

Patent Certification Under 21 CFR §314.94 and Notice of Certification of Invalidity or Noninfringement of a Patent Under 21 CFR §314.95

I. Andrx Pharmaceuticals, L.L.C. (Andrx), having a place of business at 707 East Main Street, 11th Floor, Richmond, Virginia 23219, hereby certifies to the following persons that it has filed an Abbreviated New Drug Application under 21 U.S.C. §505(j)(2)(B)(ii) for permission to sell Divalproex Sodium Delayed-release Tablets 500 mg Valproic Acid activity, that are bioequivalent to Depakote® tablets:

A. Holder of New Drug Application for Depakote®

Abbott Laboratories
100 Abbott Park Road
Abbott Park IL 60064

B. On information and belief the owner of U.S. Letters Patent Nos. 4,988,731 and 5,212,326 is:

Abbott Laboratories
100 Abbott Park Road
Abbott Park IL 60064

II. The United States Food and Drug Administration has received an Abbreviated New Drug Application (ANDA) from Andrx which contains bioequivalence data which shows that the Andrx' Divalproex Sodium Delayed-Release Tablets, 500 mg Valproic Acid activity are bioequivalent to Depakote® tablets. A Paragraph IV Certification under 21 CFR §314.94 was submitted with the ANDA.

III. The Andrx Abbreviated New Drug Application Number is 75-770.

IV. The established name for the proposed drug product is Divalproex Sodium Delayed-release Tablets 500 mg Valproic Acid activity.

V. The active ingredient for the proposed drug product is Valproic Acid; the dosage form is an oral tablet that will be sold in 500-mg Valproic Acid activity strengths.

VI. The following patents (the "listed patents") which have been listed in the Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") are known to Andrx and will either (a) not be infringed by the making, using, or selling of Andrx' Divalproex Sodium Delayed-release Tablets 500 mg Valproic Acid activity product (Andrx' Proposed Product); or (b) be invalid and/or unenforceable if the claims are asserted to read on Andrx' Proposed Product:

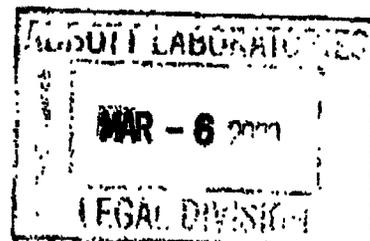
U.S. Patent No.

Expiration Date

4,988,731
5,212,326

January 29, 2008
January 29, 2008

A copy of each of these patents is attached hereto as an Appendix.



VII. The above U.S. patents, which have been listed in the Orange Book will not be infringed by Andrx' Proposed Product or, in the alternative, would be invalid or unenforceable against Andrx' Proposed Product for a number of reasons which are described below:

The listed patents will not be infringed by Andrx' Proposed Product because the claims of those patents concern particular oligomeric compositions or oral pharmaceutical dosage forms containing those oligomeric compositions which are completely different from Andrx' Proposed Product. To summarize:

- Andrx' Proposed Product is not, and does not contain, the claimed oligomeric form which is divalproex sodium. Therefore, Andrx' Proposed Product does not fall within the literal scope of the claims of the '731 or '326 patents. Neither does Andrx' Proposed Product contain the monomer of the complexed sodium valproate:valproic acid in a 1:1 ratio. Therefore, Andrx' Proposed Product does not contain any form of divalproex sodium that would infringe the listed patents under the doctrine of equivalents.
- The doctrine of equivalents cannot be applied to Andrx' Proposed Product because Andrx' Proposed Product contains a compound which is in the prior art, namely sodium valproate. The scope of the claims of the '731 and '326 patents cannot be expanded to cover prior art (including Andrx' Proposed Product) because patent protection cannot be afforded to that which is in the public domain. Accordingly, Andrx is free to use the prior art (public domain) non-oligomeric form of divalproex sodium without infringing either of the '731 or '326 patents.
- Because Andrx' Proposed Product contains a prior art compound as its active ingredient, any allegation that the '731 or '326 patents are infringed by Andrx' Proposed Product would necessarily mean that the claims of these listed patents read on the prior art. Any assertion that Andrx' Proposed Product infringes the claims of the listed patents would be an improper use of the listed patents. Thus, the '731 and '326 patents are either invalid or are unenforceable against Andrx' Proposed Product which employs a non-oligomeric and non-complexed form of divalproex sodium.

The distinctions which differentiate Andrx' Proposed Product from the claims of the listed patents are detailed below:

United States Patent No. 4,988,731

The claims of U.S. Patent No. 4,988,731 (the '731 patent) specifically require an oligomer comprising about four (4) units of complexed sodium valproate and valproic acid in a 1:1 ratio. The '731 patent contains two claims, both of which are reproduced below:

1. An oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{Na}/(\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{H}$, and containing about 4 such units.
2. An oral pharmaceutical dosage form for treating the symptoms of epileptic seizures or convulsions, containing as the active principal an oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{Na}/(\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{H}$, and containing about 4 such units.

Andrx' Proposed Product does not contain the claimed oligomer. Nor does Andrx' Proposed Product contain the monomer of complexed sodium valproate/valproic acid in a 1:1 ratio. The formulation for Andrx' Proposed Product is attached hereto as Exhibit "A."

The initial manufacturing step for Andrx' Proposed Product, utilizing divalproex sodium, is performed outside the United States and outside any United States territories subject to United States patent laws. This initial formulation step involves adding excess sodium hydroxide solution to divalproex sodium, thereby resulting in a high pH solution (pH 10.8, 50% w/w) which contains non-oligomeric, non-complexed sodium valproate. This high pH for the solution (termed "sodium divalproate pH-adjusted solution") is maintained throughout the manufacturing process; thus the oligomeric form is forever destroyed. The sodium divalproate pH-adjusted solution is then shipped into the United States where the high pH solution is diluted with alcohol and sprayed onto anhydrous lactose to form a granulation. The granulation is then tableted, and coated with cellulose acetate phthalate. A flow chart showing the steps involved in the formulation and preparation of Andrx' Proposed Product is attached hereto as Exhibit "B." Batch records from Andrx' ANDA submission (ANDA No. 75-770) are attached as Exhibit "C."

The sodium divalproate pH-adjusted solution imported into the United States contains no trace of the patented divalproex sodium oligomer, or the divalproex sodium monomer at any stage of the wet granulation or tableting process. Therefore Andrx' formulation cannot literally infringe any valid claim of the '731 patent.

The specification of the '731 patent recites several properties that are characteristic of the oligomeric divalproex sodium, and therefore can be used to identify the claimed compound. These properties include NMR spectra, mixed melting-point determination, IR spectra, and X-ray diffraction. See '731 patent at col. 2, lines 14-16. In addition, the claimed oligomer is described as a crystalline, stable solid which has the advantage of being non-hygroscopic. Independent testing of Andrx' Proposed Product clearly establishes that the oligomeric form of divalproex sodium is completely absent at all stages of the manufacturing process that occur within the United States.

Using these and other assays, side-by-side comparison of the claimed oligomer in solution, in powder form, and as final product with analogous forms used in Andrx' Proposed Product confirms that Andrx' Proposed Product does not contain the claimed oligomer. The data from these comparative tests suggest that Andrx' Proposed Product uses the prior art compound, sodium valproate. The results of these comparative assays are summarized below and are fully presented in the attached Exhibit D.

Summary of Characterization Test Results for Andrx' Proposed Product v. Patented Product

Test	Solution (50% w/w)		Granulation Material		Finished Product	
	Sodium Divalproate pH-adjusted solution	Patented Divalproex sodium oligomer (solution)	Andrx' Proposed Product Granulation	Patented Divalproex sodium oligomer	Andrx' Proposed Product	Depakote® (500 mg tablet)
pH	10.8	7.1	—	—	6.7	4.6
Infrared Peak near 1685 cm ⁻¹ ?	No	Yes (1707)	No	Yes (1696)	No	Yes (1701)
Melting Point (°C)	—	—	>152	~100	—	—
Hygroscopicity *	—	—	2.9	0.1	2.1**	0.4**
X-ray Diffraction (°/2θ)	—	—	5.9, 6.9	7.3	5.75, 6.8	7.2

* Measured as % weight gain after 45 minutes at room temperature (80% rel. humidity)

** Tablet core material

As shown in the above table, Andrx' Proposed Product is clearly distinct from the claimed oligomeric compound of the '731 patent. Specifically, the divalproate sodium pH-adjusted solution used in the preparation of Andrx' Proposed Product has a pH of 10.8. This is significantly higher than the pH of 7.1 measured for the patented divalproex sodium oligomer in solution at an identical concentration. The high pH for the solution used in the manufacturer Andrx' Proposed Product completely disrupts and forever destroys the claimed oligomeric form. Neither can the monomer exist at this high pH. The pH measurements for the final formulated tablets of Andrx' Proposed Product is also much higher than the Depakote® tablets.

The IR spectra for Andrx' Proposed Product further illustrate its distinction from the claimed oligomeric divalproex sodium. A distinctive peak at about 1685 cm⁻¹ is identified in the IR spectra for the patented divalproex sodium oligomer. This distinctive peak is consistently present in solution, in the active ingredient (drug substance), and in the final Depakote® product. The distinctive divalproex sodium peak is completely absent in Andrx' Proposed Product (solution, granulation, and final product). The IR spectra for Andrx' Proposed Product mimics that of the prior art compound, sodium valproate (see Exhibit D).

Moreover, Andrx' Proposed Product has a melting point much higher than the patented oligomer. Andrx' Proposed Product showed no physical change between 180°C and 400°C (the upper limit of the melting point apparatus). The claimed oligomer is recited as having a melting point range of 98-100°C, which was confirmed by Andrx' tests.

Another distinctive characteristic of Andrx' Proposed Product is that it is hygroscopic. The non-hygroscopic property of the claimed oligomer was relied on by the patentee of the '731 patent to establish a patentable distinction from the compounds in the prior art (see '731 patent, col. 2, lines 25-26 and lines 58-61). Thus, the hygroscopicity of Andrx' Proposed Product illustrates its similarity to the prior art compounds and supports the position that it falls outside the claims of the '731 patent both literally and under the doctrine of equivalents.

Finally, the X-ray diffraction pattern exhibited by Andrx' Proposed Product is clearly different from the X-ray diffraction pattern exhibited by the patented oligomers. The distinctive pattern for Andrx' Proposed Product shows a doublet peak at 5.75-5.9 and 6.8-6.9 units, whereas the patented oligomer does not exhibit the doublet peak. Instead, the patented oligomer exhibits a single peak at about 7.5 units. The X-ray diffraction pattern is a strong indication that Andrx' Proposed Product is a completely different compound from the patented oligomer.

In view of these side-by-side tests, Andrx' Proposed Product is shown to be distinct, and therefore does not literally infringe the claims of the '731 patent.

Further, Andrx' formulation cannot infringe any valid claim of the '731 patent under the doctrine of equivalents. Both the specification and the prosecution history of the '731 patent admit that sodium valproate and valproic acid are known prior art compounds that have been used for the treatment of epileptic seizures and convulsions. Additionally, valproic acid and valproic acid salts, such as sodium salts, have long been known to be useful in the treatment of epileptic seizures and convulsions. See generally, United States Patents Nos. 4,261,974 and 4,292,425, 4,301,176 and 4,323,507. Therefore, because Andrx imports into the United States sodium divalproate pH-adjusted solution which contains the prior art, non-oligomeric sodium valproate and this compound is employed at all stages of the formulation process for Andrx' Proposed Product, the claims of the '731 patent cannot be expanded under the doctrine of equivalents to include Andrx' Proposed Product.

Finally, it is noted that the '731 patent fails to contain any claims that recite a process for forming the claimed oligomer or pharmaceutical formulation containing the claimed oligomer. Accordingly, there can be no valid claim of infringement of the '731 patent under 35 U.S.C. § 271(g).

