over a larger area of the ileo-cecal segment during the dissolution process than are the tablets. Thus not only is the release rate of the granules lower than the tablets, the dose is distributed over a greater area. Both of these differences will influence the kinetics of appearance of 5-ASA in plasma because of the known pre-systemic metabolism of 5-ASA.

Once 5-ASA is released in the intestinal target region, carrier-mediated, saturable, transepithelial 5-ASA transport occurs into the mucosal cells (Zhou SY *et al* 1999). In the epithelial cells, two processes will have a major impact on the topical and systemic concentrations of 5-ASA: pre-systemic metabolism by acetylation to the N-Ac-5-ASA (Klotz U *et al* 1993) and intestinal transport in the basolateral to apical direction back into the gut lumen (Goebell H *et al* 1993, Layer PH *et al* 1995).

The active transport from the basolateral to the apical site for both compounds is accomplished by the membrane bound drug efflux pump P-glycoprotein (Zhou SY *et al* 1999). When the 5-ASA active transport process is saturated, 5-ASA as well as N-Ac-5-ASA is systemically absorbed via the paracellular pathways and systemically absorbed 5-ASA is further metabolized by the liver. The 5-ASA appearing in plasma is therefore primarily a function of the concentration that has been absorbed via the paracellular pathway after saturation of the active transport process. Thus, it might be speculated that, due to the slower rate of release of 5-ASA from the granules in the present study and the rate of dose dilution due to granule spreading, the transport process is not saturated, leading to a greater conversion of 5-ASA to N-Ac-5-ASA and therefore a blunting of the plasma 5-ASA kinetics of the granules relative to that predicted from the *in vitro* dissolution kinetics.

It might then be expected that a greater percentage of released mesalamine appearing in plasma from the granules would be in the form of N-Ac-5-ASA. Although the Draft Guidance does not require a determination of the N-Ac-5-ASA kinetics it is important to point out that the

Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

granules do indeed show a greater conversion of 5-ASA to N-Ac-5-ASA which is reflected in their respective AUC values compared to that derived from the delayed release only tablets. This comparison is shown below in Table V.

Table V: Pharmacokinetics (Mean ± S.D.) of 5-ASA, N-Ac-5-ASA and Drug-Metabolite Ratio

	Granules			Tablets		
Pharmacokinetic Parameters	5-ASA	N-Ac-5-ASA	Ratio N-Ac-5-ASA/ 5-ASA	5-ASA	N-Ac-5-ASA	Ratio N-Ac-5-ASA/ 5-ASA
C_{max} (ng/mL)	428.89 ± 261.93	986.09 ± 435.68	2.77 ± 1.27	1241 ± 1304.7	1736.60± 1321.00	2.53 ± 1.47
T_{max} (hr)	4.11 ± 0.96	4.36 ± 1.01	1.08 ± 0.16	5.14 ± 1.23	5.50 ± 1.16	1.08 ± 0.16
AUC (ng*h/mL)	968.32 ± 628.84	6407 ± 2026.04	6.26 ± 2.39	2205.8 ± 1766.52	8638.93 ± 4052.11	4.69 ± 2.93

The above data again raise the possibility that the plasma pharmacokinetic profile of 5-ASA delivered by the Apriso® formulation does not allow a complete kinetic evaluation of the formulation performance for delivery of mesalamine to the colon. Rather, the criteria set forth in the Draft Guidance appear to characterize the initial rate of mesalamine release. Inclusion of an analysis of N-Ac-5-ASA is essential to fully characterize formulation performance.

Without additional measures, it cannot be assumed that two formulations that are bioequivalent in their plasma 5-ASA pharmacokinetic metrics still deliver the remainder of the unreleased dose to the ascending colon in a bioequivalent manner. As discussed below, bioequivalence for delivery of this unreleased mesalamine will require both formulations to transit and disperse at equal rates throughout the ascending colon. This will be a function of the similarity of the physicochemical characteristics of the two formulations.

4. Colonic Transit Is a Function of Formulation Dosage Form

The scintigraphy study described above presents data relative to the effect of formulation composition on colonic transit. While both formulations transit the upper GI tract in similar time periods, their profiles begin to diverge when they reach the ileo-cecal segment as shown in Table VI and Figure 8.

