CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20937

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENTS

Final Rule published: July 29, 1997
Effective date: August 28, 1997

Categorical Exclusions

What categorical exclusions apply to CDER applications?

§ 25.31 Human drugs and biologics.

The classes of actions listed in this section are categorically excluded and, therefore, ordinarily do not require the preparation of an EA or an EIS:

(a) Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, if the action does not increase the use of the active moiety.

(b) Action on an NDA, abbreviated application, or a supplement to such applications, or action on an OTC monograph, if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.

(c) Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

(d) Withdrawal of approval of an NDA or an abbreviated application.

(e) Action on an IND.

What is the definition of increased use?

> Increased use of a drug or biologic product may occur if the drug will be administered at higher dosage levels, for longer duration or for different indications than were previously in effect, or if the drug is a new molecular entity. The term "use" also encompasses disposal of FDA-regulated articles by consumers.

Note: § 25.31(a) and (b) apply to both substances that occur naturally in the environment and those that do not. § 25.31(c) applies only to substances that occur naturally in the environment. However, the substances may be obtained from natural sources, biological systems or chemically synthesized.

Type of Action	Old Regulations	New Regulations
NDA results in increased use of an active moiety (e.g., new molecular entities, new indications, Rx to OTC switch, some new dosage forms)	EA required	EA required only if: (1) the estimated concentration of the active moiety at the point of entry into the aquatic environment is 1 part per billion (ppb) or greater (Note this is equivalent to ~40,700 kg of active moiety per year assuming non-localized use and without considering metabolism or degradation processes); or (2) in the case of naturally occurring substances, the criterion listed under #1 is met AND the action significantly alters the concentration or distribution of the substance, its metabolites, or degradation products in the environment.
NDA does not result in increased use of an active moiety (e.g., some formulation changes, some new dosage forms, some prodrugs)	EA required	Categorically excluded
Efficacy supplement results in increased use of an active moiety (e.g., new indications including those for previous off-label uses, higher dose/longer duration of dose, inclusion of patient population specifically excluded previously in the labeling)	EA required	Same as NDA that increases use
Efficacy supplement does not result in increased use of an active moiety (e.g., lower dose, shorter duration of use or exclusion/limiting a patient population)	Categorically excluded	Categorically excluded
INDs	Categorically excluded	Categorically excluded
CMC Supplements	Categorically excluded	Categorically excluded
Abbreviated Applications	Categorically excluded	Categorically excluded

Note: FDA will require at least an EA for any specific action that ordinarily would be excluded if extraordinary circumstances indicate that the specific proposed action may significantly affect the quality of the human environment (Extraordinary circumstance provision).

EXTRAORDINARY CIRCUMSTANCES

As required under 40 CFR 1508.4, FDA will require at least an EA for any specific action that ordinarily would be excluded if extraordinary circumstances indicate that the specific proposed action may significantly affect the quality of the human environment (see 40 CFR 1508.27 for examples of significant impacts). Examples of such extraordinary circumstances include:

(a) Actions for which available data establish that, at the expected level of exposure, there is the potential for serious harm to the environment; and

(b) Actions that adversely affect a species or the critical habitat of a species determined under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Flora and Fauna to be endangered or threatened or wild flora or fauna that are entitled to special protection under some other Federal law.

Who decides the existence of an extraordinary circumstance?

The delegation of authority for determining the existence of an extraordinary circumstance is the Commissioner _ Dr. Woodcock _ Dr. Williams _ Nancy Sager. No other persons in CDER have the authority.

What are the Chemist's responsibilities?

1. The EA group should be consulted regarding any application (including supplements to change biomass source) submitted that involves wild plants and animals as biomass sources for the active pharmaceutical ingredient. If the chemist is aware (e.g., IND pre-meeting) that an application will be filed involving wild plants and animals, they should advise the applicant/sponsor to consult the EA group.

2. The EA group should be consulted if a categorical exclusion claim has been submitted, but, the chemist believes the application may fall under the extraordinary circumstance provision.

FILING REQUIREMENTS

What needs to be filed?

All applications (e.g., NDAs, ANDAs, AADAs, INDs) or petitions requesting agency action require the submission of an EA or a claim of categorical exclusion. A claim of categorical exclusion shall include a statement of compliance with the categorical exclusion criteria and shall state that to the applicant's knowledge, no extraordinary circumstances exist. Failure to submit an adequate EA for an application or petition requesting action by the agency of a type specified in § 25.20, unless the agency can determine that the action qualifies for exclusion under §§ 25.30, 25.31, 25.32, 25.33, or 25.34, is sufficient grounds for FDA to refuse to file or approve the application or petition. An EA adequate for filing is one that addresses the relevant environmental issues. An EA adequate for approval is one that contains sufficient information to enable the agency to determine whether the proposed action may significantly affect the quality of the human environment.

What does a categorical exclusion claim look like?

A person submitting an application or petition of a type subject to categorical exclusion under §§ 25.30, 25.31, 25.32, 25.33, or 25.34, or proposing to dispose of an article as provided in §§ 25.30(d) or 25.32(h), is not required to submit an EA if the person states that the action requested qualifies for a categorical exclusion, citing the particular categorical exclusion that is claimed, and states that to the applicant's knowledge, no extraordinary circumstances exist.

Example: The requested action, approval of NDA 00-000, qualifies for a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR § 25.31(b). To the applicant's knowledge, no extraordinary circumstances exist that would warrant the preparation of an environmental assessment.

Are data or other information required to support/justify the categorical exclusion claim?

No. For example, an applicant need not supply the calculation showing that the expected introduction concentration into the environment is < 1 ppb. We do have the authority to request additional information as needed to establish that the categorical exclusion criteria have been met, but this should be rare and any such requests should be discussed with the EA group before the applicant is contacted.

REVIEWS/CONSULTS

What type of review is needed for a Categorical Exclusion claim?

The submission of a categorical exclusion should be documented by the chemist in the chemistry review and a positive statement(s) regarding the acceptance of the categorical exclusion should be included.

Examples:

1. A categorical exclusion has been submitted under 21 CFR § 25.31(b). There is no information (e.g., use of wild plants or animals as a biomass source) that indicates that additional environmental information is warranted.

2. A categorical exclusion has been submitted under 21 CFR § 25.31(c). Approval of this naturally occurring product is not expected to significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment. There is no information that indicates extraordinary circumstances exist that would warrant the submission of additional environmental information.

What should be done if an Environmental Assessment is submitted, but, the action appears to qualify for a categorical exclusion?

Discuss with the EA group to determine if the EA should be consulted to them or if it appears that the issue should be discussed with the applicant who then may be asked to submit a categorical exclusion statement. During the time period right after the new regulations are implemented it is not necessary to discuss each EA that may appear to now qualify for a categorical exclusion with the EA group. See "IMPLEMENTATION" for guidance.

What should be done if an Environmental Assessment is submitted and it needs to be reviewed?

Consult it to the EA group.

IMPLEMENTATION

When the final rule becomes effective there will be many pending applications or applications that will be submitted shortly thereafter that will have EAs not necessary under the new regulations.

1. After the final rule becomes effective, applicants may amend their application to withdraw environmental information and submit a claim of categorical exclusion if the action now qualifies for one. If the FONSI has been signed on or before the effective date, the environmental information may not be withdrawn.

2. If the applicant does not submit an amendment to their application converting an EA to a categorical exclusion when it appears that it is appropriate, the division (chemist or PM depending on standard procedures) may contact the applicant, advise them that they now appear to qualify for a categorical exclusion and suggest that the applicant may want to review their EA and amend their application, if appropriate, to withdraw environmental information and submit a claim of categorical exclusion.

   Most applications will qualify for categorical exclusion under the new regulations because the expected introduction concentration (EIC) into the aquatic environment is less than 1 ppb. Information regarding the expected introduction concentration into the environment is normally at the end of EA format item 6. The standard EIC calculation is included in the EA Industry Guidance on page 14 and the calculation should be based on the kg of the active moiety used in applicant's entire product line for that active moiety.

3. Any application that requires an EA review under the NEW regulations should be consulted to the EA group. Any consults that are received for applications that appear to meet the criteria for categorical exclusion will be returned to the division unless there is documentation included with the consult that indicates that the applicant is aware of the new regulations but still wishes for the EA review to be completed rather than claiming a categorical exclusion. If returned, the division may contact the applicant as described in #2.