United States Patent No. 5,212,326

U. S. Patent No. 5,212,326 (the '326 patent) which is a continuation of the '731 patent discussed above, also provides protection only for the oligomeric form of the sodium valproate valproic acid complex. The broadest claims from the '326 patent are reproduced below:

1. An oligomer having a 1:1 molar ration of sodium valproate and valproic acid of the unit formula, $(\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{Na}/(\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{H}$ and containing about 4 to 6 such units.
2. An oral pharmaceutical dosage form for treating the symptoms of epileptic seizures or convulsions, containing as the active principal an oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{Na}/(\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{H}$, and containing about 4 to 6 units.
3. An oligomer having a 1:1 molar ration of sodium valproate and valproic acid of the unit formula, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{Na}/(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{H}$ and containing about 6 such units.

4. An oral pharmaceutical dosage form for treating the symptoms of epileptic seizures or convulsions, containing as the active principal an oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{Na}/(\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{H}$, and containing about 6 such units.

5. An oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{Na}/(\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{H}$, and having physical/chemical properties as follows: (a) stable, white crystalline powder; (b) melting point of 98° to 100°C; and (c) an infrared spectrum having strong absorption bands at about 2957, 2872, 2932, 1685, 1555 and 1370 cm^{-1} .

Claims 1-4 of the '326 patent require an oligomer comprising from 4 to 6 units of sodium valproate and valproic acid. Claim 5 of this patent requires an oligomer comprising units of sodium valproate and valproic acid and having specific properties.

Andrx' formulation cannot literally infringe any valid claim of the '326 patent because the divalproate sodium pH-adjusted solution that is imported into the United States for preparation of Andrx' Proposed Product does not contain any trace of sodium divalproex oligomer as claimed in the '326 patent. Further, no detectable amount of the sodium divalproex oligomer is present at any stage of Andrx' wet granulation or tablet formation process for Andrx' Proposed Product. See generally, discussion of Andrx' Proposed Product vis-à-vis the '731 patent, above, and the accompanying data. Therefore, the Andrx formulation cannot literally infringe any valid claim of the '326 patent. The melting point and IR spectra of Andrx' Proposed Product do not match the properties listed in claim 5 of the '326 patent. Specifically, the patented oligomer is claimed as a white crystalline powder exhibiting a melting point of 98°-100°C and strong IR bands at 2957, 2872, 2932, 1685, 1555 and 1370 cm^{-1} . As detailed in the discussion of non-infringement of the '731 patent, above, and the accompanying data presented in Exhibit D, the melting point for Andrx' Proposed Product is much higher than 98°-100°C and does not exhibit a characteristic IR peak at or near 1685 cm^{-1} .

Andrx' formulation also cannot infringe any valid claim of this patent under the doctrine of equivalents. The established knowledge that sodium valproate and valproic acid were used for treating epileptic seizures and convulsions more than one year prior to the filing date of the '326 patent or its '731 patent remove Andrx' Proposed Product the scope of equivalents for the claims of the '326 patent. The Andrx formulation contains only sodium valproate, a prior art compound. Therefore, the claims of the '326 patent cannot be properly asserted to include the Andrx formulation because the claims would read on the prior art.

Because the '326 patent also fails to contain any claims that recite a process for forming the claimed oligomer or a pharmaceutical formulation containing the claimed oligomer, there can be no valid claim of infringement under 35 U.S.C. § 271(g).

For the above reasons, Andrx' Proposed Product will not infringe any claims in the listed patents.

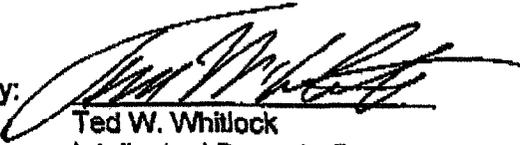
It is hereby certified that on March 1, 2000, a copy of this Notice has been sent by registered mail, return receipt requested, and by EXPRESS MAIL, return receipt requested, to Abbott as the holder of New Drug Application for Depakote® Tablets and owner of U.S. Patent Nos. 4,988,731 and 5,212,326 in an envelope addressed to:

Abbott Laboratories
100 Abbott Park Road
Abbott Park IL 60064

Respectfully,
Andrx Pharmaceuticals, L.L.C.

March 1, 2000

By:



Ted W. Whitlock
Intellectual Property Counsel
707 East Main Street, 11th Floor,
Richmond, Virginia 23219

Exhibit A

Formulation for Andrx' Proposed Product

Formulation for Andrx' Proposed Product (Modified Divalproate Sodium 500mg Valproic Acid Activity)

<i>Solution Preparation (Modified Divalproate Sodium Solution, code 170)</i>		<i>022W29001</i>			
Ingredient	Code	mg/tablet	%	Total %	kg
Divalproex Sodium	1047	536.41	53.830		260.000
Sodium Hydroxide	2075	39.87	6.938		33.510
Purified Water	2104	*	39.232		189.490
Total:		576.28	100.00		483.000

<i>Granulating (Modified Divalproate Sodium Granules, code 171)</i>		<i>171R001 Part 1-7 (Batch Size: 116.69 kg)</i>			
Ingredient	Code	mg/tablet	%	Total %	kg
Modified Divalproate Sodium (Sodium Valproate) Solution	170	576.28	69.111	62.20	11.519
Isopropyl Alcohol, USA	2094		*		14.572
Anhydrous Lactose, NF	2031	257.57	30.889	27.80	5.149
Total:		833.85	100.00	90.00	16.67

<i>Blending (Modified Divalproate Sodium Blend, code 172)</i>		<i>172R001</i>			
Ingredient	Code	mg/tablet	%	Total %	kg
Modified Divalproate Sodium (Sodium Valproate) Granules	171	833.85		90.00	102.510
Crospovidone, NF (Polyplasdone XL)	2072	32.43		3.50	3.987
Anhydrous Lactose, NF	2031	46.33		5.00	5.695
Colloidal Silicon Dioxide, NF (Cab-O-Sil, M5)	2032	4.63		0.50	0.570
Magnesium Stearate, NF	2028	9.27		1.00	1.139
Total:		926.50		100.00	113.90

<i>Tableting (Modified Divalproate Sodium DR Tablets (Uncoated), code 181)</i>		<i>181R001</i>			
Ingredient	Code	mg/tablet	%	Total %	kg
Modified Divalproate Sodium Blend	172	926.50			110.0

<i>Seal Coating (Modified Divalproate Sodium DR Tablets (Seal Coated), code 182)</i>		<i>182R001</i>			
Ingredient	Code	mg/tablet	%	Total %	kg
Modified Divalproate Sodium DR Tablet (Uncoated)	181	926.50		97.00	108.300
Hydroxypropyl Methylcellulose, USP (Methocel E5 Premium)	2116	11.46		1.20	1.340
Hydroxypropyl Cellulose, NF (Klucel EF)	2021	11.46		1.20	1.340
Magnesium Stearate, NF	2028	5.73		0.60	0.670
Ethanol, SDA 3A 190 Proof	2104		*		30.145
Total:		955.16		100.00	111.65

<i>Enteric Coating (Modified Divalproate Sodium DR Tablets (Enteric Coated), code 183)</i>		<i>183R001</i>			
Ingredient	Code	mg/tablet	%	Total %	kg
Modified Divalproate Sodium DR Tablet (Seal Coated)	182	955.16		92.50	110.710
Cellulose, NF (CAP)	2111	61.96		6.00	7.181
Diethyl Phthalate, NF (DEP)	2197	15.49		1.50	1.795
Isopropyl Alcohol, USP (99% pure)	2094		*		31.418
Acetone, NF	2101		*		31.418
Total:		1032.60		100.00	119.686

<i>Color Coating (Modified Divalproate Sodium DR Tablets (Color Coated), code 184)</i>		<i>184R001</i>			
Ingredient	Code	mg/tablet	%	Total %	kg
Modified Divalproate Sodium DR Tablet (Enteric Coated)	183	1032.60		97.24	118.510
Opadry Blue, YS-1-10749-A	2203	28.67		2.70	3.291
Vanillin, NF	2192	0.32		0.03	0.037
Purified Water, USP	2104		*		29.615
Candelilla Wax Powder, FCC	2130	0.32		0.03	0.037
Total:		1061.91		100.00	121.875

Exhibit B

Flow Chart for Preparation of Andrx' Proposed Product

**Manufacturing Process for Andrx Proposed Product
(Modified Divalproate Sodium Delayed-release Tablets,
500 mg Valproic Acid Activity)**

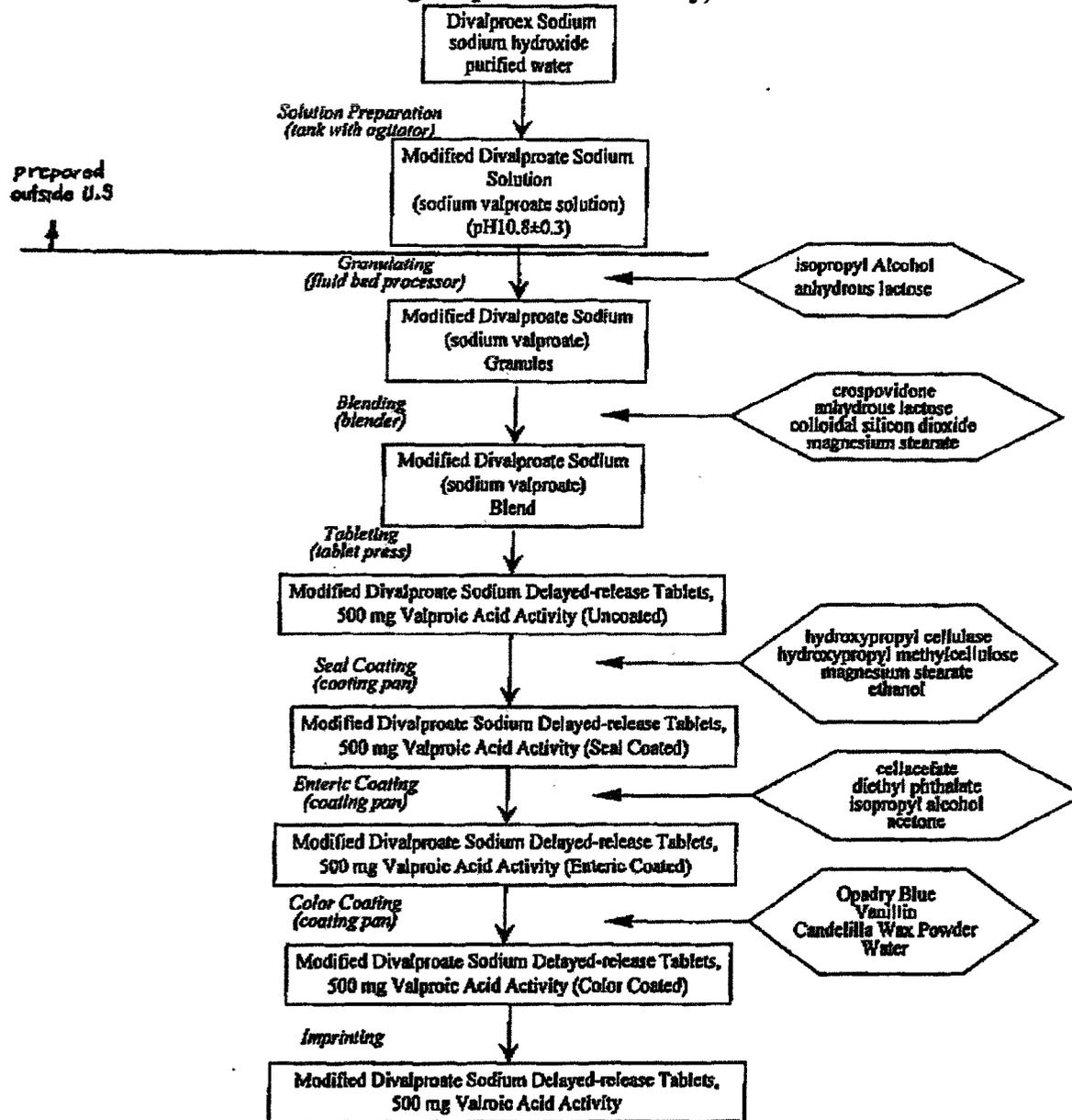


Exhibit C

Batch Records for ANDA Submission (ANDA No. 75-770) for
Andrx' Generic Depakote®

SELOC
FRANCE
19, route de Meulan
78520 LIMAY

FEUILLE DE TRAVAIL

DIVALPROEX SODIUM SOLUTION

Produit : SIC 98134 formulation

Visas Chef de projet <u>CVC</u> Atelier R & D <u>OLS</u> Laboratoires R & D <u>JMB</u> Qualité <u>VS</u>	Technique selon : technique client Andrx Pharmaceuticals du 28/04/99 Feuille de travail originale juin 99	Vérification avant lancement après lancement		Charge P 1
		<u>OP</u>	<u>OT</u>	
		Page n° 1 P1340000	Total des pages : 15	

