DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892
715 Executive Plaza North

Memorandum

Date: November 15, 1991

From: Chief, Investigational Drug Branch

Re: Antineoplaston

To: Decision Network

Attached is a summary of a review of a best case series of antineoplastons in the treatment of brain tumors which was conducted by CTEP at the Burzynski Research Institute and some background information on antineoplastons A10 and AS2-1. Seven patient cases were presented at the site visit and the records, pathology slides and scans documenting response were reviewed. It was the opinion of the site visit team that antitumor activity was documented in this best case series and that the conduct of Phase II trials was indicated to determine the response rate.

At the DN meeting, Dr. Burzynski will present some brief background data on antineoplastons and Dr. Nicholas Patronas, a neuroradiologist from the Clinical Center who was on the site visit team, will review the radiologic findings for the committee.

Antineoplastons are being proposed for DN IV (Phase II trials). We feel the first step is to confirm the observations of Dr. Burzynski in brain tumors. Initially 3 or 4 Phase II trials would be conducted (one trial in each of the following diseases: glioblastoma multiforme, anaplastic astrocytoma, pediatric brain tumors and possibly low grade astrocytomas) using antineoplastons A10 and AS2-1 in exactly the same manner Dr. Burzynski gave them in the cases we reviewed. A decision regarding subsequent trials (e.g.--other tumors, additional Phase I development, Phase III trials in brain tumors, etc) would be deferred until the results of these initial trials were known.

Dr. Burzynski is willing to provide sufficient antineoplaston A10 and AS2-1 for these studies. The only impact on DCT would be the IND filing and the use of our clinical trials resources.

Michael J. Hawkins, M.D.

cc: Dr. Burzynski

DEPARTMENT OF HEALTH & HUMAN SERVICES

National Institutes of Health
National Cancer Institute

Momorandum

Date October 30, 1991

From Head, Quality Assurance and Compliance Section, RAB, CTEP

Subject Review of Brain Tumor Cases Treated With Antineoplastons

To See Distribution

On October 4, 1991, CTEP staff (Dr. Michael Hawkins, Dr. Michael Hamilton, Dr. Dorothy Macfarlane) and invited consultants (Dr. Nicholas Patronas, neuroradiologist, NIH Clinical Center, and Dr. James Nelson, neuropathologist, AFIP) visited the offices of Dr. Stanislaw Burzynski in Houston, Texas to review seven selected brain tumor cases which Dr. Burzynski felt represented the best responses achieved with Antineoplastons A-10 and AS2-1 treatment. Following is a summary of each case history, as described by Dr. Burzynski, and the assessment of slides and scans by the review team.

Patient #1 (E.L.)

46 year old white female who experience Jacksonian seizures and was diagnosed as having right parietal lobe glioblastoma multiforme in October 1987. Resected 11/10/87 at University of Maryland Hospital, and received radiation therapy following surgery. Tumor recurred in February 1988.

Presented to Dr. Burzynski in March 1988. Treated initially with Antineoplaston A10 capsules, AS2-1 injections and oral low dose methotrexate. Received only 8 days of MTX. Received intermittent steroids from 4/6/88 through 6/1/88. Considered a CR by 11/28/88 CT scan. Continued on full-dose treatment (0.5 to 1.0 gm A10 capsules daily, plus 2 gm AS2-1 IV daily) until 4/3/89. At that time, she was placed on AS2-1 capsules for maintenance therapy. In summer of 1989 patient discontinued treatment and in 8/89 recurrence was documented on MRI scan. Resection for recurrent glioblastoma multiforme at Johns Hopkins 11/28/89. Died 4/90.

Pathology review: Slides from 11/10/87 resection confirm glioblastoma multiforme.

Radiology review: Marked decrease in tumor size, possible complete response from 11/28/88 through 3/28/89 by CT. Recurrence possibly as early as 5/30/89 CT.

Patient #2 (P.W.)

36 year old female who first presented in 1974 with Bell's palsy. It is not clear that this event was related to the

later tumor which was first suspected in summer 1987. A stereotactic biopsy of the brain stem on 7/27/87 revealed anaplastic astrocytoma, stage IV, Grade 3. Received radiation therapy at UCSF (total 73Gy) until October 1987. Progression noted on scans of 2/88 and 4/88.