Table VI: Transit Times of Mesalamine Granules and Tablets

	GRANULES (hr.)			TABLETS (hr.)		
	Mean ± SD	**Min**	**Max**	**Mean ± SD**	**Min**	**Max**
Duration in UI	3.31 ± 1.03	1.33	5.00	3.83 ± 0.89	2.33	5.00
Duration in IC	2.85 ± 2.21	0.33	8.33	1.72 ± 0.33	1.72	3.83
Duration in AC	9.49 ± 5.39	5.33	21.67	6.14 ± 1.89	3.67	9.33
Duration in IC+AC	12.33 ± 5.65	5.67	24.34	7.86 ± 2.25	4.00	10.99

It is apparent from the data in Table VI that once the two dosage forms leave the small intestine, the granules transit at a slower rate than the tablets. In addition, the variability in the data increases. By the time both formulations have transited the ascending colon, the total duration from the time of the initiation of drug release is 12.33 hours for the granules and 7.86 hr for the Tablets. Figure 8 shows the distribution of the transit data by subject.

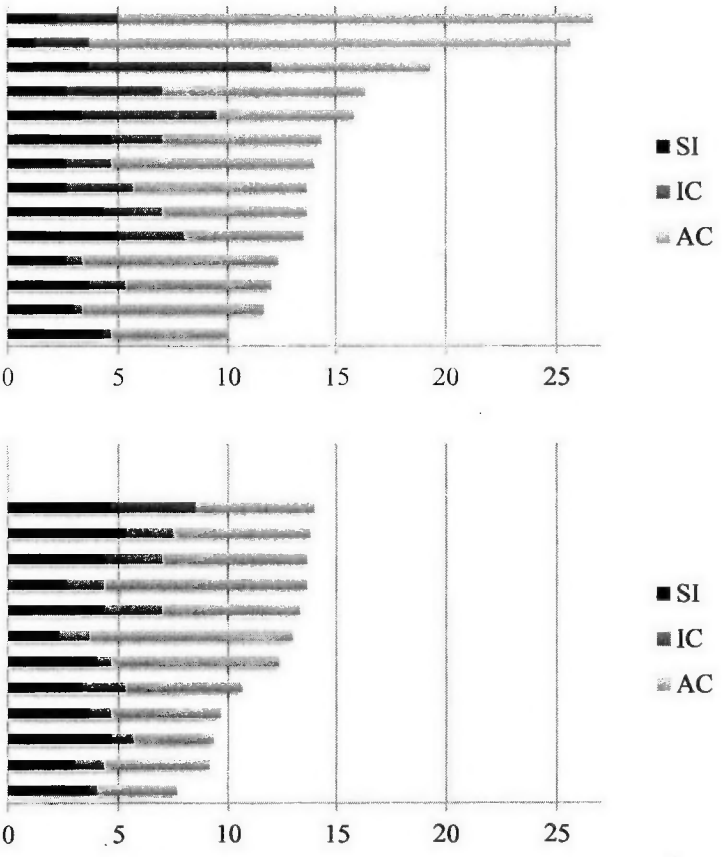


Figure 8: Transit time for the Granules (upper, N=14) or Tablets (lower, N=12) through the GI tract through the ascending colon. SI = small intestine, IC = ileo-cecal region, AC = ascending colon.

It is not surprising that a formulation containing dispersible granules would take longer to transit the ileo-cecal and ascending colon region. The surface area contact would be much greater than a single dosage unit such as a tablet. This undoubtedly is also responsible for the increased variability in the transit data seen when the subjects are dosed with the granules.

While small intestinal transit in humans appears to be only marginaly influenced by a variety of dosage form differences (Davis SS *et al* 1986), additional variables that influence colonic transit have been reported. These include the size and density of the particles (Tuleu C *et al* 1999). In a study, performed in animals, small intestinal transit was not influenced by size (710 to 1600 mm). However, small particles (710-1000 μm) of high density (1.5 g/cm^3) were

Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

found to have the longest transit in the cecal-colonic region (14 hr.) while small particles of low density (0.9 g/cm^3) had the shortest transit time (4.2 hr).