MATIERES PREMIERES	N° CODE LOT	N° CONTROLE	U	QTE DELIVREE	VISA M	VISA A
20 049 W 29001 20 049 W 29002 Divalproex sodium 20 049 W 29003 Origine: P1 P2 1 2 Standard 265 kg - suite au verso page n° 1	P1	42469/1	kg	30,000	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
	P1	42469/2		7,000	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
	P2	42470/1		17,800	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
	P2	42470/2		17,200	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
	ch 1	42731/1		25,000	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
	ch 1	42731/2		25,000	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Sodium hydroxyde en pastilles très pur MERCK réf 1064829050 (Ph Eur)	---	42836/1	kg	34,150 2	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Eau déminéralisée CONFIDENTIEL	44032	/	l	174 17	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Méthanol	110092	43122	l	100	<input checked="" type="checkbox"/>	/
Acétone	110004	/	l	/	/	/

000386

CONFIDENTIEL

matieres premières	n° cader, lot	n° controle	U	qte DePurce	Visa H.	Visa A
Lot 049w 29003	cho1	42731/3	Kg	25,00	✓	✓
		42731/4		25,00	✓	✓
		42731/5		25,00	✓	✓
Dive P... .. Lot 049w 29004	cho2	42789/1		25,00	✓	✓
		42789/2		25,00	✓	✓
		42789/5		18,00	✓	✓

CONFIDENTIEL



pcas Divalproex sodium solution Translation of executed batch record

Batch Processing Instructions

		BATCH RECORD		
		DIVALPROEX SODIUM SOLUTION		
		Product : SIC 98134 formulation		
Approvals: Project manager R&D plant R&D laboratory Quality	Technique: According to customer's technique ANDRX pharmaceutical dated April 28 th 1999 B.P.I. original June 1999	before launch Page N°1 P1340000	Check After launch	Batch pages : 15 total

Raw Material	Code N°	Lot N°	Analysis N°	unit	Quantity delivered:	Warehouse - Sign:	operator signature:
Lot 049 w29001	P1		42469/1		30.000		
Lot 049w29002	P1		42469/2	Kg	7.000		
Lot 049w29003	P2		42470/1		17.800		
Divalproex sodium	Batch 1		42470/2		17.200		
	Batch 1		42731/1		25.00		
					42731/2	25.00	
Origin : P1 P2 and 1 and 2							
Sodium hydroxide highly pure MERCK ref 1064828050	Lot 8383532			Kg			
Purified water	44032						
Methanol	110092						
Acetone	11004						

MASTER FORMULA

Product: **Divalproex Sodium Granules**

Revision #: New

Product Code #: 171

Batch Size: 16.67 kg

Lot #: 171R001

Description: **White to off-white granules**

Issued by: Michelle Domany Date: 7/20/99

MASTER FORMULA

Ingredients	Part: <u>1</u> <u>11/28/99</u>	Weight %	Raw Material Code #	Material Rec. #	Exp. Date	Amount per batch (kg)	Weighed by	Checked by	Date	Mfg Check by	Date
Divalproex Sodium Solution		69.11	170	<u>9907042</u>	<u>07-01</u>	19.99*	<u>Ⓢ</u>	<u>AL</u>	<u>7-22-99</u>	<u>RLC</u>	<u>7-22-99</u>
Anhydrous Lactose, NF		30.89	2031	<u>9903019</u>	<u>04-01</u>	5.15	<u>Ⓢ</u>	<u>AL</u>	<u>7-22-99</u>	<u>RLC</u>	<u>7-22-99</u>
Isopropyl Alcohol, USP		**	2094	<u>9906066</u>	<u>07-01</u>	14.57	<u>Ⓢ</u>	<u>AL</u>	<u>7-22-99</u>	<u>RLC</u>	<u>7-22-99</u>
Total:		100				16.67 (excluding solvent)					

NOTE: * Composed of 8.47 kg water which will evaporate during processing and 11.52 kg solid content which is accounted for batch size and % weight.
 ** Evaporated during processing.

0711667.000

Master Record Approval		Batch Approval	
Prepared by: <u>J. P. [Signature]</u>	Date: <u>7-20-99</u>	Reviewed by: <u>J. P. [Signature]</u>	Date: <u>8-11-99</u>
Reviewed by: <u>Joseph [Signature]</u>	Date: <u>7/20/99</u>	Approved by: <u>Diana [Signature]</u>	Date: <u>08-19-99</u>
Reviewed by: <u>[Signature]</u>	Date: <u>7/20/99</u>		
Approved by: <u>[Signature]</u>	Date: <u>7/20/99</u>		
Approved by: <u>[Signature]</u>	Date: <u>7/20/99</u>		

000402

MASTER FORMULA

Product: **Divalproex Sodium Granules**

Revision#: New

Product Code #: 171 Batch Size: 16.67 kg

Lot #: 171R001

Description: White to off-white granules

Issued by: Mabelle Domany Date: 7/20/99

MASTER FORMULA

Ingredients	Part: <u>2 mg / 100 mg</u>	Weight %	Raw Material Code #	Material Rec. #	Exp. Date	Amount per batch (kg)	Weighed by	Checked by	Date	Mfg Check by	Date
Divalproex Sodium Solution		69.11	170	<u>9907042</u>	<u>07-01</u>	19.99*	<u>@</u>	<u>AL</u>	<u>7-23-99</u>	<u>DL</u>	<u>7-23-99</u>
Anhydrous Lactose, NF		30.89	2031	<u>9903019</u>	<u>04-01</u>	5.15	<u>@</u>	<u>AL</u>	<u>7-23-99</u>	<u>DL</u>	<u>7-23-99</u>
Isopropyl Alcohol, USP		**	2094	<u>9906066</u>	<u>07-01</u>	14.57	<u>@</u>	<u>AL</u>	<u>7-23-99</u>	<u>DL</u>	<u>7-23-99</u>
Total:		100				16.67 (excluding solvent)					

NOTE: * Composed of 8.47 kg water which will evaporate during processing and 11.52 kg solid content which is accounted for batch size and % weight.

** Evaporated during processing.

1711667.000

Master Record Approval		Batch Approval	
Prepared by: <u>J. P. Brown</u>	Date: <u>7-20-99</u>	Reviewed by: <u>J. P. Brown</u>	Date: <u>8-17-99</u>
Reviewed by: <u>Joseph Lopez</u>	Date: <u>7/20/99</u>	Approved by: <u>Bill W. Brown</u>	Date: <u>8-19-99</u>
Reviewed by: <u>[Signature]</u>	Date: <u>7/20/99</u>		
Approved by: <u>[Signature]</u>	Date: <u>7/20/99</u>		
Approved by: <u>Alex Melinda</u>	Date: <u>7/20/99</u>		

000424

Andrx Pharmaceuticals, Inc.

MASTER FORMULA

Product: Divalproex Sodium Granules

Revision #: New

Product Code #: 171

Batch Size: 16.67 kg

Lot #: 171R001

Description: White to off-white granules

Issued by: Shahida Domesy Date: 7/20/99

MASTER FORMULA

Ingredients	Part:	Weight %	Raw Material Code #	Material Rec. #	Exp. Date	Amount per batch (kg)	Weighed by	Checked by	Date	Mfg Check by	Date
Divalproex Sodium Solution	<u>3^{1/2}</u>	69.11	170	<u>9901042</u>	<u>07-22-01</u>	19.99*	<u>@</u>	<u>DL</u>	<u>7-23-99</u>	<u>REC</u>	<u>7-24-99</u>
Anhydrous Lactose, NF		30.89	2031	<u>9903019</u>	<u>04-06-01</u>	5.15	<u>@</u>	<u>DL</u>	<u>7-23-99</u>	<u>REC</u>	<u>7-24-99</u>
Isopropyl Alcohol, USP		**	2094	<u>9906030</u>	<u>06-18-01</u>	14.57	<u>@</u>	<u>DL</u>	<u>7-23-99</u>	<u>REC</u>	<u>7-24-99</u>
Total:		100				16.67 (excluding solvent)					

NOTE: * Composed of 8.47 kg water which will evaporate during processing and 11.52 kg solid content which is accounted for batch size and % weight.
 ** Evaporated during processing.

1711667.000

Master Record Approval		Batch Approval	
Prepared by: <u>J. B. B...</u>	Date: <u>7-20-99</u>	Reviewed by: <u>J. B. B...</u>	Date: <u>8-17-99</u>
Reviewed by: <u>Joseph Choi</u>	Date: <u>7/30/99</u>	Approved by: <u>Freddie Navam</u>	Date: <u>08-19-99</u>
Reviewed by: <u>[Signature]</u>	Date: <u>7/20/99</u>		
Approved by: <u>[Signature]</u>	Date: <u>7/20/99</u>		
Approved by: <u>Alex Melendi</u>	Date: <u>7/20/99</u>		

000447

ΑΝΟΤΗ ΚΡΑΤΗΜΕΝΟΧΗΜΙΚΑ, Α.Ε.

MASTER FORMULA

Product: Divalproex Sodium Granules

Revision #: New

Product Code #: 171

Batch Size: 16.67 kg

Lot #: 171R001

Description: White to off-white granules

Issued by: Michelle Demary Date: 7/20/99

MASTER FORMULA

Ingredients	Part: <u>4</u> ¹¹⁰ _{7/20/99}	Weight %	Raw Material Code #	Material Rec. #	Exp. Date	Amount per batch (kg)	Weighed by	Checked Date	Mfg Check by	Date
Divalproex Sodium Solution		69.11	170	<u>9907042</u>	<u>07-22-01</u>	19.99*	<u>Ⓟ</u>	<u>RL 7-26-99</u>	<u>RLC</u>	<u>7-26-99</u>
Anhydrous Lactose, NF		30.89	2031	<u>9903019</u>	<u>04-01-01</u>	5.15	<u>Ⓟ</u>	<u>RL 7-26-99</u>	<u>RLC</u>	<u>7-26-99</u>
Isopropyl Alcohol, USP		**	2094	<u>9906066</u>	<u>07-07-01</u>	14.57	<u>Ⓟ</u>	<u>RL 7-26-99</u>	<u>RLC</u>	<u>7-26-99</u>
Total:		100				16.67 (excluding solvent)				

NOTE: * Composed of 8.47 kg water which will evaporate during processing and 11.52 kg solid content which is accounted for batch size and % weight.
 ** Evaporated during processing.