Presented to Dr. Burzynski in May 1988 with paralysis of right side of face, diplopia, decreased strength in right upper extremity, right ear hearing loss, headaches and problems with balance and memory. Started on Antineoplaston A10 capsules, AS2-1 IV and low dose oral methotrexate from 5/25/88 until 7/12/88, when she was switched to IV A10 (30 gm/day) and IV AS2-1 (15 gm/day) given overnight. This dose and schedule was continued until 8/10/89 when patient was switched to maintenance doses of oral A10 and AS2-1. Received IV Decadron 2mg/day from 5/29/88 through 9/7/88. No steroids given since that date. Called CR at 1/23/89 MRI. All treatment discontinued on 1/21/90 and patient remains in CR (last MRI 1/29/91). Residual facial nerve palsy, no other symptoms.

Pathology review: Slides from 7/21/87 stereotactic biopsy: consistent with anaplastic astrocytoma--small specimen (1 mm fragment) artifact distorts nuclei. Could be lower or higher grade astrocytoma.

Radiology review: From 1/23/89 MRI through latest MRI on 1/29/91 there is only a small cavity (1 cm or less) at the former tumor site which probably represents the site of biopsy. The previously seen tumor parenchyma is no longer present. Possible CR.

Patient #3 (J.K.)

47 year old white male who presented in April 1897 with deafness, progressive weakness and occasional seizures. Subtotal resection at UCSF April 24, 1987. Diagnosed as anaplastic astrocytoma close to the Foramen of Monroe. Patient treated at UCSF with radiation therapy + BUdR, which was stopped because of an exfoliative dermatitis. Patient next treated with combination of Procarbazine, CCNU, and vincristine which led to prolonged leukopenia and peripheral neuropathy. Progressed on treatment and switched to beta interferon (12/87 to spring 88). In June, 1988 started chemotherapy with DFMO and MGBG, but no response.

Presented to Dr. Burzynski 7/13/88 and started daily IV A10 and AS2-1 (overnight infusions). Showed slow progression initially, then stabilization by spring/summer 1989. On 5/22/89, antineoplaston dose was decreased and patient placed on AS2-1 capsules. By spring 1990, CTs showed progression of former tumor and appearance of new lesions. Restarted 4/12/90 on daily IV A10 (1 gm/kg/day) and AS2-1 (0.17 gm/kg/day) by continuous infusion pump. In June dose of AS2-1 was increased to 0.23 gm/kg/day and decadron was added from 6/27/90 to

7/25/90. In September 1991, decreased A10 dose by 60% and AS2-1 dose by 25%. Called PR in 10/91; approaching CR. Telephone follow up on the day of our visit; patient reported some memory deficit, but otherwise fine.

Pathology review: Slides from original subtotal resection showed infiltrating glioma (astrocytoma or mixed astrocytoma/oligodendroglioma), borderline anaplastic glioma.

Radiology review: Very aggressive tumor. Original tumor showed "fleshy" component of 4.5 cm on 8/24/88. Latest CT on 9/6/91 shows cavity of 4.0 cm with "fleshy" component of 1.3 cm, which may be residual tumor or calcium deposit. Numerous new lesions appeared starting with 11/88 CT, but all had disappeared by 12/19/90 CT. Good PR, possible CR.

Patient #4 (P.M.)

7 year old white male who presented with diplopia, nausea and vomiting in 11/85. CT on 11/7/85 showed suprasellar mass and hydrocephalus. Shunt placed 11/8/85. On 11/11/85 underwent craniotomy and biopsy at Mayo Clinic. Diagnosed as Stage IV astrocytoma, histologic Grade 1, inoperable. Treated with vitamins and laetrile originally. At the beginning of 1988, the patient experienced headaches and tumor progression was noted. A second shunt was placed.

Presented to Dr. Burzynski 4/18/88. Started on A10 capsules, AS2-1 IV and low dose methotrexate. In June 1988, a slight increase in tumor size was noted. On 6/23/88 patient was switched to overnight IV A10 (1 gm/kg/day) and IV AS2-1 (0.5 gm/kg/day). Progressive decrease in tumor size was noted; called a PR on basis of 4/17/90 MRI. Changed to continuous infusion A10 and AS2-1 at same doses on 5/29/90. Latest MRI on 8/2/91 shows further decrease in tumor size.