4. The EA group will be closing out the consults on those NME applications in their queue that appear to qualify for a categorical exclusion under the new regulations and returning this information to the PM. If the applicant has not already amended their application to include a categorical exclusion, the division should follow #2 above. The EA group will also be returning to the PMs the bar coded volumes from their files for EAs that have been reviewed previously but EA deficiencies are pending (i.e., no FONSI has ever issued).

	MP-1177/10	Formula 1:B1432p34D	Pass
	MP-1177/10	Formula 1:B1432p34E	Pass
36. 1101/05/92/046	MP-1196	B1749p13	Pass
37. 1101/05/92/031B	2-MEA	B1658p69	Pass
38. 1101/05/93/018-E	MP-1177/10	Lot 1: E9205PR	Pass
		Lot 2: S91144	Pass
39. 1101/05/93/050	MP-1177/10	Lot 1: C9307PR	Pass
		Lot 2: J9307PR-A	Pass
40. 1101/05/94/028	MP-1177/10	B1658p57	Pass
41. 1101/03/95/014-E	MP-1177/10T	E9205PR	Pass
42. 1101/05/92/004	MP-1177/10	S91144	Pass
43.	MP-1196	B1808p29(4)	Pass
44. 1101/05/91/032	MP-1177/10	B1501p106	Pass
45.	MP-1196	B1808p35(4)	Pass
46. 1101/05/94/016-E	MP-1177/10	Glass: C9307PR	Pass
		Plastic: S94110-D	Pass
MULTIPLE DOSE			
47. 1101/05/91/029	MP-1177/10T	B1432p80	Pass
48. 1101/05/91/033	MP-1177/10T	B1501p106	Pass
49.	MP-1196	CRM3573	Pass
50.	MP-1196	CRM3573	Pass
51.	MP-1196	CRM3573	Pass
52.	MP-1196	CRM3571	Pass
53. 1101/05/91/011-E	MP-1177/1	B1580p003	Pass
	MP-1177/5	B1580p003	Pass
	MP-1177/10	B1580p003	Pass
	Gadolinium Citrate	B1263p152	Pass
REPRODUCTIVE TOXICOLOGY			
54. 1101/05/92/017	MP-1177/10	B1658p57	Pass
55. 1101/05/92/022	MP-1177/10	S92120-C	Pass
56. 1101/05/92/038-E	MP-1177/10	B1658p57	Pass
57. 1101/05/92/023-E	MP-1177/10	B1658p57	Pass
58. 1101/05/92/024	MP-1177/10	S92120-C	Pass
59. 1101/05/92/016-E	MP-1177/10	Glass: C9307PR	Pass
		Plastic: S94110-D	Pass
60. 1101/05/92/025	MP-1177/10	S92120-C	Pass
GENOTOXICOLOGY			
61. 1101/05/92/012	MP-1177/10	S92120-A	Pass
62. 1101/05/92/013	MP-1177/10	S92120-A	Pass
63. 1101/05/92/014	MP-1177/10	S92120-A	Pass
64. 1101/05/92/015	MP-1177/10	S92120-A	Pass
SPECIAL TOXICOLOGY			
65. 1101/05/93/011	MP-1177/10	E9205PR	Pass
66. 1101/05/93/016	MP-1177/10	E9205PR	Pass
67. 1101/05/92/029	MP-1177/10	B1658p57	Pass
68. 1101/05/92/019	MP-1177/10	B1658p57	Pass
69. 1101/05/93/022	MP-1177	S92120-C	Pass
70.	MP-1177/10	CRM3386	Pass
71. 1101/05/93/027-E	MP-1177/10	E9205PR	Pass
72. 1101/05/93/028-E	MP-1177/10	E9205PR	Pass
73. 1101/05/93/031	MP-1177/10	E9205PR	Pass

Background Information

The following table contains urinary mineral elimination data presented in response to a request from the medical group. The purpose of providing these data is to put human mineral elimination data from clinical studies of gadoversetamide into perspective.

Optimark induced urinary mineral elimination as follows:

in Humans

Iron	<0.3 mg greater than placebo at 0.5 mmole/kg
Zinc	8 mg at 0.1 mmole/kg within 24 hr 17 mg at 0.5 mmole/kg within 24 hr
Copper	No data

in Animals

Iron	No data
Zinc	No data
Copper	No data

It appears that the level of iron eliminated (300 ug) in response to an exaggerated dose of Optimark (0.5 mmole/kg) is greater than reported urinary elimination rates in normal adults (25-131 ug/day) but lower than daily intakes (6-13 mg/day, 10% or 0.6-1.3 mg assumed to be bioavailable) and body stores (300-1000 mg). Therefore, iron elimination does not appear to be of concern.

The level of urinary zinc elimination (8 mg/24 hr) following a diagnostic dose of Optimark (0.1 mmole/kg) is 3 orders of magnitude greater than normal adult elimination (350-525 ug/day). The recommended bioavailable intake of zinc is about 2.2 mg/day. Therefore, it appears that it would take at least several days of recommended intake to compensate for the loss due to Optimark.

Human data for the effect of Optimark on copper elimination were not available.

Intake, Elimination, and Body Composition Data for Fe, Zn, and Cu*						
Mineral	Age Group**	Recommended Intake (mg/day)***	Daily Urinary Elimination (µg/day)	Daily Elimination -All Routes (ug/day)	Body Stores (mg)	Body Composition (mg/kg)
iron	neonates					94
	infants	5-15				
	children	4-10	3.6			
	adolescent					
	-boys	10-20		650-1300		
	-girls	10-27		600-900		
	-menstruating			700-2300		
	adults		88-131			74 (3.7 g/50 kg)
	-men	6.5-13	25	650-1300	1000	
	-women	6-9		600-900	300	
	-menstruating	7-23		700-2300		
	-pregnant	16.5-35		1650-3500		
zinc	neonates	12/6/3	380			20
	infants	11/6/3				
	children	16/8/4				
	adolescent					
	-boys	28/14/7				
	-girls	26/13/7				
	adults		353-520			28 (1.4 g/50 kg)
	-men	22/11/6	525			
	-women	22/11/6				
	-menstruating					
	-pregnant	26/13/6****				
copper	neonates	0.5-0.7	7.9			4.7
	infants	0.7-1.0				
	children	1-2.5	30.1			
	adolescent	2-3				
	adults	2-3	36-50			1.7 (85 g/50 kg)
	-men		24.2			
	-women		19.2			
	-menstruating					
	-pregnant					

* Data from:

** An attempt was made to estimate values for age categories specified in the FDAs pediatric guidelines. Values for age groups are crude estimates for the purpose of putting drug induced mineral elimination data into perspective. For actual values and corresponding age groups, see the tables. FDAs age ranges are:

Neonates	birth to 1 month
Children	2-12 years
Infants	1 month-2 years
Adolescents	12-16 years
Adults	>16 years

*** For iron, 10% GI absorption assumed. For Zinc, GI absorption depends on bioavailability; values given for 10%, 20% and 40% bioavailability

**** Requirement increases by 20% over duration of pregnancy. Requirement even higher during lactation.

Nonclinical Study Laboratories, Study dates, and GLP

Nonclinical Study Laboratories, Study dates, and GLP				
Type	Study #	Laboratory	Study Initiation Date	GLP
PK	1. 1101/05/92/008	Mallinckrodt, Inc. Hazlewood, MO	03/17/92	yes
	2. 1101/05/92/054-E	Mallinckrodt, Inc. Hazlewood, MO	10/05/92	no
	3. 1101/05/92/087	Mallinckrodt, Inc. Hazlewood, MO	11/05/92	yes
	4.		09/10/93	yes
	5. 1101/05/92/041-E	Mallinckrodt, Inc. Hazlewood, MO	06/29/92	no
	6. 1101/05/92/007	Mallinckrodt, Inc. Hazlewood, MO	03/03/92	yes
	7. 5057		10/04/94	yes
	8. 1101/05/92/042	Mallinckrodt, Inc. Hazlewood, MO	06/22/92	yes
	9. 1101/05/92/075	Mallinckrodt, Inc. Hazlewood, MO	10/07/92	yes
	10.		05/23/94	yes
	11. 1101/05/92/051	Mallinckrodt, Inc. Hazlewood, MO	08/17/92	yes
	12. 1101/00/94/002	Mallinckrodt, Inc. Hazlewood, MO	report date-March 1994	no
	13. 1101/05/94/018		10/14/94	yes
	14. 1101/05/94/026-E	Mallinckrodt, Inc. Hazlewood, MO	10/26/94	no
	15. 1101/05/92/053	Mallinckrodt, Inc. Hazlewood, MO	09/10/92	yes
	16. 1101/00/92/022	Mallinckrodt, Inc. Hazlewood, MO	report date-11/18/92	no
	17. 1101/00/92/023	Mallinckrodt, Inc. Hazlewood, MO	report date-11/11/92	no
	18. 1101/00/92/020	Mallinckrodt, Inc. Hazlewood, MO	report date-11/18/92	no
	19. 1101/00/92/021	Mallinckrodt, Inc. Hazlewood, MO	report date-11/13/92	no
	20. 1101/05/93/032-E	Mallinckrodt, Inc. Hazlewood, MO	07/12/93	no