1711667.000

Master Record Approval		Batch Approval	
Prepared by: <u>Ji. Pappas</u>	Date: <u>7-20-99</u>	Reviewed by: <u>Ji. Pappas</u>	Date: <u>8-17-99</u>
Reviewed by: <u>Joseph Gior</u>	Date: <u>7/20/99</u>	Approved by: <u>Andriou-Navaw</u>	Date: <u>08-19-99</u>
Reviewed by: <u>[Signature]</u>	Date: <u>7/20/99</u>		
Approved by: <u>[Signature]</u>	Date: <u>7/20/99</u>		
Approved by: <u>Alex Melidis</u>	Date: <u>7/20/99</u>		

694000

Andrx Pharmaceuticals, Inc.

MASTER FORMULA

Product: Divalproex Sodium Granules

Revision #: New

Product Code #: 171

Batch Size: 16.67 kg

Lot #: 171R001

Description: White to off-white granules

Issued by: Michelle Dorney Date: 7/20/99

MASTER FORMULA

Ingredients	Part: <u>5</u> <u>MD</u> <u>7/20/99</u> %	Weight %	Raw Material Code #	Material Rec. #	Exp. Date	Amount per batch (kg)	Weighted by	Checked by	Date	Mfg Date	Check Date
Divalproex Sodium Solution		69.11	170	<u>9907042</u>	<u>07-22-01</u>	19.99*	<u>Q</u>	<u>DL</u>	<u>7-27-99</u>	<u>DL</u>	<u>7-27-99</u>
Anhydrous Lactose, NF		30.89	2031	<u>9903019</u>	<u>04-06-01</u>	5.15	<u>Q</u>	<u>DL</u>	<u>7-27-99</u>	<u>DL</u>	<u>7-27-99</u>
Isopropyl Alcohol, USP		**	2094	<u>9906061</u>	<u>07-07-01</u>	14.57	<u>Q</u>	<u>DL</u>	<u>7-27-99</u>	<u>DL</u>	<u>7-27-99</u>
Total:		100				16.67 (excluding solvent)					

NOTE: * Composed of 8.47 kg water which will evaporate during processing and 11.52 kg solid content which is accounted for batch size and % weight.

** Evaporated during processing.

1711667.000

Master Record Approval		Batch Approval	
Prepared by: <u>Ji Boying</u>	Date: <u>7-20-99</u>	Reviewed by: <u>Ji Boying</u>	Date: <u>8-17-99</u>
Reviewed by: <u>Joseph Choi</u>	Date: <u>7/20/99</u>	Approved by: <u>Eric M. Wawon</u>	Date: <u>08-19-99</u>
Reviewed by: <u>DL</u>	Date: <u>7/20/99</u>		
Approved by: <u>Michelle Dorney</u>	Date: <u>7/20/99</u>		
Approved by: <u>DL Stalder</u>	Date: <u>7/20/99</u>		

000492

MASTER FORMULA

Product: **Divalproex Sodium Granules**

Revision #: New

Product Code #: 171

Batch Size: 16.67 kg

Lot #: 171R001

Description: **White to off-white granules**

Issued by: Michelle Dorman Date: 7/20/99

MASTER FORMULA

Ingredients	Part:	Weight %	Raw Material Code #	Material Rec. #	Exp. Date	Amount per batch (kg)	Weighed by	Checked by	Date	Mfg Check by	Date	
Divalproex Sodium Solution	<u>6</u>	<u>7/20/99</u>	69.11	170	<u>9907042</u>	<u>07-22-01</u>	19.99*	<u>[Signature]</u>	<u>DL</u>	<u>7-28-99</u>	<u>LKH</u>	<u>7/28/99</u>
Anhydrous Lactose, NF			30.89	2031	<u>9903019</u>	<u>04-06-01</u>	5.15	<u>[Signature]</u>	<u>DL</u>	<u>7-28-99</u>	<u>LKH</u>	<u>7/28/99</u>
Isopropyl Alcohol, USP			**	2094	<u>9906066</u>	<u>07-07-01</u>	14.57	<u>[Signature]</u>	<u>DL</u>	<u>7-28-99</u>	<u>LKH</u>	<u>7/28/99</u>
Total:			100				16.67 (excluding solvent)					

NOTE: * Composed of 8.47 kg water which will evaporate during processing and 11.52 kg solid content which is accounted for batch size and % weight.
 ** Evaporated during processing.

1711667.000	
Master Record Approval	Batch Approval
Prepared by: <u>[Signature]</u> Date: <u>7-20-99</u>	Reviewed by: <u>[Signature]</u> Date: <u>8-17-99</u>
Reviewed by: <u>[Signature]</u> Date: <u>7/20/99</u>	Approved by: <u>[Signature]</u> Date: <u>08-19-99</u>
Reviewed by: <u>[Signature]</u> Date: <u>7/20/99</u>	
Approved by: <u>[Signature]</u> Date: <u>7/20/99</u>	
Approved by: <u>[Signature]</u> Date: <u>7/20/99</u>	

000516

MASTER FORMULA

Product: **Divalproex Sodium Granules**

Revision #: New

Product Code #: 171

Batch Size: 16.67 kg

Lot #: **171R001**

Description: **White to off-white granules**

Issued by: J. Landa Biazil Date: 7/28/99

MASTER FORMULA

Ingredients	Part: <u>7</u>	Weight %	Raw Material Code #	Material Rec. #	Exp. Date	Amount per batch (kg)	Weighted by	Checked by	Date	Mfg Check by	Date
Divalproex Sodium Solution		69.11	170	<u>9907042</u>	<u>07-22-01</u>	19.99*	<u>Ⓢ</u>	<u>AL</u>	<u>7-29-99</u>	<u>AL</u>	<u>7/29/99</u>
Anhydrous Lactose, NF		30.89	2031	<u>9903019</u>	<u>04-06-01</u>	5.15	<u>Ⓢ</u>	<u>AL</u>	<u>7-29-99</u>	<u>AL</u>	<u>7/29/99</u>
Isopropyl Alcohol, USP		**	2094	<u>9906066</u>	<u>07-07-01</u>	14.57	<u>Ⓢ</u>	<u>AL</u>	<u>7-29-99</u>	<u>AL</u>	<u>7/29/99</u>
Total:		100				16.67 (excluding solvent)					

NOTE: * Composed of 8.47 kg water which will evaporate during processing and 11.52 kg solid content which is accounted for batch size and % weight.
 ** Evaporated during processing.

1711667.000	
Master Record Approval	Batch Approval
Prepared by: <u>J. Biazil</u> Date: <u>7-20-99</u>	Reviewed by: <u>J. Biazil</u> Date: <u>7-17-99</u>
Reviewed by: <u>Joseph Doe</u> Date: <u>7/20/99</u>	Approved by: <u>Subu C. Navam</u> Date: <u>08-19-99</u>
Reviewed by: <u>[Signature]</u> Date: <u>7/20/99</u>	
Approved by: <u>[Signature]</u> Date: <u>7/20/99</u>	
Approved by: <u>Alex Malindi</u> Date: <u>7/20/99</u>	

000539

Andrx Pharmaceuticals, Inc.

1 of 10

Product: Divalproex Sodium Blend

Revision #: New

Product Code #: 172 Batch Size: 113.90 kg Lot #: 172R001

Description: White to off-white granule mixture

Issued by: Michelle Doman

Date: 8/2/99

MASTER FORMULA

Ingredient	Weight %	Material Code #	Material Rec #/Lot#	Amount per Batch (kg)	Weighed by	Checked by	Date	Mfg. Ch'k by	Date
Divalproex Sodium Granules	90.0	171	172R001 Part 1	14.72	Ⓞ	AL	8-3-99	NA	8/3/99
			172R001 Part 2	14.37	Ⓞ	AL	8-3-99	NA	8/3/99
			172R001 Part 3	14.87	Ⓞ	AL	8-3-99	NA	8/3/99
			172R001 Part 4	14.59	Ⓞ	AL	8-3-99	NA	8/3/99
			172R001 Part 5	14.24	Ⓞ	AL	8-3-99	NA	8/3/99
			172R001 Part 6	14.20	Ⓞ	AL	8-3-99	NA	8/3/99
			172R001 Part 7	14.99	Ⓞ	AL	8-3-99	NA	8/3/99
Crospovidone, NF (Polypiasdone XL)	3.5	2072	9510008	3.987	Ⓞ	AL	8-3-99	NA	8/3/99
Anhydrous Lactose, NF	5.0	2031	9904032	5.695	Ⓞ	AL	8-3-99	NA	8/3/99
Colloidal Silicon Dioxide, NF (Cab-O-Sil M5)	0.5	2032	9710054	0.569	Ⓞ	AL	8-3-99	NA	8/3/99
Magnesium Stearate, NF	1.0	2028	9903007	1.139	Ⓞ	AL	8-3-99	NA	8/3/99
Total				113.90					

000562

172.000

Formula Approval		Batch Approval	
Prepared by: <u>J. Doman</u>	Date: <u>7-30-99</u>	Reviewed by: <u>J. Doman</u>	Date: <u>8-4-99</u>
Reviewed by: <u>Michelle Doman</u>	Date: <u>7/30/99</u>	Approved by: <u>Michelle Doman</u>	Date: <u>08-20-99</u>
Approved by: <u>Michelle Doman</u>	Date: <u>7/30/99</u>		
Approved by: <u>Michelle Doman</u>	Date: <u>8/2/99</u>		

Andrx Pharmaceuticals, Inc.

A 01 11

Product: Divalproex Sodium Delayed-Release Tablets, 500 mg Valproic Acid Activity (Uncoated)

181R001

Revision #: 001

Product Code #: 181

Batch Size: 110.0 Kg

Lot #: _____

Description: White to off-white, oval shape tablet.

Issued by: Dolores O'Connor

Date: 8/6/99

MASTER FORMULA

Ingredient	Weight %	mg/tablet	Code	Material Lot #	Amount per Batch (kg)	Weighed by	Checked by	Date	Mfg. Ch'k by	Date
Divalproex Sodium Blend	100.0	927	172	172R001	110.0	<u>[Signature]</u>	<u>[Signature]</u>	8-6-99	<u>[Signature]</u>	8/6/99
Total	100.0	927			110.0					

000577

181.001

Formula Approval		Batch Approval	
Prepared by: <u>[Signature]</u>	Date: <u>8-5-99</u>	Reviewed by: <u>[Signature]</u>	Date: <u>8/19/99</u>
Reviewed by: <u>[Signature]</u>	Date: <u>8/6/99</u>	Approved by: <u>[Signature]</u>	Date: <u>08-19-99</u>
Approved by: <u>[Signature]</u>	Date: <u>8/6/99</u>		
Approved by: <u>[Signature]</u>	Date: <u>08-06-99</u>		

Product: Divalproex Sodium Delayed-Release Tablets, 500 mg Valproic Acid Activity (Seal Coated)

Revision #: New

Product Code #: 182

Batch Size: 111.65 kg

Lot #: 182R001

Description: White to off-white, oval shape tablet

Issued by: Michelle Domany

Date: 8/19/99

Master Formula

Ingredients	Weight %	Material Code #	Material Lot#/Rec.#	Amount per batch (kg)	Weighed by	Checked by	Date	Mfg. Chk by	Date
Divalproex Sodium Delayed-Release Tablets, 500 mg Valproic Acid Activity (Uncoated).	97.0	181	<u>181R001</u>	<u>108.30**</u>	<u>@</u>	<u>ac</u>	<u>8-9-99</u>	<u>waf</u>	<u>8/9/99</u>
Hydroxypropyl Methylcellulose, USP (Methocel B5 Premium)	1.2	2116	<u>9808006</u>	<u>1.34</u>	<u>@</u>	<u>ac</u>	<u>8-9-99</u>	<u>waf</u>	<u>8/9/99</u>
Hydroxypropyl Cellulose, NF (Klucel HF)	1.2	2021	<u>9803016</u>	<u>1.34</u>	<u>@</u>	<u>ac</u>	<u>8-9-99</u>	<u>waf</u>	<u>8/9/99</u>
Magnesium Stearate, NF	0.6	2028	<u>9903007</u>	<u>0.67</u>	<u>@</u>	<u>ac</u>	<u>8-9-99</u>	<u>waf</u>	<u>8/9/99</u>
Ethanol, SDA 3A 190 Proof	*	2104	<u>9906034</u>	<u>30.15***</u>	<u>@</u>	<u>ac</u>	<u>8-9-99</u>	<u>waf</u>	<u>8/9/99</u>
Total	100			<u>111.65</u>					

*Evaporated during the coating process.