Additional factors that influence the transit and distribution of a dosage form throughout the colon are the mucoadhesive nature of the polymers comprising the dosage form and the swelling properties of the matrix core (Goto T *et al* 2006). The colon also has a lower motility than the small intestine which will allow increased interaction of the formulation components with the mucus layer. Relative to the small intestine, the colon has a thicker mucus layer (Atuma C *et al* 2001) and a slower mucus turnover rate (Lehr CM *et al* 1991). Mucoadhesion of two formulations during transit in the colon may therefore be influenced by their respective components. In a study in dogs, the mean proximal colon transit time of carbopol 980 (15.3 ± 4 h) was found to be significantly longer than that of the polycarbophil AA-1 (10.0 ± 5.7 h) and ethylcellulose (7.1± 4 h) ($p < 0.05$). (McGirr MEA *et al* 2009)

The fact that these variables may influence colonic transit without appreciably affecting small intestinal transit suggests that two different formulations could arrive at the ileal-cecal region at the same time, release a portion of their contents at the same rate, measurable in plasma, then move at differing rates through the colon, where the remainder of the dose is distrbuted. Unless the plasma profile reflects the remainder of the dose released in the colon, these two formulations could not be deemed to be bioequivalent when, in fact, they do not provide bioequivalent quantities of active drug to the same site of action at the same rate.

Shown in Figure 9 is a summary comparison of the transit, dissolution and pharmacokinetic parameters for the delayed-release tablets and the delayed and extended release granules. It is readily apparent that the tablet releases virtually 100% of the mesalamine dose prior to entering the ascending colon. For the tablet, 100% release occurs virtually coincident with the plasma mesalamine C_{max}.

In contrast, the granules release approximately 40% of the dose after entering the ascending colon. This portion of the mesalamine dose is released over the next 4 hr and during that time the granules have dispersed through the first 45% of the ascending colon. It should be apparent that a formulation with the same dissolution characteristics as the granules, but with the transit time similar to the tablets would result in a different distribution of the released mesalamine in the ascending colon. For such a formulation, the same dose of mesalamine would be distributed over approximately 90% of the ascending colon.

Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

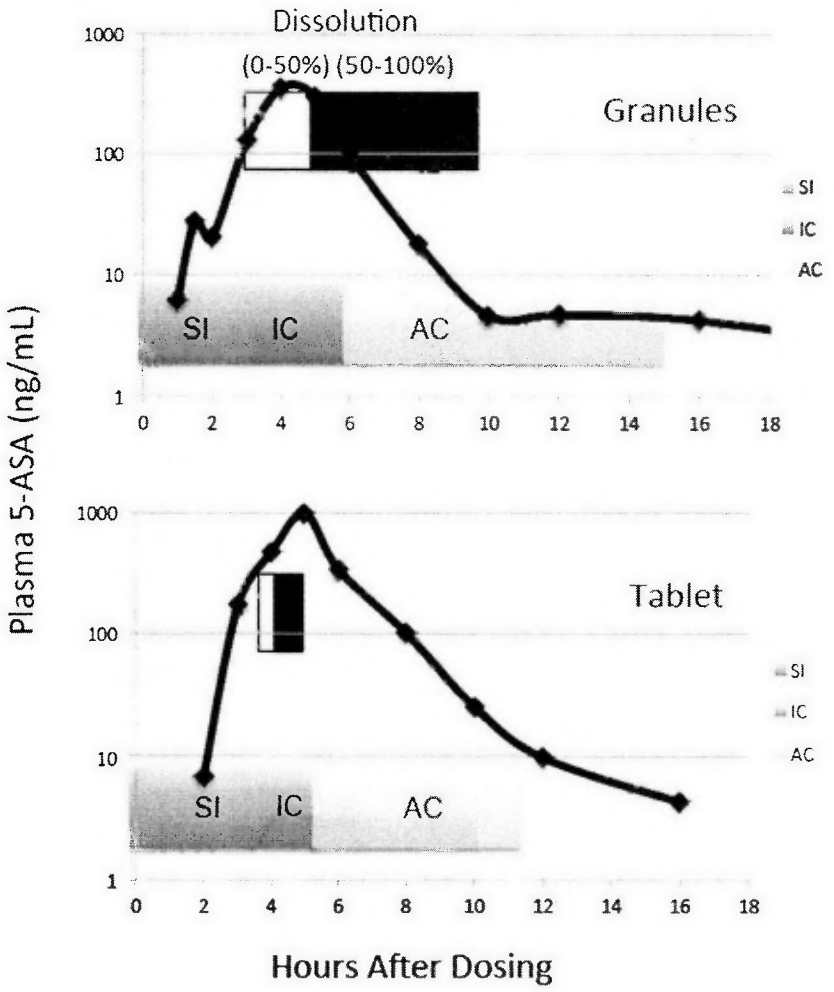


Figure 9: Summary representation of the transit, dissolution and plasma pharmacokinetics of 5-ASA released from delayed release tablets and delayed and extended release granules. The results are based on the dissolution data of Figures 4 and 5, the transit data of Table VI and the pharmacokinetic data of Figures 6 and 7. The dissolution duration is represented by the shaded and black bar and is separated in to the first 50% (shaded) of the dose released and the remainder (black) of the dose released. SI=small intestine, IC=Ileo-colonic and AC=ascending colon.

It is clear from this summary that two dosage forms will not yield bioequivalent delivery of mesalamine to the ascending colon unless they have the same dissolution kinetics and the same transit times. The highest probability of attaining bioequivalent colonic transit would be for both dosage forms to have an identical composition and polymer cross-linking architecture. However, in the absence of such an identity and in the absence of a direct measure of transit, there can be no assurance that two formulations will distribute equally throughout the colon as they continue to release the drug. Such a non-bioequivalent distribution of the dose to the colon could very well impact the efficacy of the formulation. A potential formulation-specific metric that may provide such information is considered further in the following section.

Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

5. Distribution of 5-ASA in the Colon Reflects Different Formulation Design Goals Among the Various Approved 5-ASA Drugs

The Draft Guidance focuses exclusively on the active compound 5-ASA. FDA has assumed that if two formulations deliver 5-ASA to the GI tract at the same rate and in the same quantity then the two formulations are bioequivalent. The foregoing discussion has addressed the weaknesses in relying solely on plasma pharmacokinetics of 5-ASA to predict colonic delivery when the methodology does not profile the complete dissolution of the dosage form *in vivo*. It is also possible to misinterpret the performance of a dosage form when only the active drug, 5-ASA is considered. That is because N-Ac-5-ASA, the inactive metabolite of 5-ASA, is a valuable indicator of the distribution of its active precursor within the colon, and without considering this, the Draft Guidance lacks the robustness required to unequivocally confirm bioequivalence.

Metabolism of 5-ASA in the colon is an additional measure of its residence time and distribution. As previously pointed out, 5-ASA is converted to N-Ac-5-ASA through acetylation. This takes place in the colonic mucosa while very little acetylation is contributed by the colonic microbiome (Allgayer H *et al* 1989, Tucker MA *et al* 1989). Studies have shown that systemic drug and metabolite do not enter intestinal cells even from intravenous injection (Shafii A *et al.*, 1982; Fischer C *et al* 1983) and intestinal secretion of systemic drug and metabolite is even more unlikely after oral absorption. Though oral N-Ac-5-ASA has been believed to be therapeutically ineffective, intestinal metabolite tissue levels do correlate with the therapeutic effect (Easterbrook J *et al* 1998*).* Thus a measure of luminal N-Ac-5-ASA is a measure of the extent of distribution and interaction of the released 5-ASA with the colonic epithelia. This suggests that one measure of the relative distribution of two similar dosage forms in the colon could be the relative concentrations of luminal 5-ASA and N-Ac-5-ASA. The data discussed below shows that even when equivalent quantities of 5-ASA are delivered to the colon, the metabolism of 5-ASA within the colon is formulation dependent.

Study MPPK1001 (Apriso® NDA 022-361, Module 5, Volume 21) was a single-center, open-label, randomized, crossover study of 3 treatments in 3 periods, each separated by a minimum washout of 7 days. Treatments were administered orally, and were as follows:

Treatment A: 800 mg Asacol (2 x 400 mg tablets) BID for 4 days

Treatment B: 800 mg Apriso® Granules BID for 4 days

Treatment C: 1600 mg Apriso® Granules (2 x 800 mg) QD for 4 days

The outcome of the study is shown below in Table VI. The three treatments were similar in the total mesalamine (5-ASA plus N-Ac-5-ASA) recovered from the soluble fraction of fecal samples over the course of the four-day treatment and collection period. In fact, with a somewhat larger sample size, the 90% CI values may have been within a range where bioequivalence would be declared for this measure between the three treatments.

Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

Table VI: 5-ASA and N-Ac-5-ASA in the Soluble Fraction of Fecal Samples over 4 days of Dosing

	Asacol Tab.	Apriso® Granules		Ratio (90% CI)		
	Txt A (N=28)	Txt B (N=28)	Txt C (N=28)			
	800 mg BID	800 mg BID	1600 mg QD	B/A	C/A	C/B
Component	(mmol)	(mmol)	(mmol)			
5-ASA	7.50 ± 3.83	4.64 ± 2.54	5.26 ± 3.16	62 (48, 75)	69 (56, 83)	113 (90, 135)
N-Ac-5-ASA	2.31 ± 1.46	4.23 ± 2.15	3.20 ± 1.79	182 (165, 200)	136 (119, 154)	75 (65, 84)
5-ASA plus N-Ac-5-ASA	9.82 ± 4.69	8.88 ± 4.07	8.46 ± 4.46	90 (77, 102)	85 (73, 98)	95 (81, 109)

Clearly, the two formulations had delivered the same total amount of mesalamine to the target organ over the four day period of dosing. It should be reiterated that this is the endpoint which the Draft Guidance seeks to validate; quantitatively equivalent delivery of mesalamine to the colon from two formulations.

However, when the percentage of mesalamine appearing as unmetabolized or metabolized 5-ASA is examined, an entirely different conclusion may be made. As is evident, the granule formulation results in a greater conversion of the released 5-ASA to N-Ac-5-ASA than is seen for the tablet formulation. This difference is illustrated in the time-course data shown below in Figure 10.

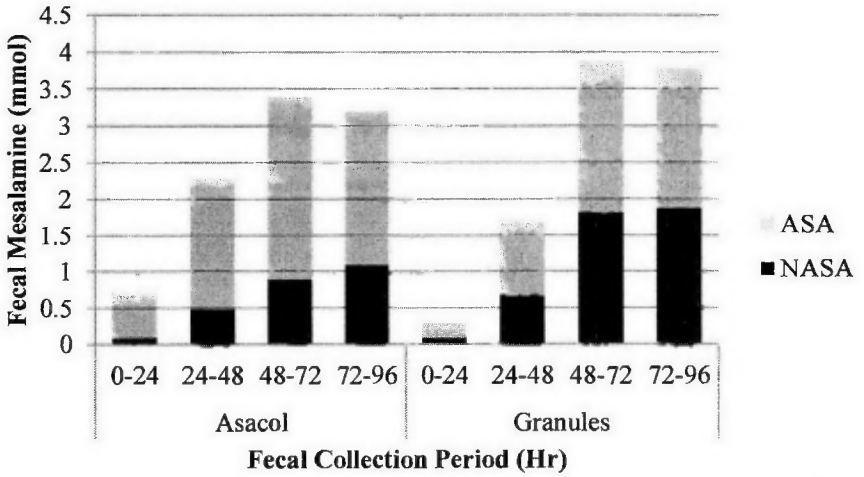
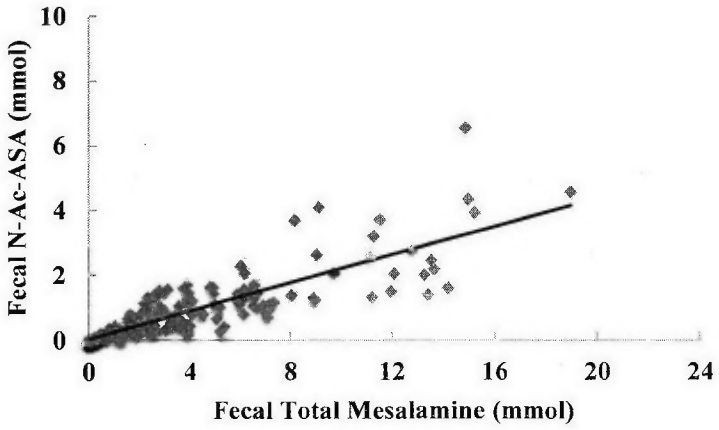


Figure 10: Comparison of soluble fecal mesalamine levels over 4 days of dosing with either Asacol 800mg BID or Apriso® granules 800 mg BID. Top portion of each bar is 5-ASA while bottom portion is N-Ac-ASA.