2. Summary Information for Nonclinical Studies				
Type	Study #	Laboratory	Study Initiation Date	GLP
Pharm	21. [no number]		not given	no
	22. 1101/05/92/036-E	Mallinckrodt, Inc. Hazlewood, MO	06/12/92	no
	23. 1101/05/92/078-E	Mallinckrodt, Inc. Hazlewood, MO	10/05/92	no
Safety Pharm	24. 1101/05/92/028	Mallinckrodt, Inc. Hazlewood, MO	05/01/92	yes
	25. 1101/05/92/061	Mallinckrodt, Inc. Hazlewood, MO	01/05/93	yes
	26. 1101/05/93/015-E	Mallinckrodt, Inc. Hazlewood, MO	01/13/93	no
	27. 1101/05/93/029-E PH 1018-MM-001-94		02/14/94	no
	28. PH-84		08/27/92	no

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3. Summary Information for Nonclinical Studies				
Type	Study #	Laboratory	Study Initiation Date	GLP
Single Dose Tox	29. 1101/05/91/027 91/MLT003/1110		09/18/91	yes
	30. 1101/05/92/003	Mallinckrodt, Inc. Hazlewood, MO	01/15/92	yes
	31. 1101/05/92/031	Mallinckrodt, Inc. Hazlewood, MO	05/07/92	yes
	32. 1101/05/94/008	Mallinckrodt, Inc. Hazlewood, MO	04/07/94	no
	33. 1101/05/93/021	Mallinckrodt, Inc. Hazlewood, MO	04/19/93	no
	34. 1270/05/93/038	Mallinckrodt, Inc. Hazlewood, MO	08/17/93	no
	35. 1101/05/90/024-E	Mallinckrodt, Inc. Hazlewood, MO	10/19/90	no
	36. 1101/05/92/046	Mallinckrodt, Inc. Hazlewood, MO	08/10/92	yes
	37. 1101/05/92/031	Mallinckrodt, Inc. Hazlewood, MO	05/07/92	no
	38. 1101/05/93/018-E	Mallinckrodt, Inc. Hazlewood, MO	05/18/93	no
	39. 1101/05/93/050	Mallinckrodt, Inc. Hazlewood, MO	11/18/93	no
	40. 1101/05/94/028		03/16/95	yes
	41. 1101/03/95/014-E	Mallinckrodt, Inc. Hazlewood, MO	03/14/94	no
	42. 1101/05/92/004	Mallinckrodt, Inc. Hazlewood, MO	01/28/92	yes
	43.		07/02/93	yes
	44. 1101/05/91/032 91-3729		10/29/91	yes
	45.		07/02/93	yes
	46. 1101/05/94/016-E	Mallinckrodt, Inc. Hazlewood, MO	06/06/94	no

4. Summary Information for Nonclinical Studies				
Type	Study #	Laboratory	Study Initiation Date	GLP
Multidose Tox	47. 1101/05/91/029 92/MLT002/0312		09/06/91	yes
	48. 1101/05/91/033 91-3733		10/29/91	yes
	49.		08/23/93	yes
	50.		02/02/94	yes
	51.		03/01/94	yes
	52.		08/09/94	yes
	53. 1101/05/91/011-E	Mallinckrodt, Inc. Hazlewood, MO	04/01/91	no
Repro Tox	54. 1101/05/92/017 12/931339		04/21/92	yes
	55. 1101/05/92/022 17/930511		06/09/92	yes
	56. 1101/05/92/038-E 15/921171		06/01/92	no
	57. 1101/05/92/023-E 16/921513		08/26/92	no
	58. 1101/05/92/024 14/930473		08/26/92	yes
	59. 1101/05/92/016-E 13/920874		04/01/92	no
	60. 1101/05/92/025 18/930713		06/18/92	yes

5. Summary Information for Nonclinical Studies				
Type	Study #	Laboratory	Study Initiation Date	GLP
Geno Tox	61. 1101/05/92/012 TA488.501088		02/28/92	yes
	62. 1101/05/92/013 TA488.701020		02/28/92	yes
	63. 1101/05/92/014 TA488.337004		02/28/92	yes
	64. 1101/05/92/015 TA488.122		02/28/92	yes
Special Tox	65. 1101/05/93/011	Mallinckrodt, Inc. Hazlewood, MO	03/29/93	no
	66. 1101/05/93/016	Mallinckrodt, Inc. Hazlewood, MO	04/12/93	no
	67. 1101/05/92/029	Mallinckrodt, Inc. Hazlewood, MO	04/28/92	yes
	68. 1101/05/92/019	Mallinckrodt, Inc. Hazlewood, MO	06/11/92	yes
	69. 1101/05/93/022	Mallinckrodt, Inc. Hazlewood, MO	04/21/93	no
	70. I-92-254		September 1992	US-no JP-yes
	71. 1101/05/93/027-E PH 1022-MM-002-93		06/17/93	no
	72. 1101/05/93/028-E PH 1022-MM-001-94		01/11/94	no
	73. 1101/05/93/031 SRI B50-TXR-1		07/01/93	no
Modified version of table provided by Sponsor.				

Pharmaco-/Toxicokinetics Studies

1.-20. Pharmaco- and toxicokinetic studies were reviewed separately in Pharm/Tox Review #2 for NDA 20-237. The summary of those studies was copied into the next section of this review.

Summary of Pharmaco-/Toxicokinetics

The following 2 tables provide summary data for across species comparisons.

The first table shows that:

-the volume of distribution in all species dosed with 0.1 mmol/kg is approximately equal to the extracellular fluid volume
-the volume of distribution and early phase $t_{1/2}$ for dogs receiving 0.9 mmole/kg were greater than for dogs at 0.1 mmole/kg
-the elimination kinetics of 0.1 and 0.9 mmole/kg appear to be similar in animals
-The rat and dog plasma AUC values were about 6-fold and 2.5-fold lower respectively than the mean human serum AUC
-the rat and dog late phase plasma $t_{1/2}$ s were 6-fold and 2.3-fold shorter (respectively) than for human
-the rat and dog plasma clearance rates were 8- and 3-fold greater than human clearance rates respectively.
-biotransformation and protein binding of MP-1177/10 were not detected

Table of Comparative Pharmacokinetic data
Human data from package insert and clinical studies
Mean animal data summarized from submitted studies

Species	Human	rat	dog	
Dose (mmole/kg)	0.1	0.1 or 0.9	0.1	0.9
V_d at steady state (ml/kg)	162 ±25			
$V_{d\ area}$		200	220	314
V_d approximately equal to extracellular fluid volume	yes	yes	yes	no
plasma/serum AUC (ug · hr/ml)	mean of 4 studies=807	154, 128 (at 0.1 mmole/kg)	318	
plasma $t_{1/2\ distr}$ (min)	13.3 ± 6.8		1.32	24.6
plasma $t_{1/2\ elim}$ (min)	103.6 ±19.5	20, 14.4	44	53, 40
plasma clearance (ml/hr/kg)	72 ±16.3	590	208	254
renal clearance (ml/hr/kg)	69 ±15.4			
data supports that drug is elim by glomerular filtration	yes			
biotransformation	not detected	not detected	not detected	not detected
protein binding	in vivo -not tested in vitro-no	in vivo-no in vitro-no	in vivo -not tested in vitro-no	

The second table shows:

-rapid urinary elimination of MP-1177/10 in all species
-a very small percentage of the total activity was eliminated in feces
-low levels of activity following MP-1177/10 administration persisted in liver and kidney but tended to decrease slowly over time.
-low levels of activity following MP-1177/10 administration persisted in bone but tended to increase slowly over time.
-^{153}Gd MP-1177/10 does appear to distribute to fetuses after administration to pregnant rats
-^{153}Gd MP-1177/10 does distribute to milk following administration to nursing rats
-anephria in rats blocks the major route of elimination in rats. Hepatobiliary excretion does not significantly compensate for the blocked urinary route. Biodegradation of MP-1177/10 in anephria was not studied. However, it is a concern.