**Actual amount transferred from tableting

***To make the coating suspension with a solid content of 10%

sdval182.000

Formula Approval		Batch Approval	
Prepared by: <u>Ji. Boyang</u>	Date: <u>8-6-99</u>	Reviewed by: <u>Ji. Boyang</u>	Date: <u>8-17-99</u>
Reviewed by: <u>Joseph Chen</u>	Date: <u>8/6/99</u>	Approved by: <u>Shirley M. Navam</u>	Date: <u>08-23-99</u>
Approved by: <u>Dubs</u>	Date: <u>8/6/99</u>		
Approved by: <u>Shirley M. Navam</u>	Date: <u>08-09-99</u>		

000592

Andrx Pharmaceuticals, Inc.

Page 1 of 11

Product: Divalproex Sodium Delayed-Release Tablets, 500 mg Valproic Acid Activity (Enteric Coated)

Revision #: New

Product Code #: 183

Batch Size: 119.686 kg

Lot #: 183H001

Description: White to off-white, oval shape tablet

Issued by: V. ELANDIA

Date: 8/12/99

Master Formula

Ingredients	Weight %	Material Code #	Material Lot#/Rec.#	Amount per batch (kg)	Weighed by	Checked by	Date	Mfg Ch'k	Date
Divalproex Sodium Delayed-Release Tablets, 500 mg Valproic Acid Activity (Seal Coated)	92.5	182	182R001	110.71**	@	ac	8-13-99	Waf	8/13/99
Cellulose, NF	6.0	2111	9809007	7.121	@	ac	8-13-99	Waf	8/13/99
Diethyl Phthalate, NF	1.5	2197	9809006	1.795	@	ac	8-13-99	Waf	8/13/99
Isopropyl Alcohol, USP	*	2094	4907067	31.42***	@	ac	8-13-99	Waf	8/13/99
Acetone, NF	*	2101	9906056	31.42***	@	ac	8-13-99	Waf	8/13/99
Total	100			119.686					

*Evaporated during the coating process.
 **Actual amount transferred from seal coating.
 ***To make the coating solution with a solid content of 10%.

Formulas Approval		Batch Approval	
Prepared by: <u>J. E. Bostrom</u>	Date: <u>8-12-99</u>	Reviewed by: <u>J. E. Bostrom</u>	Date: <u>8-17-99</u>
Reviewed by: <u>[Signature]</u>	Date: <u>8/12/99</u>	Approved by: <u>Brian M. Cravens</u>	Date: <u>08-23-99</u>
Approved by: <u>[Signature]</u>	Date: <u>8/12/99</u>		
Approved by: <u>V. ELANDIA</u>	Date: <u>8/12/99</u>		

809000

Product: Divalproex Sodium Delayed-Release Tablets, 500 mg Valproic Acid Activity (Color Coated)

Revision #: New

Product Code #: 184 Batch Size: 121.875 Kg Lot #: 184R001

Description: Blue, oval shape tablet Issued by: U. ELARAO Date: 8/12/99

Master Formula

Ingredients	Weight %	Material Code #	Material Lot#/Rec.#	Amount per batch (kg)	Weighed by	Checked by	Date	Mfg.Ch'k by	Date
Divalproex Sodium Delayed-Release Tablets, 500 mg Valproic Acid Activity (Enteric Coated)	97.24	183	<u>183R001</u>	<u>118.51**</u>	<u>Ⓟ</u>	<u>ac</u>	<u>8-13-99</u>	<u>LMH</u>	<u>8/13/99</u>
Opadry Blue (YS-1-10749-A)	2.70	2203	<u>9906016</u>	<u>3.291</u>	<u>Ⓟ</u>	<u>ac</u>	<u>8-13-99</u>	<u>LMH</u>	<u>8/13/99</u>
Vanillin, NF	0.03	2192	<u>9809004</u>	<u>0.037</u>	<u>Ⓟ</u>	<u>ac</u>	<u>8-13-99</u>	<u>LMH</u>	<u>8/13/99</u>
Purified Water, USP	*	2014	<u>8-13-99</u>	<u>29.62</u> <u>29.26***</u> <u>M/10/99</u>	<u>Ⓟ</u>	<u>ac</u>	<u>8-13-99</u>	<u>LMH</u>	<u>8/13/99</u>
Candelilla Wax Powder, FCC	0.03	2130	<u>9905058</u>	<u>0.031</u>	<u>Ⓟ</u>	<u>ac</u>	<u>8-13-99</u>	<u>LMH</u>	<u>8/13/99</u>
Total		100.00		<u>121.875</u>					

*Evaporated during the coating process.
 **Actual amount transferred from enteric coating.
 ***To make a suspension with solid content of 10% (Opadry Blue).

184.000

Formula Approval		Batch Approval	
Prepared by: <u>Ji. Balyog</u>	Date: <u>8-12-99</u>	Reviewed by: <u>Ji. Balyog</u>	Date: <u>8-17-99</u>
Reviewed by: <u>[Signature]</u>	Date: <u>8/12/99</u>	Approved by: <u>Andri Sulhawan</u>	Date: <u>08-19-99</u>
Approved by: <u>[Signature]</u>	Date: <u>8/12/99</u>		
Approved by: <u>U. ELARAO</u>	Date: <u>8/12/99</u>		

000624

Exhibit D

**Side-by-side comparison of Depakote[®] v. Andrx' Proposed Product
(Raw Data)**

pH Measurement of Andrx's Starting Material, Intermediate and Finished Product vs Reference Material

A. Andrx's Starting Material and Reference Material at 50 % Concentration (w/w)

Samples		pH
Andrx's material	Imported solution*	10.8
Ref. material	Sodium valproate solution	10.5
Ref. material	Divalproex sodium solution	7.1

B1. Andrx's Intermediate and Reference Material at 50 % Concentration (w/w)

Samples		pH
Andrx's material	granulation solution	10.2
Ref. material	Sodium valproate solution	10.5
Ref. material	Divalproex sodium solution	7.1

B2. Andrx's Intermediate and Reference Material at 0.09 % Concentration (w/w)

Samples		pH
Andrx's material	granulation solution	6.8
Ref. material	Sodium valproate solution	7.7
Ref. material	Divalproex sodium solution	4.8

C. Andrx's Finished Product and Reference Material at 0.09 % Concentration (w/w)

Samples		pH
Andrx's material	Finished product solution	6.7
Ref. material	Depakote® Tablet solution	4.6

Note: All samples were prepared by dissolving the corresponding solid material in a CO₂ free water, except the Andrx's imported solution (*).

Melting Point Measurement of Andrx's Starting Material and Intermediate vs Reference Material

A. Andrx's Starting Material and Reference Material

Samples		Physical Observation
Andrx's material	Spray dried powder*	No change on the physical appearance (color change or melting) were observed from 80 to 400°C
Ref. material	Sodium valproate	No change on the physical appearance (color change or melting) were observed from 80 to 400°C
Ref. material	divalproex sodium	The material melted between 99-100°C.

* The sample was prepared from the spray drying of Andrx's imported solution (pH ~ 10.8).

B. Andrx's Intermediate and Reference Material

Samples		Physical Observation
Andrx's material	Granulation	The white sample turned to brownish at ~149°C, melted at ~152°C to yield a dark brown liquid, solidified at ~154°C, and partially melted at ~185°C.
Andrx's material	The core material of finished product*	The white sample turned to yellow (~120°C), to light brown (~132°C), to medium brown (~136°C), and to dark brown (~138°C). The dark brown material partially melted at ~157°C, and completely charred until ~270°C.
Ref. material	The core material of Depakote® Tablet**	The white sample turned to yellow (~178°C), to light brown (~196°C), to medium brown (~199°C), and to dark brown (~280°C). The dark brown material completely charred from 280 to 400°C (no melting was observed).

* The sample was obtained by breaking Andrx's finished product and collecting the inner solid without the coating layer.

** The sample was obtained by breaking Depakote® Tablets and collecting the inner solid without the coating layer.

Hygroscopicity Study of Andrx's Starting Material, Intermediate and Finished Product vs Reference Material @ RT/ 80% RH

A. Andrx's Starting Material and Reference Material

Samples		Weight Gain (%)						
		30 min	45 min	60 min	90 min	2 hr	4 hr	24 hr
Andrx	Spray dried powder*	4.3	5.5	8.5	10.4	12.0	14.9	47.2
Ref.	Divalproex sodium	0.1	0.1	0.1	0.1	0.1	0.1	0.1

* The sample was prepared from the spray drying of Andrx's imported solution (pH ~ 10.8).

B. Andrx's Intermediate and Reference Material

Samples		Weight Gain (%)						
		30 min	45 min	60 min	90 min	2 hr	4 hr	24 hr
Andrx	Granulation	1.9	2.9	3.6	5.3	6.8	NA	NA
Andrx	The core tablet of finished product*	1.6	2.1	3.1	3.8	4.4	5.3	20.0
Ref.	The core tablet of Depakote® Tablets**	0.3	0.4	0.5	0.6	0.7	0.8	3.5

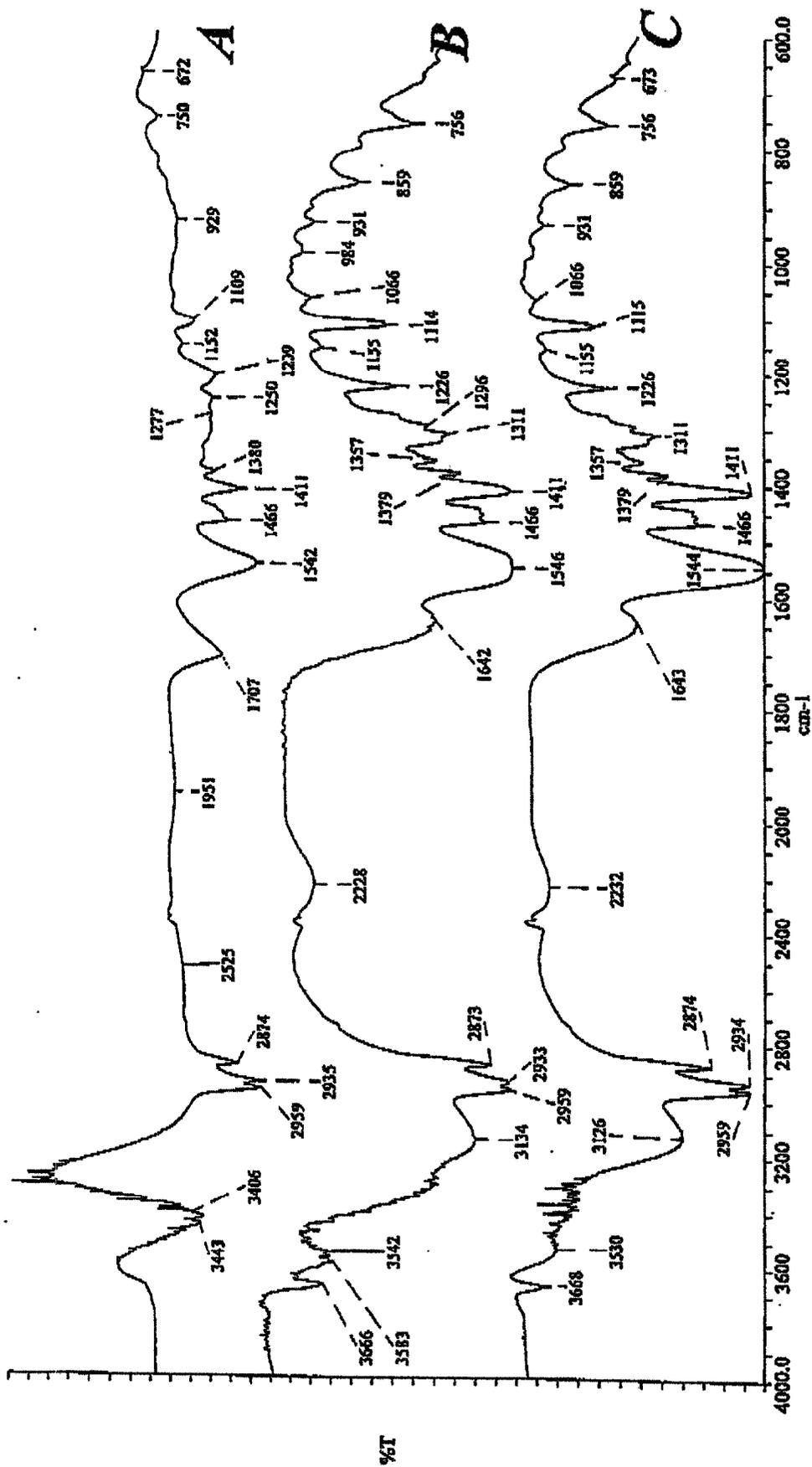
* The sample was obtained by removing the coating layer from Andrx's finished product.