It is apparent from the data shown in Figure 10 that while the total soluble fecal mesalamine recovered throughout the four days of treatment with each formulation is not markedly different, the percentage of the dose, which has been converted to N-Ac-5-ASA, is significantly greater when subjects are dosed with the granule rather than the tablet formulation. This might be expected of a formulation that distributes the dose over a greater surface area during the time in which it releases its contents.

If the proportion of the mesalamine dose converted to N-Ac-5-ASA from 5-ASA is a function of the formulation, it would be expected that this correlation would be similar over a range of mesalamine concentrations. This relationship is shown below for the data from all time periods during which fecal samples were collected (Figure 11). As is clearly evident, there is a strong correlation between the total mesalamine and N-acetyl-5-ASA, and this relationship is specific to each formulation. For Asacol, N-Ac-5-ASA is generated at a rate of 0.235 mmol/mmol of total fecal mesalamine, while for the Apriso® granules this rate is 0.468 mmol/mmol of total fecal mesalamine. This might imply that the surface area of the colon on which the mesalamine is distributed by the granule formulation is approximately double the surface area exposed to the dose provided by the tablet formulation. Clearly, these two formulations cannot be considered to be bioequivalent, as they do not distribute the active drug over the same surface area in the target organ. Without considering a metric that directly compares formulation performance in the colon, the Draft Guidance lacks the robustness required to unequivocally confirm bioequivalence.



Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

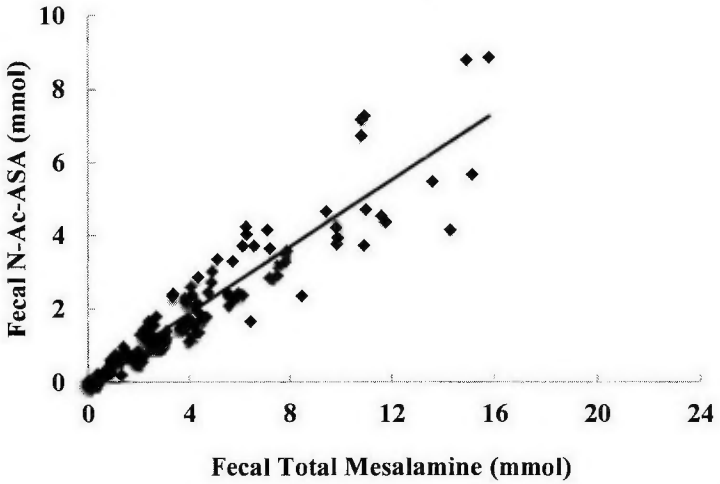


Figure 11: Proportion N-Ac-5-ASA versus the total mesalamine recovered from fecal samples at all time points from all subjects from Study MPPK1001. Top panel, Asacol (800mg BID); bottom panel, Apriso® granules (800 mg BID). The two data sets are significantly different, P<0.0001.

6. Pharmacokinetic Profiles in Healthy Subjects are not Predictive of Profiles in Ulcerative Colitis Patients Treated with Apriso®

Apriso® is indicated for the maintenance of remission of patients with mild to moderate ulcerative colitis. Remission of disease activity is defined primarily as a resolution of clinical symptoms and endoscopically observable mucosal healing. However, it is well appreciated that in most cases the colonic mucosa does not return to a histologically "normal" appearance. A recent review of the various accepted definitions of disease remission showed that only 3 out of 25 definitions used in clinical studies included histologic criteria (Travis SP *et al* 2011). Early studies by Riley *et al* (1991) showed that in a cohort of 82 UC patients who were in endoscopically verified remission for a duration of greater than 12 months, histological evidence verified crypt architectural irregularities (58%), acute inflammatory activity (32%), acute inflammatory cell infiltrate (28%), crypt abscesses (11%) and mucin depletion (11%). Unless the Test formulation is identical in physico-chemical composition to the RLD, it is possible that the interaction of the two formulations with the diseased mucosal surface will differ. Given the importance of dosage-form distribution in the delivery of Apriso® granules to the colon, such a difference in mucosal-granule interaction may not be detected in normal volunteers. For these reasons, Salix recommends establishing bioequivalence under fed and fasted conditions with Apriso® in patients with ulcerative colitis (UC) in remission instead of healthy subjects.