Other pertinent pharmacokinetic information derived from animal PK studies:

-Optimark and Magnevist appear to be pharmacokinetically equivalent in rats
-MP-1177/10 is not taken up by RBCs in rats and dogs
-elimination of MP-1177/10 in rat bile is negligible (by direct analysis of bile)
-R_1 and R_2 Relaxivity values are similar for Optimark and Magnevist in rats
-analysis of blood, excreta, and tissue homogenate extracts following ^{153}Gd MP-1177/10 did not reveal metabolites.
-persistent low levels of activity in bone, liver, and kidney and a large non-extractable fraction of activity from feces of rats suggest that a small fraction of MP-1177 undergoes biodegradation with release of gadolinium. This is probably true for all gadolinium agents.
-the minor peak found at up to 5% the MP-1177/10 levels was found to be Gd-EDTA which formed on the column and is considered to be an analytical artifact. This is not to be confused with the nonextractable activity of organs and feces.
-MP-1177/10 caused reversible blockage of calcium elimination in a 4-week dog study. Since MP-1177/10 does not significantly interfere with calcium detection in the 2 methods utilized, it is concluded that this result was accurate.

Toxicokinetic comparison:

The data support that body surface area dose comparisons are appropriate.

Table of Comparative Pharmacokinetic data (CONTINUED)
Human data from package insert
Mean animal data summarized from submitted studies

Species		Human	rat	anephric rat	dog
Dose (mmole/kg)		0.1	0.1 or 0.9	0.1	0.1
cumulated urinary elimination (% dose)	30 min 4 hr 24 hr 48 hr 4 d 7 d	95.5 ±17.4	87-97 93-97 95-98 93-98	0.2	85 88, 83 90, 84
cumulated fecal elimination (% dose)	24 hr 48 hr 4 d 7 d		2.1, 3.2 4.6, 3.8 8.4		1.5 2.2, 0.6
t1/2 excretion					
4-hr distribution	liver kidney stomach sm intestine lg intestine stom contents sm int contents lg int contents carcass		0.22 0.60 0.02 0.04 0.03 0.03 0.55 1.51 1.85	4.44 0.86 0.87 1.3 1.3 0.51 4.02 0.36 76.8	
24-hr retention (% dose/organ)	liver kidney muscle bone skin		0.21 0.48 0.03 0.01		
48-hr retention (% dose/organ)	liver kidney muscle bone skin		0.09-0.14 0.37 0.08-0.12 0.12-0.24 0.18-0.21		
7 day retention (% dose/organ)	liver kidney muscle bone skin		0.10 0.18 0.31		
placental transfer to fetus			yes		
Distribution to milk			yes		

Pharmacology Studies

21. **Title:** An Investigation of the Properties of OptiMARK™ for MRI Enhancement of Cerebral Metastatic Disease Part A: Illustrative case reports, dose comparisons, contrast enhancement values, macrohistopathology Part B: Tumor permeability determination Part C: Blinded neuroradiological interpretation, microhistopathology

Synopses:

Part A: Optimark was tested at doses of 0.05 to 0.5 mmole/kg for its ability to enhance intracerebral VX2 carcinomas (adenocarcinomas) in New Zealand White Rabbits. Contrast enhanced scans were compared to histopathologic detections of lesions. Optimark was compared to Magnevist at 0.1 mmole/kg. The Sponsor concluded that 1) Optimark is effective for enhancing intracerebral tumors at 0.1 mmole/kg, 2) tumors identified with Magnevist at 0.1 mmole/kg were also identified with Optimark at 0.1 mmole/kg 3) it was necessary to administer 0.2 mmole/kg to enhance all tumors 4) peak enhancement was observed 1 min after dosing 5) peak "contrast enhancement value" increased with increasing dose to a plateau value at >0.4 mmole/kg.

Part B: *An in vivo method of measuring the blood brain barrier forward transfer constant (K) and the cerebral plasma volume (V_p) in rabbit brain tumors using a 1.5T MRI scanner was developed. Values obtained compared favorably with those obtained using X-ray CT. Functional maps showing the distribution of K and V_p in the brain were generated. The mean values of K measured in tumor and normal regions were 0.017 ± 0.015 and 0.0017 ± 0.0013 ml/min/g respectively. The mean value of V_p in tumor regions was 0.039 ± 0.043 ml/g.* A value for V_p was not given for normal brain.

Part C: In this section, the Sponsor reported that blinded neuroradiologists' readings of T1-weighted images of rabbit brains (with implanted VX2 tumors) revealed cerebral metastatic tumors as small as 0.06 mm^2. Optimark was also reported to identify meningitis associated with tumor seeding.

22. **Title:** Direct Comparison of Renal MR Contrast Enhancement using MP-1177/10 Injection and Magnevist® (Study 1101/05/92/036-E)

Synopsis: MR contrast enhancement of the kidneys was studied in rabbits receiving Magnevist or Optimark (0.1 mmole/kg) (7-day cross-over design). Signal-to-noise ratios of selected regions of interest of each kidney were comparable for both agents. The majority of Optimark images were found to be equivalent to Magnevist images by 2 blinded radiologists.

23. **Title:** Molar Relaxivity Rates of MP-1177/10 and Magnevist® in Water and BSA solution (Study 1101/05/92/078-E)

Synopsis: Optimark and Magnevist were compared for their ability to alter T1 and T2 relaxation times in vitro. Relaxivity (R1 and R2) values were calculated from measured T values by determining the slope of the 1/T vs concentration plots. Small differences in relaxivity (R1 and R2)) values were found for Optimark and Magnevist. The Sponsor concluded that the relaxivities of Optimark were similar to Magnevist and that the slightly higher values for Optimark would not affect in vivo imaging.

Safety Pharmacology Studies

24. **Title:** Hemodynamic Effects of MP-1177/10 Injection, Injected at a Dose Rate of 1.0 ml/kg/min in Anesthetized Dogs

Study #: 1101/05/92/061

Species/Strain/Source: dog/Beagle.

Sex/age/body weight: male/7 months/9.5-10.2 kg

Dose information:

Formulation: MP-1177/10, control=0.9% saline

Concentration(s): 0.5 M

Dosages: 0, 0.1, 0.3, 0.5, 0.7, 1.0 mmole/kg

Route of administration: iv

Volume of administration: 2.0, 0.2, 0.6, 1.0, 1.4, and 2.0 ml/kg respectively

Rate of administration: 1.0 ml/kg/min dose followed by 5 ml saline flush via infusion pump

Study design and schedule: Each of 6 anesthetized dogs received 6 doses at least 30 min apart as follows:

Dog ID	Sequence of Doses of MP-1177/10*					
92-58	A	B	C	D	E	F
92-59	B	C	D	E	F	A
92-60	C	D	E	F	A	B
92-61	D	E	F	A	B	C
92-63	E	F	A	B	C	D
92-64	F	A	B	C	D	E

*A=1.0 mmole/kg
B=0.3 mmole/kg
C=0.0 mmole/kg (2 ml saline)
D=0.5 mmole/kg
E=0.1 mmole/kg
F=0.7 mmole/kg

PROCEDURE	TIME OF PROCEDURE /DATA COLLECTION
Acclimation	3 days
anesthetized with sodium thiamylal 20 mg/kg and prepped for maintenance anesthesia by spontaneous inhalation of isofluorane/oxygen	prior to dosing
-installed catheter attached to blood pressure transducer into left femoral artery to measure BP -installed catheter into left femoral veil for MP-1177/10 administration -placed needle electrodes for Lead II ECG to detect arrhythmias and measure heart rate -advanced pig tail catheter to left ventricle via right femoral artery to measure of LVP	following anesthesia and prior to dosing
acclimated to surgical procedures	time not given
dose administration	time=0
measurements made: HR, mean BP, systolic BP, diastolic BP, LV max systolic P, LV end diastolic P, dP/dt	baseline and t=0,. 15, 30, 60, 120 and 240 sec for each of the 6 doses. Each dose was separated by at least 30 min.