Pathology review: Slides from original biopsy. Well - differentiated astrocytoma, possibly juvenile pilocytic astrocytoma.

Radiology review: Pre-treatment scans show a hypothalamic mass plus trilocular cyst. Main component of cyst + tumor in hypothalamus followed through serial scans. There was a substantial decrease in size of both solid and cystic components, with the decrease in the cystic part more dramatic. Decrease in solid component of approximately 40-50%.

Patient #5 (H.E.)

40 year old white female diagnosed in 12/89. Craniotomy and partial resection on 12/31/89; glioblastoma multiforme of left temporal lobe. Received 6000 rads from January 18 to March 7,

1990. MRI on 4/9/90 showed progression after radiation therapy. Biopsied 5/9/90.

Presented to Dr. Burzynski on 5/24/90 with headaches, right-sided weakness and slurring of speech. Started on continuous infusion A10 (1 gm/kg/day) and AS2-1 (0.33 gm/kg/day). Called PR by 7/25/90 MRI. Progressed and switched to antineoplastons + methotrexate + vincristine. Continued to progress and died 1/1/91.

Pathology review: Slides from 12/31/89 partial resection showed glioblastoma multiforme. Slides from biopsy of 5/9/90 show residual tumor with extensive necrosis, cell density less than original tumor and more giant cells present. These changes are associated with radiotherapy and/or chemotherapy.

Radiology review: Unusually large tumor in 4/90 which decreased in size (39%) after treatment with antineoplastons. Had progressed by next MRI two months later, with former cavity filled in by tumor.

Patient #6 (R.W.)

10 year old male who had a VP shunt on 12/27/87. On 8/18/89 a mass was identified in the region of the hypothalamus. Stereotactic biopsy on 8/28/89 revealed glioblastoma, Stage IV, Grade 3. Received radiation therapy from 10/4/89 to 11/15/89 (total 5500 rads). Progressed 1/2/90, with increased tumor size and enhancement, and new area of tumor in ependyma and lateral ventricle.

Presented to Dr. Burzynski on 4/12/90 with hearing and memory deficits. Started on continuous infusion A10 (1 gm/kg/day) and AS2-1 (0.34 gm/kg/day). Doses decreased 4/17/90 because of high uric acid and given decadron 4/17 and 4/18; returned to full dose antineoplastons 4/24/90. Received decadron for nausea and vomiting 5/2-23/90. Off treatment on 5/9 through 5/11 and again 5/16 through 5/20 because of elevated uric acid. Re-started on 50% original dose 5/21/90. Dose increased on 6/5/90 to A10 (45 gm/day) and AS2-1 (15 gm/day). Single IV dose of decadron on 6/7/90. Decreased antineoplaston doses on 11/1/90 to A10 30gm/day and AS2-1 12.5 gm/day. A10 dose decreased again on 1/2/91 to 24 gm/day. Received single dose IV decadron on 1/16/91; no decadron since. Called CR on 11/1/90 Antineoplaston dose decrease in 4/91; still on treatment and still in CR.

Pathology review: Slides from original stereotactic biopsy in 1989. Glioma consistent with anaplastic astrocytoma. Differential: anaplastic astrocytoma or spindle cell variant of oligodendroglioma.

Radiology review: Original pre-treatment MRI on 1/2/90 showed a hypothalamic mass with subependymal spread; measured main

tumor in hypothalamus only. By 8/22/90, enhancement of ventricle had disappeared. By 10/25/90, there is no enhancement seen. Abnormal, probably scar tissue, in the former tumor bed. CR, which remains unchanged through 7/1/91 MRI.

Patient #7 (H.M.)

30 year old white male who was diagnosed with astrocytoma Stage IIIB following craniotomy and biopsy of left frontal lesion in October 1987. Received radiation therapy during October-November 1987.

Presented to Dr. Burzynski on 7/8/88 with recent increase in right-sided weakness. Started on overnight infusions of A10 (135 gm/kg/day) and AS2-1. Received varying doses of steroids continually from beginning of treatment to present. IV antineoplastons discontinued 3/31/89. Started AS2-1 capsules 4/4/89 and added A10 capsules and low dose methotrexate on 5/17/89. On 11/3/89 progression was noted and intermittent IV bolus AS2-1 begun. Switched to continuous infusion A10 (90 gm/day) and AS2-1 (25 gm/day) on 5/1/90. A10 discontinued on 6/8/90. By August 1990, former tumor appeared calcified.