7. Published Pharmacokinetic Parameters for Establishing Bioequivalence are not Adequate

As indicated in Table 1 (above), FDA's bioequivalence recommendations group mesalamine products into two groupings. In Group 1, comprised of Apriso® and Pentasa®, bioequivalence criteria were established as meeting 90% CI that require C_{max}, AUC_{0-3}, AUC_{3-t},

Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

and AUC_{0-t}. In Group 2, comprising all other mesalamine products, bioequivalence criteria were established as meeting 90% CI for the PK parameters C_{max}, AUC_{8-48}, AUC_{0-t}. While the rationale for stipulating these requirements for Pentasa® and other products is consistent with their release and PK profiles, Salix believes that these conditions are not appropriate for Apriso®. Apriso® was specifically designed to deliver 5-ASA to the colon, the target organ for exerting pharmacological activity. Therefore, establishing bioequivalence for the pharmacokinetic parameter AUC_{8-t}, the parameter that best reflects exposure to the colon is critical for predicting the therapeutic efficacy of any generic versions of Apriso®. Therefore, AUC_{0-3}, AUC_{3-t}, and AUC_{8-t} in addition to T_{max}, C_{max}, AUC_t, and AUC_{inf} would be appropriate.

Therefore, Salix is requesting that FDA require any studies intended to establish bioequivalence to Apriso® must be carried out in ulcerative colitis patients in remission and the 90% CI must be contained within the conventional 80-125% limits for the PK parameters C_{max}, AUC_{0-3}, AUC_{3-t}, AUC_{8-t}, AUC_t, and AUC_{inf} for 5-ASA and N-Ac-5-ASA.

8. Bioequivalence Guidance Previously Recommended by the Division of Gastroenterology Products

The studies summarized in this Citizen Petition were included in the Apriso® NDA 22-301. The reviewing division at FDA (Division of Gastroenterology Products) has therefore had the opportunity to review the results of these studies and communicate to the Sponsor its own recommendations for determining bioequivalence of two Apriso® formulations, of identical composition but manufactured in two different facilities (Meeting Minutes, March 24, 2009). This following excerpt summarizes the *in vivo* studies requested by the Division in the meeting minutes:

> Please note that you need to establish bioequivalence for both 5-ASA and N-Ac-5-ASA. It is suggested that you use T_{max}, mean absorption time, and mean residence time in the intestine to estimate the percentage of the dose released for absorption in the colon for the studied and approved products each, and compare such data between the two products. Such a comparison would be helpful for understanding how the studied product behaves in the intestine as compared to the approved product. In addition, you would need to establish clinical bioequivalence between Apriso® and (the studied product).

The Guidance given by the Division of Gastroenterology Products clearly recognizes the necessity to compare the residence and distribution of two granule formulations in the GI tract as additional criteria for the determination of bioequivalence. The data presented in Table VI and Figure 11 indicate that quantitation of N-Ac-ASA and 5-ASA in the soluble fraction of fecal samples collected during bioequivalence studies may provide such a measure. It should be noted that the coefficient of variation is within the same range (25-50%) as that observed for the standard pharmacokinetic metrics utilized for determining bioequivalence of mesalamine formulations. In addition, the use of the rate of N-Ac-ASA generation (mmol NASA per mmol

Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

of total recovered mesalamine) as a metric also controls for variability in stool volumes and sample recovery.

C. Conclusion

The Draft Guidance appears to adequately profile the *in vitro* dissolution characteristic of the Apriso® formulation. It also requires *in vivo* pharmacokinetic profiling that appears to detect differences in formulation performance observed in the *in vitro* dissolution profile. From the data presented, it appears that the following deficiencies remain in the Draft Guidance:

- At least 50 % of the mesalamine dose remains in the formulation at time points when there is little meaningful additional signal detected in plasma.