Results:

Measurement	Effects
HR	slight drop over 30 sec returned to baseline by 4 min.
mean BP	decreased at doses >0.1 mmole/kg, the decrease at 1.0 mmole/kg was 24% at 30-60 sec; 0.7 and 1.0 mmole/kg animals did not fully recover by the end of the 4 min recording period
systolic BP	same as mean BP
diastolic BP	same as mean BP
LV max systolic P	same as mean BP
LV end diastolic P	no effects
dP/dt	effect was not dose related i.e. all doses produced a similar reduction, the rate of return to baseline was not dose related.

ECG data were not submitted.

Random arrhythmias and premature ventricular conductions were reported by the Sponsor but data were not provided.

Reviewer comments:

No effect at 0.1 mmole/kg. At higher doses, decreases in HR were slight and transient. Decreases in blood pressure began to resolve within 30 to 60 sec; Animals in the 0.7 and 1.0 mmole/kg group did not fully recover to baseline by the end of the 4 min recording period.

Blood pressure dropped without a compensatory increase in heart rate. The Sponsor suggested that the baroreceptor response was blunted by anesthesia.

Observed arrhythmias and premature ventricular conductions (PVC) (observed in 5 of the 6 animals) were attributed by the Sponsor to the left ventricular catheter since they were not associated with any particular treatment and they occurred randomly. However, the design of this study did not allow a definitive conclusion to be drawn about PVCs.

25. **Title:** Hemodynamic Effects of MP-1177/10 with 10% Excess Ligand in anesthetized Dogs after Intravenous Administration (Mannitol control included)
Study #: 1101/05/92/028
Species/Strain/Source: dog/Beagle
Sex/age/body weight: male/eight months/10.8-11.8 kg
Dose information:
Formulation: MP-1177/10, controls=0.9% saline and 20% mannitol
Concentration(s): of MP-1177/10=0.5 M
Dosages: saline, mannitol, and 0.1, 0.3, 1.0, and 3.0 mmole/kg MP-1177/10
Route of administration: iv
Volume of administration: 6.0, 6.0, 0.2, 0.6, 2.0, 6.0
Rate of administration: 24 ml/min
Study design and schedule: Each of 6 anesthetized dogs received 6 doses at least 30 min apart as shown in the following table. Note that this study, unlike the previous study, included a mannitol control.

Dog ID	Sequence of Doses of MP-1177/10*					
92-39	A	B	C	D	E	F
92-34	B	C	D	E	F	A
92-35	C	D	E	F	A	B
92-36	D	E	F	A	B	C
92-37	E	F	A	B	C	D
92-38	F	A	B	C	D	E

*A=2 ml 0.9% saline
B=6 ml of 20% mannitol
C=1.0 mmole/kg
D=0.3 mmole/kg
E=0.1 mmole/kg
F=3.0 mmole/kg

PROCEDURE	TIME OF PROCEDURE /DATA COLLECTION
Acclimated	3 days prior to study
Anesthetized with sodium pentobarbital, 30 mg/kg	prior to catheterization
administered supplemental doses of sodium pentobarbital	as needed to maintain anesthesia (15 min acclimation after supplemental dose before next dose in sequence)
-catheterized left femoral artery and attached to pressure transducer -catheterized left femoral veil for administration of test substances and anesthetic -placed needle electrodes for lead II ECG -advanced pig tail catheter to left ventricle via right femoral artery	prior to dosing
acclimated to surgical procedures	time not given
dose administration	t=0
5 ml saline flush	immediately after dosing
measured: HR, arterial BP, pulse pressure, PR interval, corrected QT interval, dP/dt, LV systolic P, LV end diastolic P The method of QT interval correction was not specified.	immediately prior to injection, at the completion of injection (t0), 15,30,60,120, and 240 sec

Results:

Measurement	Effects
HR	slight decrease in heart rate immediately following dose administration in MP-1177/10 groups showed signs of recovery by 60-120 sec but not full recovery by the end of the 4 min recording period
mean arterial BP	dose related drop in mean arterial BP (up to 30 mm drop in high dose), maximum effect at 30 sec, high dose animals did not fully recover by the end of the 4 min recording period, mannitol had no effect
pulse pressure	no effect of MP-1177/10 except high dose which raised pulse pressure slightly during dose administration, mannitol raised pulse pressure significantly more than the high dose; pulse pressure in high dose returned to baseline by 4 min, pulse pressure in mannitol group did not
PR interval	no effect compared to controls
corrected QT interval	no effect compared to controls
dP/dt	no effect of MP-1177 compared to saline control
LV systolic P	dose related drop in pressure showed recovery by 4 min in all but high dose (3.0 mmole/kg)
LV end diastolic P	high dose and mannitol elevated pressure which persisted through the 4 min recording period in both groups

Random arrhythmias and premature ventricular conductions were reported by the Sponsor but data were not provided.

Reviewer comments:

Effects were not detected at 0.1 mmole/kg. Effects on PR interval, corrected QT interval, and dP/dT were not detected at any dose. Drops in heart rate, mean blood pressure, and left ventricular systolic pressure returned to baseline in all but the high dose group (3.0 mmole/kg) by the end of the 4 min recording period. Increases in pulse pressure and left ventricular end diastolic pressure (LVEDP) were observed only in the high dose (3.0 mmole/kg). Pulse pressure returned to baseline by the end of the recording period; LVEDP did not.

As in the previously reviewed study, observed premature ventricular beats were attributed to the left ventricular catheter. Again, this study was not designed to make conclusions about the cause of premature ventricular beats.

26. **Title:** A Comparison of the Hemodynamic Effects of MP-1177/10 Injection and Magnevist® in Anesthetized Dogs
Study #: 1101/05/93/015-E
Species/Strain/Source: dog/Beagle
Sex/age/body weight: male/7-8 months/10.4-11.2 kg
Dose information:
Formulation: Optimark and Magnevist
Concentration(s): 0.5 M
Dosages: 0.1, 0.3 and 1.0 mmole/kg
Route of administration: iv
Volume of administration: 0.2, 0.6 and 2.0 ml/kg
Rate of administration: 2 ml/kg/min
Study design and schedule: Each of 6 anesthetized dogs received 6 doses at least 30 min apart as shown in the following table.

Dog ID	Sequence of Doses of MP-1177/10*					
93-2	A	B	C	D	E	F
93-3	B	C	D	E	F	A
93-4	C	D	E	F	A	B
93-5	D	E	F	A	B	C
93-6	E	F	A	B	C	D
93-8	F	A	B	C	D	E

*A=MP-1177/10 at 0.3 mmole/kg
B=Magnevist at 0.1 mmole/kg
C=Magnevist at 0.3 mmole/kg
D=Magnevist at 1.0 mmole/kg
E=MP-1177/10 at 0.1 mmole/kg
F=MP-1177/10 at 1.0 mmole/kg

PROCEDURE	TIME OF PROCEDURE /DATA COLLECTION
Acclimation	3 days
anesthetized with sodium thiamylal 20 mg/kg and prepped for maintenance anesthesia by spontaneous inhalation of isofluorane/oxygen	prior to dosing
-installed catheter attached to blood pressure transducer into left femoral artery to measure BP -installed catheter into left femoral veil for MP-1177/10 administration -placed needle electrodes for Lead II ECG to detect arrhythmias and measure heart rate -advanced pig tail catheter to left ventricle via right femoral artery to measure of LVP	following anesthesia and prior to dosing
acclimated to surgical procedures	time not given
dose administration	time=0
measurements made: HR, mean BP, systolic BP, diastolic BP, LV max systolic P, LV end diastolic P, dP/dt	baseline and t=0,. 15, 30, 60, 120 and 240 sec for each of the 6 doses. Each dose was separated by at least 30 min.