Pathology review: Infiltrating anaplastic astrocytoma.

Radiology Review: No pre-treatment scans available. A large cavitary mass is present in left frontal lobe on 8/22/88 CT. It demonstrates ring enhancement. A second component of this lesion invades the corpus callosum and crosses the midline invading the opposite frontal lobe. By 8/3/89 CT, no enhancement is seen. Areas of unusual tumor calcification appear. The calcifications increase over time extending into the entire tumor parenchyma and masking any possible enhancement on the CT scans. Remains stable until 9/19/91 when MRI shows definite enhancement. Question of whether difference seen is because 9/19/91 scan is an MRI compared to earlier scans which were all CT. Good response--possible CR?

Dorothy Macfarlane

Dorothy K. Macfarlane, M.D.

Distribution:

Dr. Michael Friedman
Dr. Michael Hawkins
Dr. Michael Hamilton
Dr. Nicholas Patronas
Dr. James Nelson
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Patient #1 (E.L.)

	CT/MRI	Largest Diameter Measurement	Notes:	
2/8/88	CT	2.3 cm	At recurrence	
3/8/88	CT	2.3 cm	Started treatment	3/ /88
4/22/88	CT	2.3 cm		
6/6/88	CT	2 cm		
7/20/88	CT	1.5 cm	Ca deposit	
9/28/88	CT	1.1 cm	Ca deposit	
11/28/88	CT	0 ?	Edge blurred: artifact or minute area of enhancement?	
1/11/89	CT	same	Ca deposit - ? of small area of enhancement	
3/28/89	CT	same		
5/30/89	CT	1.5cm		
6/2/89	CT	1.5cm?	No contrast - can't compare	
7/5/89	MRI	1.8 cm		
7/14/89	CT	1.5 cm		
8/1/89	MRI	2.0 cm		
9/5/89	MRI	2.6 cm		
10/14/89	MRI	5 cm		

Impression: Marked decrease in tumor size - possible CR

Patient #2 (P.W.)

	Measurements of Greatest Diameter				
	Scan	T_1	T_2		
	CT/MRI	Site	Tumor Only	Tumor + Edema	Notes:
2/25/88	MRI	UCSF	2.2 cm	2.8 cm	Contrast?
4/29/88	MRI	UCSF	3.0	3.5	Contrast?
7/11/88	MRI	Houston	2.2	2.6	No Contrast — started treatment 5/25/88
9/17/88	MRI	Houston	1.9	2.5	No Contrast
10/18/88	MRI	Houston	1.3	2.2	No Contrast
1/23/89	MRI	Houston	1.0	1.0	small cavity seen - biopsy site?
4/10/89					incomplete films
1/15/90	MRI	Northridge Hosp.	1.0 ?	1.0 ?	small cavity - Simmons machine - no scale
1/29/91	MRI	Princeton	1.0	1.0	small cavity with hemosiderin - no edema

Impression: From 1/23/89 scan on, both T_1 and T_2 measurements represent a small cavity, probably the site of biopsy PR to CR?

Patient #3 (J.K.)

		Lesions:					
*	CT/MRI	(R) frontal	(R) temporal	(R) Parietal	(R) Temporal Horn	(L) frontal	(L) Temporal
3/18/88	CT	2.8 cm	0	0	0	0	0
6/29/88	CT	Film missing			started treatment		7/13/88
8/24/88	CT	4.4 cm	0	0	0	0	0
11/28/88	CT	4.0 cm	8 mm	0	0	0	0
1/30/89	CT	4.0/4.2	1 cm	? dot	0	0	0
3/15/89	CT	4.2 cm	1.2 cm	? 2mm dot	0	0	0
5/15/89	CT	3.9/4.1	9-10 mm	? dot	1.8 cm	1.0 cm	8 mm
7/24/89	CT	3.9/4.0	0	0	0	9 mm	6 mm
11/6/89	CT	3.8/3.8	0	0	0	1.2 cm	3-4 mm
1/31/90	CT	3.5/3.7	0	0	0	1.1 cm	0
4/11/90	CT	3.5/3.6	0	0	0	7-8 mm	0
6/4/90	CT	3.9/3.9	0	0	0	0	0
8/6/90	CT	4.0/4.0	0	0	0	0	0
10/15/90	CT	4.0/4.0	0	0	0	0	0
12/19/90	CT	4.0 (cavity)	0	0	0	0	0
4/1/91	CT	4.0 (cavity)	0	0	0	0	0
6/28/91	CT	4.0 (cavity)	0	0	0	0	0
9/6/91	CT	*1.3 cm	0	0	0	0	0
	* Note:	All CT's done at UCSF					