- There is no meaningful way to compare the transit of the remaining dose even though there is ample evidence that transit times; a) can diverge in the colon after appearing the same in the small intestine (i.e. where the plasma measurements are made), and b) are specific to formulation chemical composition, particle size and hydrodynamic properties.

- There is no requirement to confirm that the dose remaining in the formulation after initiation of dissolution is distributed to the colon in a bioequivalent manner to that of the RLD, even though there is evidence to show that such distribution is formulation dependent even when comparable amounts of active drug are delivered to the colon.

These issues are unique to the Apriso® formulation because of the following combination of properties:

1. It is a formulation with both pH-sensitive, delayed release and extended release properties.

2. It is a formulation whose dissolution begins at the junction between the ileum and the ascending colon, which is a transition region for the transit properties of a given formulation.

3. It is a granule formulation that disperses drug before and during dissolution.

In conclusion, the bioequivalence criteria established by FDA in the Draft Guidance do not appropriately reflect Apriso®'s unique PK profile or the properties that are responsible for the clinical efficacy and safety of Apriso® in the target patient population. These criteria are therefore insufficient to establish bioequivalence of a generic mesalamine product to Apriso®.

We therefore request that, to establish bioequivalence for any ANDA that lists Apriso® as the reference listed drug, FDA:

- require bioequivalence to be established under fasted and fed conditions in patients with ulcerative colitis in remission because the altered morphology of the colonic mucosa

Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

results in N-Ac-5-ASA and 5-ASA permeability profiles that are different from healthy subjects and the interaction of the formulation physicochemical characteristics with the diseased mucosa will be formulation specific;

- require PK parameters to be computed using the plasma analytes 5-ASA, and N-Ac-5-ASA because (a) parent drug and metabolite exist in a metabolic equilibrium in the gut and in plasma, (b) this equilibrium varies as a function of the area of distribution of the formulation granules and (c) the measurement of only plasma 5-ASA for determining bioequivalence of generic formulations to the RLD does not reflect the true rate of delivery of mesalamine to the intended site of action, the colon;

- require bioequivalence be established on plasma PK parameters computed on plasma analytes 5-ASA, and N-Ac-5-ASA for the parameters C_{max}, AUC_{0-3}, AUC_{3-t}, AUC_{8-t} and AUC_t, AUC_{inf}, and T_{max}; and

- require a determination of the rate of N-Ac-5-ASA formation detected in the soluble fraction of fecal samples derived from subjects participating in the above pharmacokinetic studies.

We further request the agency not approve any ANDAs without resolving the issues raised in this Citizen Petition.

III. Environmental Impact

This petition raises no environmental impact and is subject to a categorical exclusion under 21 C.F.R. § 25.31(g).

IV. Economic Impact

An economic impact statement will be submitted at the request of the Commissioner per 21 C.F.R. § 10.30(b).

Salix Pharmaceuticals, Inc. • 8510 Colonnade Center Drive, Raleigh, NC 27615 • 1.866.646.5463 • T 919.862.1000 • F 919.862.1095 • www.salix.com

V. Certification

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: September 21, 2012. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: my employer, Salix Pharmaceuticals. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Linda G. Young, RPh, JD
Vice President, Regulatory Affairs
Salix Pharmaceuticals, Inc.
8510 Colonnade Center Drive
Raleigh, North Carolina 27615
(919) 862-1000

Copy of FedEx Express® shipping label

ORIGIN ID: RZZA (919) 862-1000
MAILROOM
SALIX PHARMACEUTICALS, INC.
8510 COLONNADE CENTER DRIVE

RALEIGH, NC 27615
UNITED STATES US

SHIP DATE: 17APR13
ACTWGT: 0.4 LB MAN
CAD: 376967/CAFE2608

BILL SENDER

TO URNESTINE ZZARAD
FDA – DOCKETS MANAGEMENT
5630 FISHERS LANE

ROCKVILLE MD 20852

REF: 220.6720.CP COVER LETTER

FedEx Express

J12131210050125

TRK# 0201 5493 1811 7312

THU – 18 APR 10:30A
PRIORITY OVERNIGHT

XC NSFA

20852
MD-US IAD

Part # 154250-354 TRITRA 09/