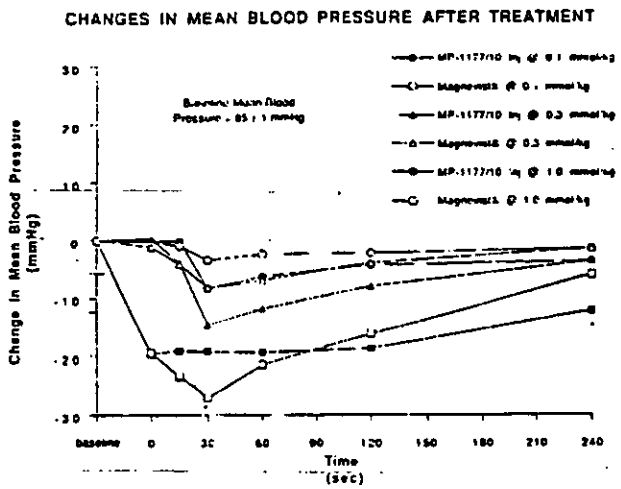
Results:

Measurement	Comparison of Effects of Magnevist and Optimark
HR	slight, transient decrease similar for both agents
mean arterial BP	all responses were interpreted by the reviewer to be similar for both agents.
systolic BP	
diastolic BP	
LV systolic P	
LV end diastolic P	
dP/dt	

Reviewer comments:

Heart rate responses were similar for both Magnevist and Omniscan at all doses.

Regarding blood pressure measurements, the Sponsor concluded that the magnitude of the lower doses were similar for both agents but the magnitude of the high dose (1.0 mmole/kg) effects of Magnevist were more pronounced than Optimark. However, in the opinion of the reviewer, heart rate and blood pressure responses to Optimark and Magnevist were similar at all doses. For an example of why the reviewer reached this conclusion, refer to the following graph of mean blood pressure.



At 30 sec, the high dose of Magnevist appears to have produced a 30% decrease in blood pressure compared to a 20% decrease for Optimark. However, the shape of the response curve is not consistent with the other dose groups or with the response curves of other studies. Therefore, this is not interpreted as a difference. Since raw data were not provided with the report, the cause for the inconsistency could not be explored.

27. **Title:** Effect of MP-1177/10 and Magnevist® on the Isolated Rat Aorta (Study 1101/05/93/029-E)

Synopsis: This study was conducted to determine the effects of the Optimark formulation, MP-1177/10, and Magnevist on epinephrine induced contraction of an isolated rat aorta preparation. Dose concentrations of 1.5, 5, and 15 mM were tested for each drug. Concentrations of 1.5 and 5 mmole/kg of both drugs had no effect on aortic contraction. 15 mM concentrations of Optimark or Magnevist reduced contraction by 3% and 6% respectively. This reduction is considered biologically insignificant.

Reviewer comment: This study supports that cardiovascular effects observed in dog cardiovascular safety studies (transient decreases in HR and BP) were not due to inhibition of sympathetic vascular smooth muscle contraction.

28. **Title:** General Pharmacological Study of MP-1177 (Study PH-84)

Synopsis: This study was composed of several experiments in mice, rats, and guinea pigs. In vivo experiments were conducted at 3 iv doses of MP-1177/10: 0.5, 1.5 and 5.0 mmole/kg. In vitro tests were conducted at the following concentrations: 1.5, 5.0 and 15.0 mM.

The following tests were positive:

1) test for spontaneous motor activity: activity in mice was decreased for 1 hour at 1.5 and 5.0 mmole/kg (NOAEL=0.5 mmole/kg, safety factor <1)
2) test for effect on thiopental anesthesia: anesthesia was prolonged in mice at 5.0 mmole/kg (NOAEL=1.5 mmole/kg)
3) test for renal function: chloride elimination was decreased by % and urine volume was increased by % in rats at 5.0 mmole/kg (NOAEL 1.5 mmole/kg for both effects, safety factor 1.2). Sodium elimination was decreased by % at 5.0 mmole/kg. Although this was not statistically significant, a dose response trend was apparent. See below for effect on other renal parameters in the same experiment.

The following tests were negative at doses up to 5 mmole/kg:

3) (continued) test for renal function: effects on urinary potassium and creatinine clearance in rats. See above for positive effects on urinary sodium, chloride, and volume in the same experiment.
4) test for anticonvulsant effect: effect on seizures induced by electroshock or pentetrazole administration in mice
5) test for effect on body temperature: rectal temperature in mice
6) test for analgesic action: acetic acid induced writhing in mice
7) test for effect on gastrointestinal transit time of charcoal excretion following oral dose in mice
8) test for renal function in rats as indicated by plasma phenolsulfonphthalein (PSP) following iv injection

The following in vitro tests were negative at concentrations up to 15 mM:

9) test for effect on smooth muscle in isolated guinea pig ileum (no action on resting tone or spasmogen induced contraction)
10) test for effect on somatic nervous system (no action on rat diaphragm contraction elicited by phrenic nerve stimulation)

Reviewer comment:

The findings in mice, decreased spontaneous motor activity lasting 1 hour (NOAEL=0.5 mmole/kg) and prolongation of thiopental anesthesia (NOEL=1.5 mmole/kg), suggested CNS depression.

Decreased chloride elimination and increased urine volume in rats at 5.0 mmole/kg was considered by the Sponsor to be a hyperosmolality effect since the sorbitol control (10 mmole/kg iv) caused the same effects % decrease in chloride, % increase in urine volume). Based on a dose response trend, decreased urinary sodium was considered by the reviewer to be an effect.

Summary of Safety Pharmacology

Cardiovascular safety studies in anesthetized dogs demonstrated that MP-1177/10 at doses between 0.3 and 3.0 mmole/kg causes transient, dose-related decreases in heart rate, arterial blood pressure (mean, systolic and diastolic), and left ventricular systolic pressure. Heart rate decreases were slight; blood pressures were decreased by up to %. These effects were not observed at 0.1 mmole/kg which means the NOEL for effects is 0.5 times the human dose of 0.1 mmole/kg based on a body surface area conversion.

The time to peak cardiovascular effects was 30-60 seconds after dosing. Doses below 0.7 mmole/kg returned to baseline by 4 min; however at doses ≥ 0.7 mmole/kg only partial recovery was apparent by the end of the 4 min recording period.

In these studies, blood pressure dropped without a compensatory increase in heart rate. The Sponsor suggested that the baroreceptor response was blunted by anesthesia and made the point that baroreceptor responses in humans would be intact.

Random arrhythmias and premature ventricular conductions (PVCs) were reported by the Sponsor. They were attributed by the Sponsor to the left ventricular catheter. Because data about the time of occurrence of premature beats were not submitted it is not possible to analyze them to answer questions such as, "Were ventricular conductions later in the study due to predisposition of the heart to early doses in the Latin square design?" It is concluded that the design of this study did not allow a definitive conclusion to be drawn about PVCs.

ECG measurements of PR interval and corrected QT interval were not seen at any dose. The method of QT interval correction was not specified.

A comparison of MP-1177/10 and Magnevist showed that they had similar cardiovascular effects.

A study of the effects of MP-1177/10 and Magnevist on epinephrine induced contraction of the isolated rat aorta demonstrated no effects at concentrations of 1.5, 5.0 and 15.0 mM. This study suggests that effects observed in dog cardiovascular safety studies (transient decreases in HR and BP) were probably not due to inhibition of sympathetic vascular smooth muscle contraction.

In a battery of 10 pharmacology assays to fulfill Japanese requirements, 3 gave positive results. The findings in mice, decreased spontaneous motor activity lasting 1 hour (NOAEL=0.5 mmole/kg) and prolongation of thiopental anesthesia (NOEL=1.5 mmole/kg), suggested CNS depression. Decreased sodium and chloride elimination and increased urine volume in rats at 5.0 mmole/kg were considered by the Sponsor to be a hyperosmolality effect since the sorbitol control (10 mmole/kg iv) caused the same effects. This is a plausible explanation but not conclusive because these are correlative data from only one source. Note that creatinine clearance was normal. The eight assays giving negative results were: anticonvulsant effect, body temperature, test for analgesic action, gastrointestinal transit time, plasma phenolsulfonphthalein (PSP) renal function test, test for effect on smooth muscle in isolated guinea pig, test for effect on somatic nervous system.

Single dose Toxicology Studies

Only pivotal study numbers 35., 40., 42., and 44. are individually evaluated in this review. All other single dose studies are summarized in tables near the end of this section.