* New lesions

* 1.3 cm "fleshy" component decreased from 4.5 cm "fleshy" component on 8/24/88. Question of whether 9/6/91 residual represents tumor or calcium.

	(L) lateral ventricle wall A	(L) lateral ventricle wall B	(L) frontal horn	(L) parietal horn	(R) Temporal	medulla
1/31/90	4 mm	3 mm	0	0	0	0
4/11/90	0	1 cm	9 mm	1.2 cm	9 mm	0
6/4/90	0	6 mm	8 mm	1.0 cm.	8 mm	8 mm suspicious
8/6/90	0	5 mm	0	5-6 mm	0	0
10/15/90	0	2 mm	0	0	0	0
12/19/90	0	0	0	0	0	0
4/1/91	0	0	0	0	0	0
6/28/91	0	0	0	0	0	0
9/6/91	0	0	0	0	0	0

Impression: Ilmi Good DP possible CR?

Patient # 4 (P.M.)

	CT/MRI	Site	Hypothalamic Cyst/Mass		Notes:		
11/7/85	CT	Wm Beaumont Hosp	2.8 cm		Enhancing portion - can't measure two diameters		
11/26/86	MRI	U. Mich.	5 x 3.0 cm		Measurement of main central part; has also unmeasured lobes both sides		
3/10/88	MRI	U. Mich.	5.5 x 3.3				
8/21/88	MRI	U. Mich.	5.0 x 2.8		Lobe on	Ⓡ has	disappeared
10/26/88	MRI	U. Mich.	4.6 x 2.7				
1/29/89	MRI	U. Mich.	4.3 x 2.5		↑ protein,	no hemorrhage	
5/31/89	MRI	U. Mich.	4.0 x 2.2		Enhancing	component	= 2.2 cm
9/26/89	MRI	U. Mich	3.6 x 2.2		Enhancing	component	= 1.9 cm
4/17/90	MRI	U. Mich.	3.4 x 1.6		Enhancing	component	= 1.5 cm
8/21/90	MRI	U. Mich.	3.4 x 1.6		Enhancing	component	= 1.5 cm + spotty
1/12/91	MRI	U. Mich	3.4 x 1.6				
8/2/91	MRI	U. Mich	3.2 x 1.0		No contrast	* see below	

Note: Hypothalamic mass with tri-locular cyst. Measured main cystic component in hypothalamus

8/2/91 MRI Note: Cerebellar pontine angle cystic projections nearly completely gone. Brain stem free of compression

Impression: Substantial decrease in size; size of cystic components' decrease greater than that of solid component. Overall about 40-50% decrease in size.

Patient #5 (H.E.)

	CT/MRI	Site	(L) Temporal			
5/18/90	MRI	Santa Fe	6.5 X 5cm			
7/25/90	MRI	Santa Fe	6.0 X 3.3cm		39% decrease in size	
9/19/90	MRI	Santa Fe	6.2 X 5.0		Progression with tumor - cavity filled in	
10/31/90	MRI	Santa Fe	7.5 X 6.3			

All scans on Simmons MRI - no scale except 5cm

Impression: 39% decrease in tumor size from 5/18 to 7/25; progression by 9/19/90.

Patient #6 (R.W.)

	CT/MRI	Site	Hypothalamus			
1/2/90	MRI	New Brunswick	5.1 X 2.2 cm			
5/15/90	MRI	same	1.0 X 0.6		Started treatment.	4/12/90
6/21/90	MRI	Houston	1.2 X 0.8		Not including horn	
8/22/90	MRI	New Brunswick	0.4 X 0.2		Enhancement of ventricle disappears	
10/25/90	MRI	same	0		No enhancement - abnormal tissue where tumor bed was	
1/7/91	MRI	same	0		same as above	
4/1/91	MRI	same	0		No enhancement - scar tissue	
7/1/91	MRI	same	0		No enhancement - same as above	

Impression: CR, 9+ months duration

Patient #7 (H.M.)