** The sample was obtained by removing the coating layer from Depakote® Tablets.

C. Andrx's Finished Product and Reference Material

Samples		Weight Gain (%)						
		30 min	45 min	60 min	90 min	2 hr	4 hr	24 hr
Andrx	Finished product	0.2	0.2	0.2	0.3	0.3	0.5	2.5
Ref.	Depakote® Tablets	0.1	0.1	0.1	0.1	0.2	0.3	1.4

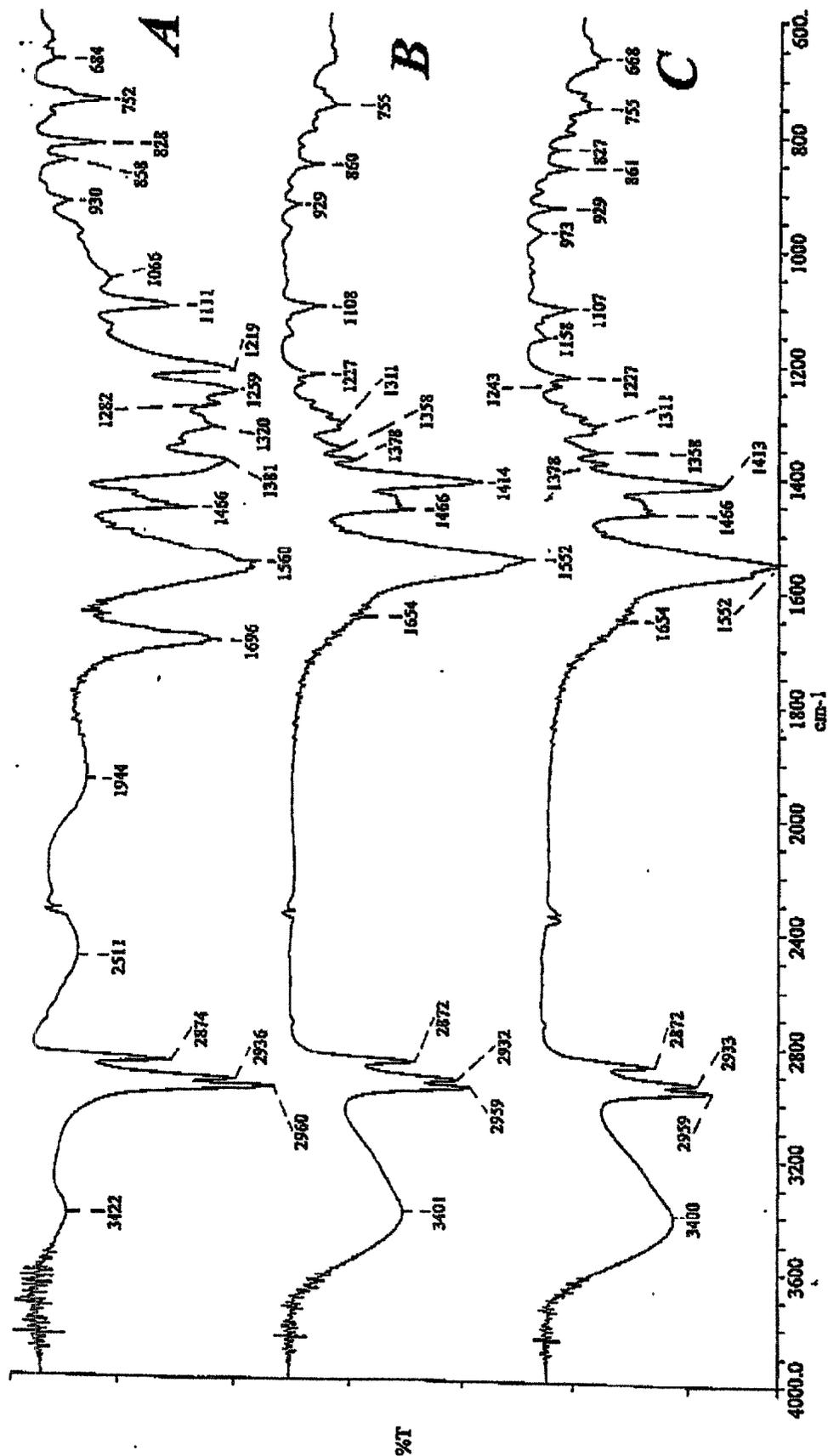
Comparative Solution IR Spectra of Andrx Starting Material and Reference Material



Notes:
 A = Divalproex sodium aqueous solution (50% w/w, pH 7.07) (water subtracted)
 B = Andrx imported divalproex sodium solution (50% w/w, pH ~ 10.8) (Lot No. 170R001) (water subtracted)
 C = Sodium valproate aqueous solution (50% w/w, pH 9.88) (water subtracted)

Sample: liquid sample in ZnSe lens. Resolution: 4 cm⁻¹

Comparative Solid-State IR Spectra of Andrx Spray Dried Powder and Reference Material



Notes:

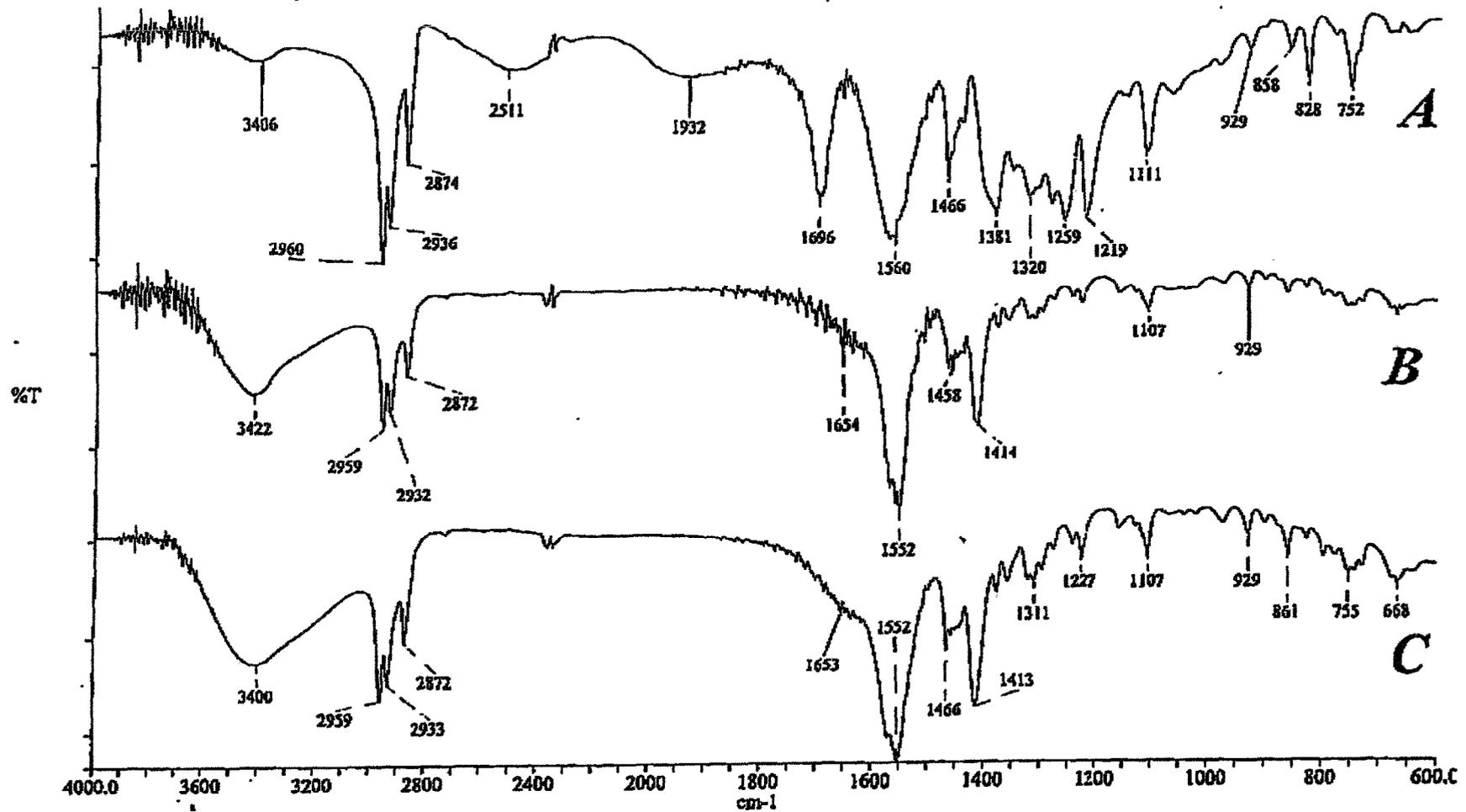
A = Divalproex sodium (Lot No. 9902044)

B = Spray dried powder of imported Divalproex sodium solution from France (Ref. SR735-54)

C = Sodium valproate (Lot No. 9809016)

Sample: KBr pellet. Resolution: 4 cm⁻¹

Comparative Solid-State IR Spectra of Andrx Intermediate Material and Reference Material