35. Title: The Effect of MP-1196 and Calcium on the Acute Toxicity of MP-1177 in Mice
Study #: Study 1101/05/90/024-E
Species/Strain/Source: mouse/
Sex/age/body weight: female/18.1-24.0 g
Dose information:

Formulations: aqueous solutions containing specified quantities of MP-1177, MP-1196, and calcium hydroxide

Concentration(s):

Experiment #	Formulation #	Concentration (mM)		
		MP-1177 (M)	MP-1196 (mM)	Calcium hydroxide (mM)
1	1	0.492	20.9	22.4
	2	0.527	23.7	33.4
	3	0.481	0	20.4
	4	0.583	24.0	0
2	5	0.502	4.7	4.8
	6	0.507	15	16.9
	7	0.513	24	27.7
	8	0	394	390

Dosages:

Experiment #	Formulation #	Doses as mmole MP-1177/kg*
1	1	15,17,20,23,26,30
	2	15,17,20
	3	10,11,13,15,17
	4	6,7,9,10,11,13,15
2	5	26,30,35
	6	23,27,31,35
	7	27,31,36
	8	12,14,16,18**

*doses rounded to the nearest whole unit
**doses of MP-1196

Route of administration: iv
Volumes of administration:

Experiment #	Formulation #	Volumes of Administration* (ml/kg, respectively)
1	1	30,34,40,46,52,60
	2	30,34,40
	3	20,22,26,30,34
	4	12,14,18,20,22,26,30
2	5	52,60,70
	6	46,54,62,7o
	7	54,62,72
	8	30,36,41,46

*volumes rounded to the nearest whole unit

Rate of administration: not specified

Study design:

See results table for dose groups and ingredient ratios. This study was conducted in 2 experiments, each including 4 formulation groups. Dosing was by the up-and-down method. Six animals per formulation were treated.

Study schedule:

PROCEDURE	TIME OF PROCEDURE /DATA COLLECTION
animals dosed iv	at 5 min intervals between mice in each formulation group
mortality and clinical observations	immediately after dosing and at 0.5,1,2, and 4 hours and daily for 7 days
body weight gain of survivors	over 7 days
termination of survivors	7 days after the injection
gross pathology	at termination

APPEARS THIS WAY
ON ORIGINAL

Results: LD_{50} values for all groups are presented in the following table. All deaths occurred immediately after injection.

Effect of Calcium and MP-1196 on the LD_{50} of MP-1177

Formulation Group	MP-1177 Doses (mmole/kg)*	Mole %			LD_{50} (mmole/kg)	MNLD[t]	MNLD as multiple of human dose***	MLD[tt]
		MP1196 as % MP1177	Ca as % MP1177	Ca as % MP1196				
Expt 1								
1	15,17,20,23,26,30	4.2	4.6	107	29	26	22	30
2	15,17,20	4.5	6.3	141	18	15	12	17
3	10,11,13,15,17	0.0	4.2	-	12	10	8	11
4	6,7,9,10,11,13,15	4.1	0.0	0	<6	0	-	not determ
Expt 2								
5	26,30,35	0.9	1.0	102	30	26	22	30
6	23,27,31,35	3.0	3.3	113	29	23	19	27
7	27,31,36	4.7	5.4	115	33	31	26	36
8	12,14,16,18**	-	-	99	16	14	12	16

*doses rounded to the nearest whole unit
**doses and LD_{50} refer to MP-1196
***based on body surface area comparison
[t]MNLD=maximum non-lethal dose
[tt]MLD=minimum lethal dose

Signs of toxicity included dyspnea, hypoactivity, and convulsions.

Most survivors in formulation groups 1-3 and 8 gained weight. All animals in group 4 died. Most survivors in formulation groups 5-7 lost weight.

Lung hemorrhage appeared at low incidence in most formulation groups. This did not seem to be dose related according to the Sponsor.

Reviewer comments:

The purpose of this study was to determine the effect of varying levels of MP-1196 and Ca relative to MP-1177.

Formulation groups 5,6, and 7 show that adding approximately equimolar quantities of MP-1196 and Ca at 1,3 and 5 % of the MP-1177 level did not affect toxicity.

MP-1177 alone was not tested which would have indicated whether or not it was necessary to add MP-1196 and calcium at all.

Groups 3 and 4 showed that adding MP-1196 alone or Ca alone to MP-1177 increases toxicity over adding the combination.

This study does not rationalize the levels of MP-1196 and Ca added to the MP-1177/10 final formulation (10%). It appears that lower equimolar concentrations of MP-1196 and Ca would be sufficient to minimize toxicity of the formulation.

To get an idea of what the LD_{50} values are for the MP-1177/10 final formulation with 10% MP-1196 and Ca added, see acute toxicity summary table at the end of the single dose section of this review. In that table, it can be seen that LD_{50} values ranged from 20-28 mmole/kg (mean=24). In this study, the LD_{50} values when equimolar quantities of MP-1196 and Ca were added at 1,3 and 5 % of the MP-1177 dose ranged 29-33 mmole/kg. It is difficult to draw a final conclusion about this since: 1) LD_{50} values appear to vary from study to study, and 2) the final formulation was not tested side by side with the test formulations in the same study.

It is noted that the approved gadolinium agents (Magnevist, Omniscan, and ProHance) contain 10% of the Ca analogs of the respective gadolinium chelates.

40. Title: A 2-Week Single Dose Intravenous Toxicity Study of MP-1177/10 in the Albino Rat
Study #: Study 1101/05/94/028
Species/Strain/Source: rat/Sprague-Dawley/Harlan Sprague-Dawley
Sex/age/body weight: male/5 weeks old/192.1-235.6 g
Dose information:

Formulation: MP-1177/10, controls received vehicle=0.9% sterile saline
Concentration(s): 0.5 M
Dosages: 0, 0.5, 5.0, 15.0 mmole/kg (0, 1, 8, and 25 times the proposed human dose of 0.1 mmole/kg based on a body surface area comparison)
Route of administration: iv
Volume of administration: 30, 1, 10, and 30 ml/kg respectively
Rate of administration: 1 ml/min

Study design:

Single Dose Study Design in Rats (1101/05/94/028)					
Dose (mmole/kg)	Multiple of Clinical Dose*	Total Number/Group		Number Terminated at Designated Time	
		♂	♀	24 hr	14 days
0	0	10	0	5	5
0.5	1	10	0	5	5
5.0	8	10	0	5	5
15.0	25	10	0	5	5
*based on body surface area comparison					

Study schedule:

PROCEDURE	TIME OF PROCEDURE /DATA COLLECTION
Acclimated	for 16 days prior to dosing
dosed iv	Time 0
observed for mortality and clinical signs	1-3 min, 1 hour, ~4 hr, 24 hr, twice daily thereafter
physical exam	prior to dosing, 7 and 13 days post dose
measured body weight	prior to dosing, 1,7,and13 days post dose
asphyxiated with CO_2 and exsanguinated	14 days post dose
conducted gross pathology (detailed)	24 hr or 14 days post dose
kidneys and testes/epididymides weighed	immed after gross exam
kidneys and testes/epididymides preserved	after weighing
histopathol kidneys & testes/epididymides	after preservation

Results:

Mortality: none

Clinical signs and physical exams: no treatment related effects

Body weight: no effects

Organ weights: no effects

Gross pathology:

-24 hr post dose: no effects
-14 days post dose: mottled pigmentation of the kidney in 3/5 animals at 15 mmole/kg

Histopathology:

Effects on testes and epididymides not observed

Mild to moderate vacuolization of the proximal convoluted tubules of the kidneys was observed as follows:

	Findings at designated times post-dose	
Dose	24 hr	14 days
0	no effects	no effects
0.5	no effects	no effects
5.0	moderate vacuolization in 4/5 animals, minimal in 1/5	no effects
15.0	moderate vacuolization in 5/5 animals	mild vacuolization in 4/5 animals, minimal in 1/5
Scale: minimal, mild, moderate, marked		

Reviewer comments:

No effects for all measures except kidney histopathology at doses up to 15 mmole/kg (25 times the human dose).

Moderate vacuolization observed in the high dose group (15.0 mmole/kg or 25 times the human dose) at 24 hr post dose, showed signs of partial resolution by 14 days.

Moderate vacuolization at 5.0 mmole/kg (8 times the human dose) observed 24 hr post dose was resolved within 14 days.