	CT/MRI	Site	(L) Frontal	Bifrontal		
* 8/22/88	CT	Bellaire	4.0 cm	4.8 cm		faint enhancement - highly necrotic
11/7/88	CT	Bellaire	3.9			
1/30/89	CT	Bellaire	3.2			very faint enhancement
3/2/89	CT	Butterworth	4.0			has crossed mid line
6/5/89	CT	Bellaire	2.3 - calcium			Calcified area 2.3 cm - no enhancement
8/3/89	CT	Bellaire	calcium	4.4 cm		Calcium deposits - bilateral no enhancement
11/2/89	CT	Bellaire	calcium	4.5 cm		Calcium increased - @ frontal and bifrontal
2/1/90	CT	Bellaire	3.0 cm	5.0 cm		No enhancement
3/5/90	CT	Bellaire	3.0 cm	5.0 cm		No enhancement
4/30/90	CT	Bellaire	3.0 cm	5.5 cm		No enhancement
6/7/90	CT	Bellaire	3.0 cm	5.5 cm		No enhancement - increased calcium bifrontal
7/16/90	CT	Butterworth	3.0 cm	5.5 cm		? area of new enhancement
8/16/90	MRI	Butterworth				No pre-contrast scan
9/19/90	MRI	Butterworth	3.1 cm	5.5 cm		Definite enhancement

* No pre-treatment scan

proved new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for the OTC uses and containing any active ingredient(s) as specified in paragraph (a) of this section is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1) and (d)(2) of this section.

(1) May 7, 1991, for products subject to paragraphs (a)(1) through (a)(19) of this section; and

(2) February 10, 1992, for products subject to paragraph (a)(20) of this section.

[55 FR 46919, Nov. 7, 1990; 55 FR 49973, Dec. 3, 1990, as amended at 56 FR 37798, Aug. 8, 1991; 56 FR 46823, Sept. 16, 1991; 56 FR 63568, Dec. 4, 1991; 57 FR 3526, Jan. 30, 1992]

EFFECTIVE DATE NOTE: At 56 FR 63568, Dec. 4, 1991, in § 310.545 paragraph (a)(7) was amended by removing the entry "Methol" including the parenthetical statement and alphabetically adding the entry "Menthol", the introductory text of paragraph (d) was revised, and paragraph (d)(3) was added, effective December 4, 1992. For the convenience of the reader, the text in effect as of December 4, 1992 appears as follows:

§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

* * * * *

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1), (d)(2), and (d)(3) of this section.

* * * * *

(3) December 4, 1992, for products subject to paragraph (a)(7) of this section that contain menthol as an antipruritic in combination with the antidandruff ingredient coal tar identified in § 358.710(a)(1) of this chapter.

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

Subpart A—General Provisions

Subpart B—Investigational New Drug Application (IND)

Subpart C—Administrative Actions

Subpart D—Responsibilities of Sponsors and Investigators

Subpart E—Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses

Subpart F—Miscellaneous

Subpart G—Drugs for Investigational Use in Laboratory Research Animals or in Vitro Tests

AUTHORITY: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371); sec. 351 of the Public Health Service Act (42 U.S.C. 262).

SOURCE: 52 FR 8831, Mar. 19, 1987, unless otherwise noted.

Subpart A—General Provisions

§ 312.1 Scope.

(a) This part contains procedures and requirements governing the use of investigational new drugs, including procedures and requirements for the submission to, and review by, the Food and Drug Administration of investigational new drug applications (IND's). An investigational new drug for which an IND is in effect in accordance with this part is exempt from the premarketing approval requirements that are otherwise applicable and may be shipped lawfully for the purpose of conducting clinical investigations of that drug.

(b) References in this part to regulations in the Code of Federal Regulations are to Chapter I of Title 21, unless otherwise noted.

§ 312.2 Applicability.

(a) *Applicability.* Except as provided in this section, this part applies to all clinical investigations of products that are subject to section 505 or 507 of the Federal Food, Drug, and Cosmetic Act or to the licensing provisions of the Public Health Service Act (58 Stat. 632, as amended (42 U.S.C. 201 et seq.)).