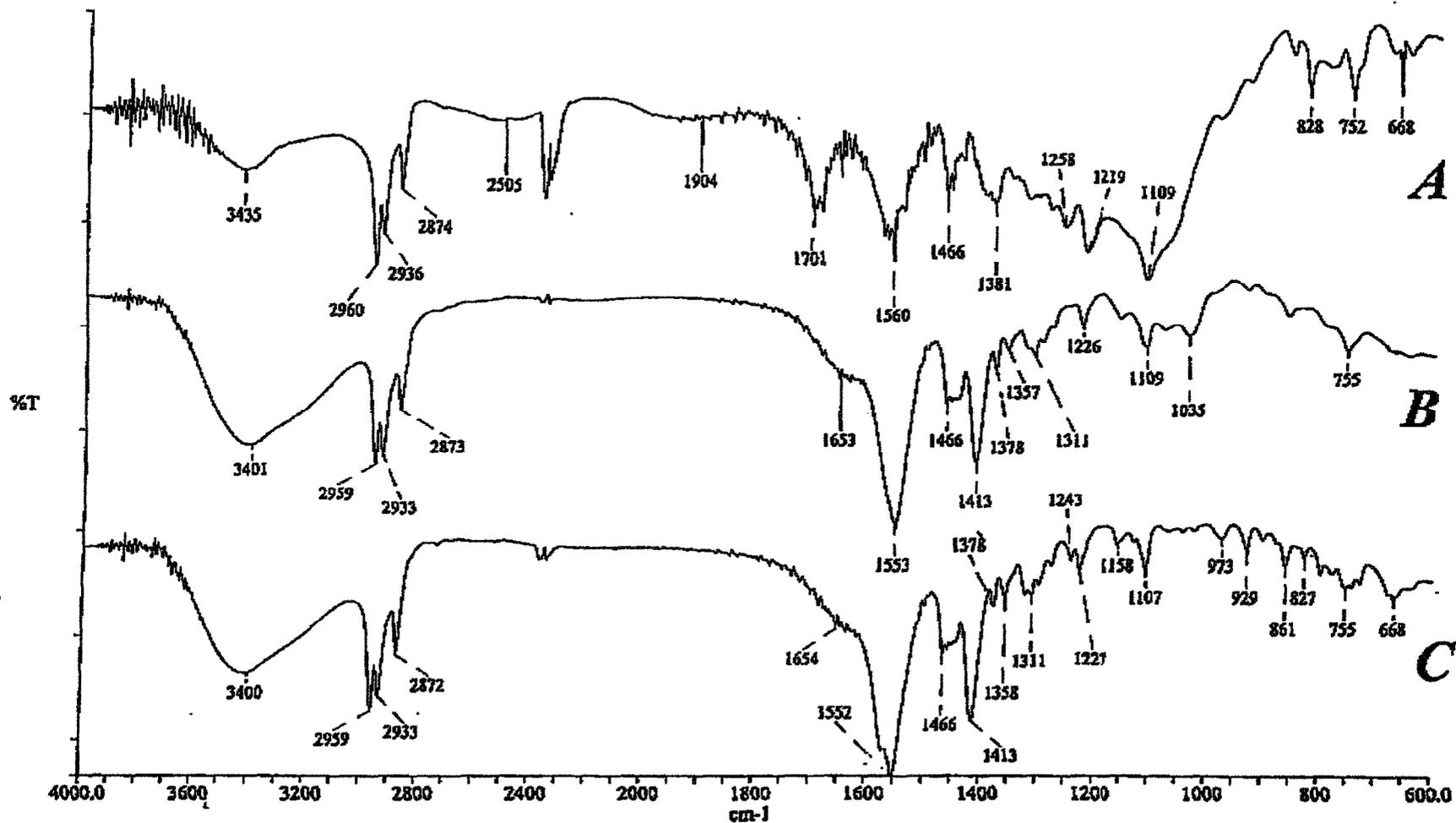


Notes:

- A = Divalproex sodium (Lot No. 9902044)
- B = Andrx Granulation (containing lactose) (Lot No. 171R001)
- C = Sodium valproate (Lot No. 9809016)

Sample: KBr pellet. Resolution: 4 cm⁻¹

Comparative Solid-State IR Spectra of Andrx Finished Product and Reference Material



Notes:

- A = Depakote® Tablet, 500 mg (Lot No. 45-404-AA-21) (coating removed)
- B = Andrx Divalproex sodium DR Tablet, 500 mg (Lot No. 184R001) (coating removed)
- C = Sodium valproate (Lot No. 9809016)

Sample: KBr pellet. Resolution: 4 cm⁻¹

X-ray Powder Diffraction Study of Andrx's Intermediate and Finished Product vs Reference Material

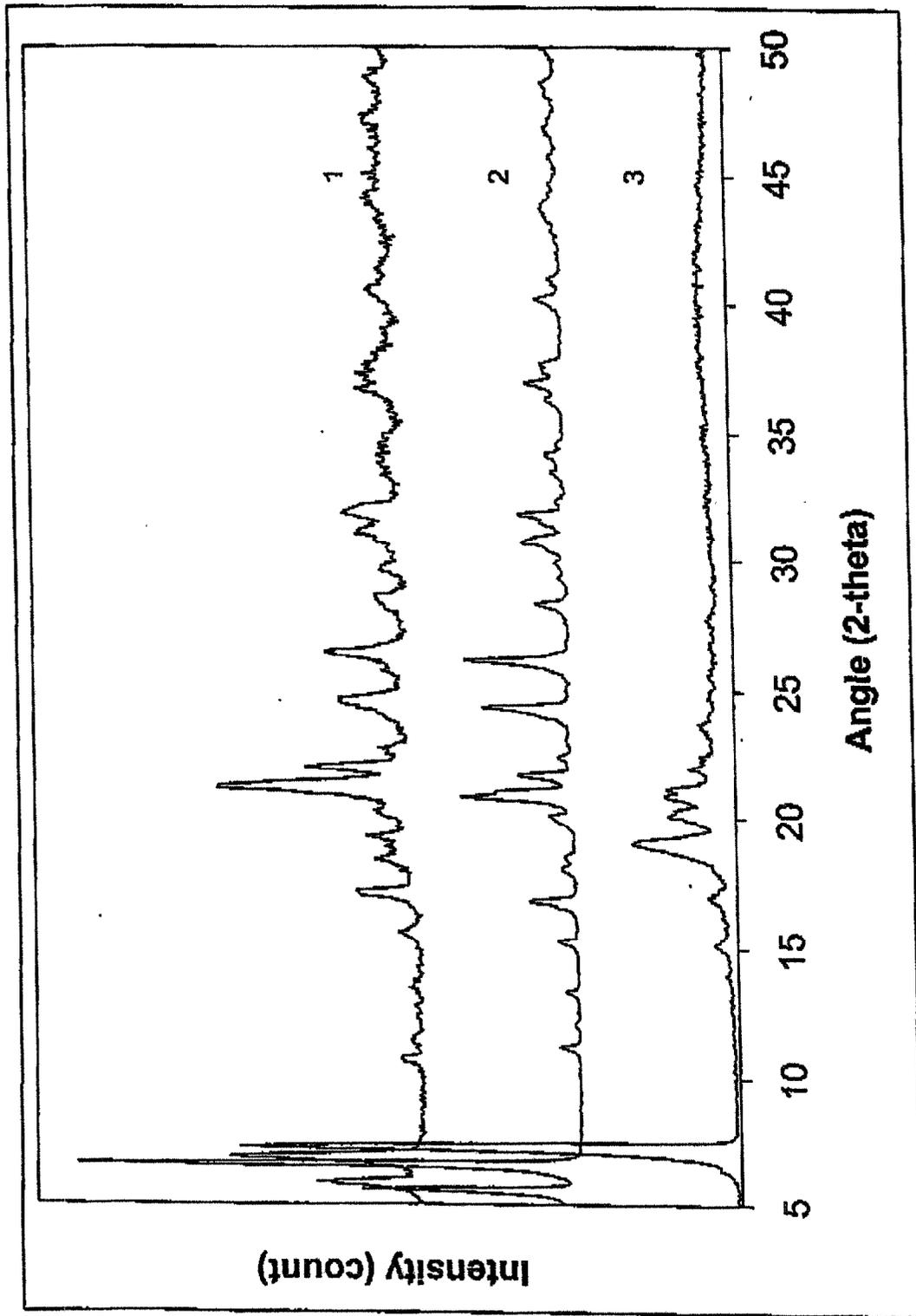
A. Andrx's Intermediate and Reference Material

Samples		Diffraction Peaks ($^{\circ}/2\theta$)
Andrx	Granulation	5.9, 7.0, 19.3, 21.3, 22.0, 24.7, 26.6, and 32.0
Reference	Sodium valproate	5.6, 6.7, 16.9, 20.9, 21.8, 24.4, 26.2, and 31.9
Reference	Divalproex sodium	7.3, 19.2, 20.4, and 21.2

B. Andrx's Finished Product and Reference Material

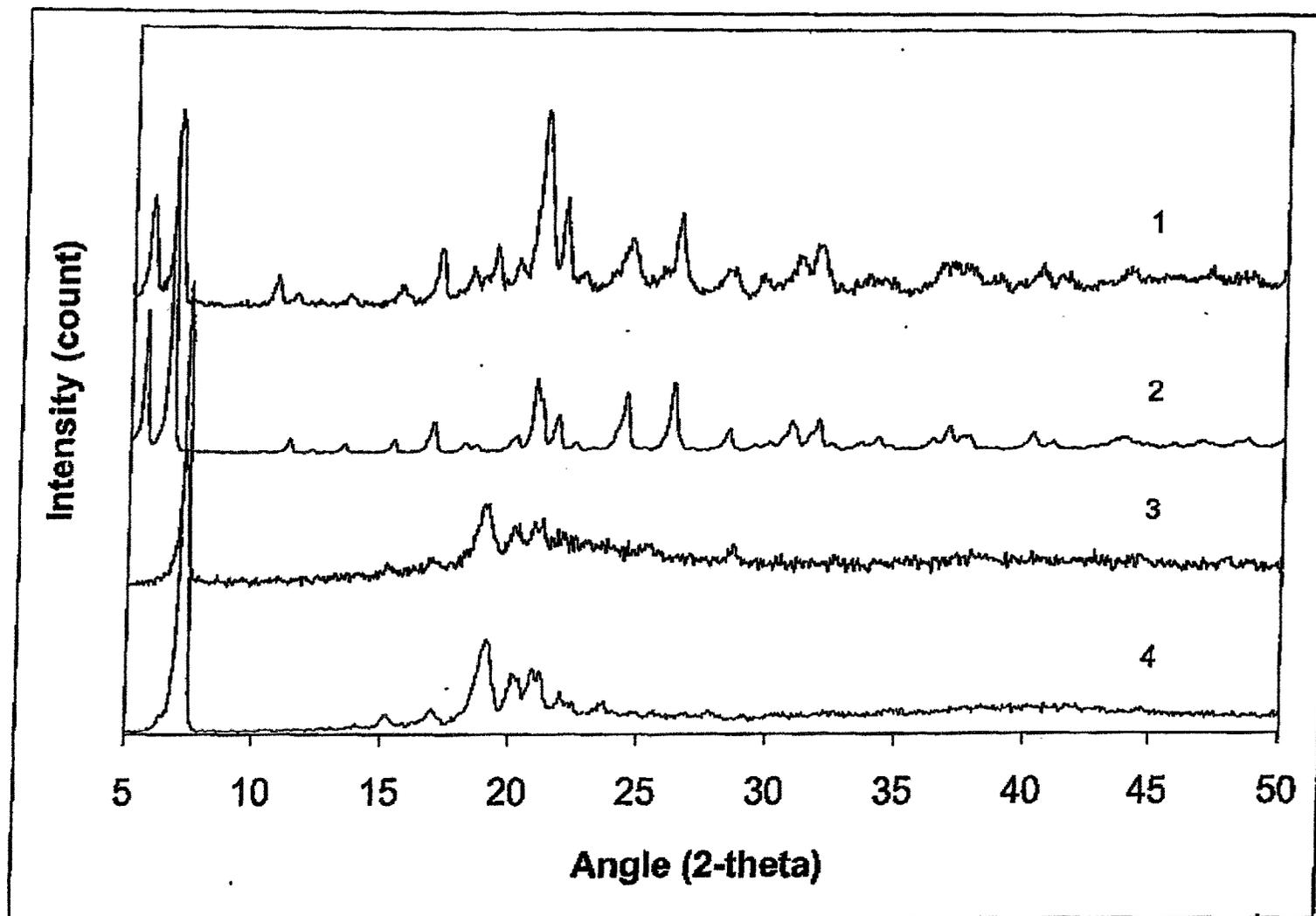
Samples		Diffraction Peaks ($^{\circ}/2\theta$)
Andrx	Finished product	5.6, 6.8, 17.1, 19.2, 21.9, 24.5, 26.4, and 31.9
Reference	Depakote[®] Tablets	7.2, 19.1 and 21.2

A. Comparative X-ray Powder Diffraction Patterns of Andrx's Intermediate vs Reference Material



1. Andrx's granulation.
2. Sodium valproate (reference material).
3. Divalproex sodium (reference material).

B. Comparative X-ray Powder Diffraction Patterns of Andrx's Finished Product vs Reference Material



1. Andrx's finished product.
3. Depakote® Tablets (reference material).
4. Divalproex sodium (reference material).

2. Sodium valproate (reference material).

Appendix

Copies of U.S. Patent Nos.