(b) *Exemptions.* (1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in Part 56 and with the requirements for informed consent set forth in Part 50; and

(v) The investigation is conducted in compliance with the requirements of § 312.7.

(2)(i) A clinical investigation involving an in vitro diagnostic biological product listed in paragraph (b)(2)(ii) of this section is exempt from the requirements of this part if (*a*) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and (*b*) it is shipped in compliance with § 312.160.

(ii) In accordance with paragraph (b)(2)(i) of this section, the following products are exempt from the requirements of this part: (*a*) blood grouping serum; (*b*) reagent red blood cells; and (*c*) anti-human globulin.

(3) A drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirements of this part if shipped in accordance with § 312.160.

(4) FDA will not accept an application for an investigation that is exempt under the provisions of paragraph (b)(1) of this section.

(5) A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.

(c) *Bioavailability studies.* The applicability of this part to in vivo bioavailability studies in humans is subject to the provisions of § 320.31.

(d) *Unlabeled indication.* This part does not apply to the use in the practice of medicine for an unlabeled indication of a new drug or antibiotic drug product approved under Part 314 or of a licensed biological product.

(e) *Guidance.* FDA may, on its own initiative, issue guidance on the applicability of this part to particular investigational uses of drugs. On request, FDA will advise on the applicability of this part to a planned clinical investigation.

§ 312.3 Definitions and interpretations.

(a) The definitions and interpretations of terms contained in section 201 of the act apply to those terms when used in this part:

(b) The following definitions of terms also apply to this part:

Act means the Federal Food, Drug, and Cosmetic Act (secs. 201-902, 52 Stat. 1040 et seq., as amended (21 U.S.C. 301-392)).

Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.

Contract research organization means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration.

FDA means the Food and Drug Administration.

IND means an investigational new drug application. For purposes of this part, "IND" is synonymous with "Notice of Claimed Investigational Exemption for a New Drug."

Investigational new drug means a new drug, antibiotic drug, or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms "investigational drug" and "investigational new drug" are deemed to be synonymous for purposes of this part.

Investigator means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Subinvestigator" includes any other individual member of that team.

Marketing application means an application for a new drug submitted under section 505(b) of the act, a request to provide for certification of an antibiotic submitted under section 507 of the act, or a product license application for a biological product submitted under the Public Health Service Act.

Sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

Sponsor-Investigator means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

Subject means a human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease.

§ 312.6 Labeling of an investigational new drug.

(a) The immediate package of an investigational new drug intended for human use shall bear a label with the statement "Caution: New Drug—Limited by Federal (or United States) law to investigational use."

(b) The label or labeling of an investigational new drug shall not bear any statement that is false or misleading in any particular and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated.

§ 312.7 Promotion and charging for investigational drugs.

(a) *Promotion of an investigational new drug.* A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

(b) *Commercial distribution of an investigational new drug.* A sponsor or investigator shall not commercially distribute or test market an investigational new drug.

(c) *Prolonging an investigation.* A sponsor shall not unduly prolong an investigation after finding that the results of the investigation appear to establish sufficient data to support a marketing application.

(d) *Charging for and commercialization of investigational drugs*—(1) *Clinical trials under an IND.* Charging for an investigational drug in a clinical trial under an IND is not permitted without the prior written approval of FDA. In requesting such approval, the sponsor shall provide a full written explanation of why charging is necessary in order for the sponsor to undertake or continue the clinical trial, e.g., why distribution of the drug to test subjects should not be considered part of the normal cost of doing business.

(2) *Treatment protocol or treatment IND.* A sponsor or investigator may charge for an investigational drug for a treatment use under a treatment protocol or treatment IND provided: (i) There is adequate enrollment in the ongoing clinical investigations under the authorized IND; (ii) charging does not constitute commercial marketing of a new drug for which a marketing application has not been approved; (iii) the drug is not being commercially promoted or advertised; and (iv) the sponsor of the drug is actively pursuing marketing approval with due diligence. FDA must be notified in writing in advance of commencing any such charges, in an information amendment submitted under § 312.31. Authorization for charging goes into effect automatically 30 days after receipt by FDA of the information amendment, unless the sponsor is notified to the contrary.

(3) *Noncommercialization of investigational drug.* Under this section, the