4,988,731

5,212,326

United States Patent [19]

Meade

[11] Patent Number: 4,988,731

[45] Date of Patent: Jan. 29, 1991

[54] SODIUM HYDROGEN DIVALPROATE OLIGOMER

[75] Inventor: Edwin M. Meade, Duncan, Canada

[73] Assignee: Abbott Laboratories, Abbott Park, Ill.

[21] Appl. No.: 117,945

[22] Filed: Nov. 9, 1987

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 68,284, Aug. 20, 1979, abandoned.

[51] Int. Cl.³ A61K 31/00; C07C 53/128

[52] U.S. Cl. 514/557; 562/606

[58] Field of Search 562/606; 514/557

[56] References Cited

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2,913,537 12/1959 Meade 260/419

4,127,604 11/1978 Chignao et al. 562/606
4,558,070 12/1985 Bauer et al. 514/557

FOREIGN PATENT DOCUMENTS

1074978 10/1954 France 562/606
2442M 4/1964 France 562/606

OTHER PUBLICATIONS

"The Pharmacological Studies on Sodium Dipropylacetate Anticonvulsant Activities and General Pharmacological Actions", K. Shuto and T. Nishigaki, *Applied Pharmacology*, 4(6), pp. 937-949 (1970).

Primary Examiner—Vivian Garner
Attorney, Agent, or Firm—Steven F. Weinstock

[57] ABSTRACT

This invention concerns certain diethyl- or dipropylacetic acid salts of sodium valproate which have physiological properties similar to those of valproic acid or sodium valproate but show highly superior stability characteristics.

2 Claims, No Drawings

strong bands indicate the stretching vibrations of the various methylene groups and the C=O in the carboxylic acid group, while the weak, broad bands at 2450 and 1900 cm^{-1} are due to intramolecularly bounded OH groups of the carboxylic acid.

EXAMPLE 2

In the fashion of Example 1 but using sodium valproate with the molar equivalents of dibutylacetic acid or diethylacetic acid, respectively, the corresponding hydrogen sodium mixed salts of the assumed structure II with $n=b$ 3 or 1, respectively, are obtained. In the instance of dibutylacetic acid, a very hygroscopic product is obtained which is very difficult to handle and therefore unsuitable for pharmaceutical dosage forms. The mixed salt obtained with diethylacetic acid is a white crystalline powder which is stable to ordinary storage conditions and essentially nonhygroscopic.

EXAMPLE 3

In a comparison of anticonvulsant activities of
 A: valproic acid (stable, liquid)
 B: sodium valproate (hygroscopic solid)
 C: compound (stable solid) of Example 1
 the oral ED₅₀ based on equimolar valproic acid equivalents are established by standard procedures. The results are as follows:

	A	B	C
Audiogenic seizures (mice)	154	141	81 mg/kg
Pentylenetetrazole seizures (mice)	<800	282	178 mg/kg
Pentylenetetrazole seizures (rats)	355	415	362 mg/kg

In a bioavailability study carried out with (A) and (C) above in various animal species, the peak blood plasma levels of oral, equimolar doses are determined according to standard procedures, 30 minutes after drug administration.

	A	C
Mouse (200 mg/kg)	133.7	207.4 mg/kg
Rat (200 mg/kg)	84.1	63.0 mg/kg
Dog (25 mg/kg)	65.2	73.6 mg/kg
Dog (25 mg/kg) AUC*	62.3	95.0 hr · mcg/ml

*Area under the curve value for 0-7 hours.

From the above examples, it will be seen that the new material has equal or better physiological properties than either valproic acid or sodium valproate. Since the new compound has far superior physical characteristics than either "monomer" from which it is made, it greatly facilitates the preparation of solid pharmaceutical dosage forms, and specific amounts can be weighed out and blended with starch and/or other binders to form a flowable powder which can be forwarded to standard 10 tableting machines after granulation. Neither the hygroscopic sodium salt of valproic acid nor the liquid valproic acid itself can be processed in this fashion without special precautions or absorbents.

The new compounds can be tableted in accordance with Example XIII of U.S. Pat. No. 3,325,361 and analogous methods. In these procedures, one or more diluents and/or excipients are used, e.g., starch, talcum powder, lubricants, disintegrators, flavoring agents, coloring agents and the like. These additives, of course, 15 are the usual pharmaceutically acceptable carriers or diluents employed in routine fashion by tablet formulations.

The above structure II is the most likely true two-dimensional view of the sodium/hydrogen divalproate 25 and seems to be confirmed by IR and nmr spectra, by molecular weight and microanalytic values. Thus, the new material should be characterized not by depicting a structural formula but by reference to a single compound of formula $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{Na}/\text{R}_2\text{CHCO}_2\text{H}$ or $[(\text{R}_2\text{CHCO}_2)(\text{R}_2\text{CHCO}_2)]\text{Na}_2\text{H}$ wherein each R is propyl, or by reference to sodium/hydrogen divalproate.

It will be understood that various changes and modifications can be made in the details of procedure, formulation and use without departing from the spirit of the invention, especially as defined in the following claims. 35

I claim:

1. An oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, 40 $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{Na}/(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{H}$, and containing about 4 such units.

2. An oral pharmaceutical dosage form for treating the symptoms of epileptic seizures or convulsions, containing as the active principal an oligomer having a 1:1 45 molar ratio of sodium valproate and valproic acid of the unit formula, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{Na}/(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{H}$, and containing about 4 such units.

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US005212326A

United States Patent [19]
Meade

[11] Patent Number: **5,212,326**
[45] Date of Patent: * **May 18, 1993**

- [54] **SODIUM HYDROGEN DIVALPROATE OLIGOMER**
- [75] Inventor: Edwin M. Meade, Duncan, Canada
- [73] Assignee: Abbott Laboratories, Abbott Park, Ill.
- [*] Notice: The portion of the term of this patent subsequent to Jan. 29, 2008 has been disclaimed.
- [21] Appl. No.: 637,828
- [22] Filed: Jan. 7, 1991

Related U.S. Application Data

- [63] Continuation of Ser. No. 117,945, Nov. 9, 1987, Pat. No. 4,988,731, which is a continuation of Ser. No. 545,719, Oct. 26, 1983, abandoned, which is a continuation-in-part of Ser. No. 68,284, Aug. 20, 1979, abandoned.
- [51] Int. Cl.⁵ C07B 53/00; A01N 37/00; A61K 31/19
- [52] U.S. Cl. 562/606

[58] Field of Search 562/606; 514/557
[56] References Cited

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4,988,731	1/1991	Meade	562/606 X

FOREIGN PATENT DOCUMENTS

1074978	10/1954	France	562/606
2442M	4/1964	France	562/606

Primary Examiner—José G. Dees
Assistant Examiner—Joseph M. Conrad
Attorney, Agent, or Firm—Steven F. Weinstock

[57] **ABSTRACT**

This invention concerns certain diethyl- or dipropylacetic acid salts of sodium valproate which have physiological properties similar to those of valproic acid or sodium valproate but show highly superior stability characteristics.

5 Claims, No Drawings

the oral ED50 based on equimolar valproic acid equivalents are established by standard procedures. The results are as follows:

	A	B	C
Androgenic seizures (mice)	154	141	81 mg/kg
Pentylenetetrazole seizures (mice)	<300	252	178 mg/kg
Pentylenetetrazole seizures (rat)	355	415	362 mg/kg

In a bioavailability study carried out with (A) and (C) above in various animal species, the peak blood plasma levels of oral, equimolar doses are determined according to standard procedures, 30 minutes after drug administration.

	A	C
Mouse (200 mg/kg)	133.7	207.4 mg/kg
Rat (200 mg/kg)	84.1	63.0 mg/kg
Dog (25 mg/kg)	65.2	73.6 mg/kg
Dog (25 mg/kg) AUC*	82.3	95.0 hr · mcg/ml

*Area under the curve value for 0-7 hours.

From the above examples, it will be seen that the new material has equal or better physiological properties than either valproic acid or sodium valproate. Since the new compound has far superior physical characteristics than either "monomer" from which it is made, it greatly facilitates the preparation of solid pharmaceutical dosage forms, and specific amounts can be weighed out and blended with starch and/or other binders to form a flowable powder which can be forwarded to standard tableting machines after granulation. Neither the hygroscopic sodium salt of valproic acid nor the liquid valproic acid itself can be processed in this fashion without special precautions or absorbents.

The new compounds can be tableted in accordance with Example XIII of U.S. Pat. No. 3,325,361 and analogous methods. In these procedures, one or more diluents and/or excipients are used, e.g., starch, talcum powder, lubricants, disintegrators, flavoring agents, coloring agents and the like. These additives, of course, are the usual pharmaceutically acceptable carriers or diluents employed in routine fashion by tablet formula-

The above structure II is the most likely true two-dimensional view of the sodium/hydrogen divalproate and seems to be confirmed by IR and nmr spectra, by molecular weight and microanalytic values. Thus, the new material should be characterized not by depicting a structural formula but by reference to a single compound of formula $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{Na}/\text{R}_2\text{CHCO}_2\text{H}$ or $[(\text{R}_1\text{CHCO}_2)(\text{R}_2\text{CHCO}_2)]\text{Na}, \text{H}$ wherein each R is propyl, or by reference to sodium/hydrogen divalproate.

It will be understood that various changes and modifications can be made in the details of procedure, formulation and use without departing from the spirit of the invention, especially as defined in the following claims.

I claim:

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2. An oral pharmaceutical dosage form for treating the symptoms of epileptic seizures or convulsions, containing as the active principal an oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{Na}/(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{H}$, and containing about 4 to 6 such units.

3. An oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{Na}/(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{H}$, and containing about 6 such units.

4. An oral pharmaceutical dosage form for treating the symptoms of epileptic seizures or convulsions, containing as the active principal an oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{Na}/(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{H}$, and containing about 6 such units.

5. An oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{Na}/(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{H}$, and having physical/chemical properties as follows:
 a. stable, white crystalline powder;
 b. melting point of 98°-100° C.; and
 c. an infrared spectrum having strong absorption bands at about 2957, 2872, 2932, 1685, 1555 and 1370 cm^{-1} .

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the oral ED50 based on equimolar valproic acid equivalents are established by standard procedures. The results are as follows:

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The above structure II is the most likely true two-dimensional view of the sodium/hydrogen divalproate and seems to be confirmed by IR and nmr spectra, by molecular weight and microanalytic values. Thus, the new material should be characterized not by depicting a structural formula but by reference to a single compound of formula $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{Na}/\text{R}_2\text{CHCO}_2\text{H}$ or $[(\text{R}_2\text{CHCO}_2)(\text{R}_2\text{CHCO}_2)]\text{Na}_2\text{H}$ wherein each R is propyl, or by reference to sodium/hydrogen divalproate.

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4. An oral pharmaceutical dosage form for treating the symptoms of epileptic seizures or convulsions, containing as the active principal an oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{Na}/(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{H}$, and containing about 6 such units.

5. An oligomer having a 1:1 molar ratio of sodium valproate and valproic acid of the unit formula, $(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{Na}/(\text{CH}_3\text{CH}_2\text{CH}_2)_2\text{CHCO}_2\text{H}$, and having physical/chemical properties as follows:

a. stable, white crystalline powder;

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c. an infrared spectrum having strong absorption bands at about 2957, 2872, 2932, 1685, 1555 and 1370 cm^{-1} .

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