Vacuolization of the proximal convoluted tubules of the kidneys was not observed in the low dose or controls (NOEL 0.5 mmole/kg, 1 times the human dose).

42. Title: Acute Intracisternal Toxicity of MP-1177/10 in Rats
Study #: 1101/05/92/004
Species/Strain/Source: rat/Sprague-Dawley
Sex/age/body weight: males and females/200-250 g
Dose information:
Formulation: MP-1177/10
Dosages: 0, 0, 50, 100, 150, 200 µmole/kg
(2 control groups: anesthesia control and saline volume control)
See "Dose analysis" for comparison of rat doses to human dose.
Route of administration: intracisternal
Volume of administration: 0, 400, 100, 200, 300, 400 µl/kg respectively
-mean absolute volumes: see table below
Rate of administration: 50 µl/sec
Study design and schedule:

PROCEDURE	TIME OF PROCEDURE /DATA COLLECTION
ether anesthesia	prior to doing
intracisternal injection via injection apparatus	time 0
Observed for mortality and signs of toxicity	immediately after inj, 0.5, 1,2,4 hr, 2 times per day until normal, daily thereafter
body weights	predose, 3,7,14 days
killed with ether	14 days postdose
brain weight	following death
gross exam of brain	following death

Dose analysis:

In the following tables, an attempt was made to relate rat brain doses of MP-1177/10 following intracisternal administration to the human brain dose following an intravenous administration of 0.1 mmol/kg.

MP-1177 is said not to cross the normal blood:brain barrier; however, it is used diagnostically to detect brain areas with impaired blood:brain barrier (which means it does cross into the brain at those sites). Substances penetrating brain areas with an impaired blood:brain barrier can theoretically affect both abnormal lesions and normal brain tissue proximal to the lesions.

The rat brain dose was assumed to be the cerebrospinal fluid concentration following an intracisternal dose of MP-1177/10. The cerebrospinal fluid concentration was estimated by dividing the MP-1177 dose by the sum of the CFS volume and the dose volume.

The maximum possible human brain dose at the site of a lesion was assumed to

be C_{max}. C_{max} was estimated by dividing the dose by plasma volume.

This intracisternal study tested if rat brain concentrations of MP-1177 21 to 64 times C_{max}, the theoretical maximum possible human brain/lesion concentration, produce observable effects such as death, convulsions, loss of coordination, etc.

Dose multiples in this study are expected to have been much greater than 21 to 64 because:

-human brain concentrations at the site of the lesion are probably much lower than C_{max}
-the quantity of exposed human brain tissue near the lesion following an iv dose is probably much less than the quantity of rat brain tissue exposed to drug following an intracisternal injection.
-washout from the site of a human brain lesion (probably blood concentration dependent) is expected to be much more rapid that the washout from the rat CSF (turnover rate≈1.4 times/day)

The quantitative relationship between rat and human brain exposures are estimated in the following tables:

Estimation of MP-1177/10 Concentration in Cerebrospinal Fluid following an Intracisternal Injection to Rats						
Intracisternal Dose (μmole/kg)	Dose Volume (μl/kg)	Dose to 225 g Rat (umole)	Dose Volume 225 g Rat (ul)	Volume of rat CSF (ul)	Total Volume (ul)	Estimated Concentration of MP-1177 in CSF (mM)
50	100	11.25	22.5	191	214	53
100	200	22.50	45.0	191	236	95
150	300	33.75	67.5	191	259	130
200	400	45.00	90.0	191	281	160
Assumptions: Homogeneous distribution of drug in CSF of arachnoid space and ventricles; CSF volume of adult rat = 0.85 μl/g body weight.						

Rat Intracisternal MP-1177/10 Concentration Expressed as a multiple of the Estimated MP-1177/10 Concentration in a Human Brain Lesion with Blood:Brain Barrier Disruption			
Intracisternal Dose (µmole/kg)	Estimated MP-1177/10 Concentration in CSF of rats following ic Administration (from above table) (mM)	Maximum Possible Brain Lesion Concentration (estimated C_{max}) following a 0.1 mmole/kg Dose to Humans (mM)	Rat Intracisternal Concentration as a Multiple of Estimated Human Brain Lesion Concentration
50	53	2.5	21 X
100	95	2.5	38 X
150	130	2.5	52 X
200	160	2.5	64 X
Assumptions: The maximum possible concentration of MP-1177 in a brain region with blood:brain barrier breakdown is C_{max} (*C_{max} was estimated to be 2.5 mM by dividing the entire dose in mmole by plasma volume.) Identical washout from human and rat brain.			

Results:

Mortality:

Treatment	Dose (µmol/kg)	Volume (µl/kg)	Sex	Deaths				#Dead/ #tested
				Hours		Days		
				0–1	2–4	2–8	9–15	
Anesthesia	0	0	M	0	0	0	0	0/5
			F	0	0	0	0	0/5
			Total	0	0	0	0	0/10
Saline		400	M	0	0	0	0	0/5
			F	0	0	0	0	0/5
			Total	0	0	0	0	0/10
MP-1177/10	50	100	M	0	0	0	0	0/5
			F	0	0	0	0	0/5
			Total	0	0	0	0	0/10
MP-1177/10	100	200	M	0	1	0	0	1/5
			F	0	0	0	0	0/5
			Total	0	1	0	0	1/10
MP-1177/10	150	300	M	1	0	0	0	1/5
			F	1	0	0	1	2/5
			Total	2	0	0	1	3/10
MP-1177/10	200	400	M	4	0	0	0	4/5
			F	3	0	1	0	4/5
			Total	7	1	0	0	8/10

A. Effect:	**death**
B. Frequency, Degree, Duration, or Time of effect:	9 deaths occurred within 1 hour. 1 death between 1 and 2 hours. 1 death between 2 and 24 hours. 1 death 9 days post inj (day 10)
C. Dose Response?:	yes
D. NOAEL (dose/kg):	Max nonlethal dose=50 umole/kg (LD_{50} =166 umole/kg)
E. NOAEL (as CSF conc ÷ C_{max})	21 X
F. NOTE:	♂ and ♀ mortality not sig different from each other

Signs of Toxicity:

A. Effects:	**Dyspnea, hypoactivity**
B. Frequency, Degree, Duration, or Time of effect:	Transient, lasting ≤4 hr
C. Dose Response?:	not apparent
D. NOAEL (dose/kg):	0 µmole/kg, observed at all doses
E. NOAEL (as CSF conc ÷ C_{max}):	-

A. Effect:	**Convulsions**
B. Frequency, Degree, Duration, or Time of effect:	in animals dying within first 2 hours
C. Dose Response?:	yes
D. NOAEL (dose/kg):	50 µmole/kg
E. NOAEL (as CSF conc ÷ C_{max}):	21

A. Effects:	**Tremors, Rearing/Pawing, Chewing, Salivation**
B. Frequency, Degree, Duration, or Time of effect:	during 1 to 4 hours post administration
C. Dose Response?:	yes
D. NOAEL (dose/kg):	50 µmole/kg
E. NOAEL (as CSF conc ÷ C_{max}):	≥ 21

One animal that died on Day 10 (from 50 µmole/kg group) showed dyspnea, hypoactivity, and chewing during the days before death.

Body Weights: All animals gained weight comparably except the single survivor in the male high dose group (which lost 20% BW during study).

Brain Weights: All brain weights comparable to controls except the following which were 5 to 15% lower than the rest:

-males and females in 150 and 200 µmole/kg groups dying during study

-single survivor in male high dose group

Gross Effects on Brain: Evidence of trauma or brain tissue abnormalities not present.

Reviewer comments:

It is difficult to compare brain exposure in rats following an intracisternal administration to brain exposure in brain tumor patients following an iv dose without making a lot of assumptions. The approach of this review has been to make assumptions which are conservative, thus reducing the possibility of underestimating human toxicity.

It is estimated that that rat intracisternal doses of 50, 100, 150, and 200 umole/kg represent brain exposures of 21, 38 , 52 and 64 times the maximum possible dose to normal brain tissue near a brain lesion in humans. This estimate is based on assumptions listed within the text of this review.

The maximum non-lethal intracisternal dose in rats is estimated to be 21 times the human iv dose of 0.1 mmole/kg and is probably higher.

The maximum no observable adverse effect levels (NOAELs) expressed as multiples of the human dose based on estimated brain dose comparisons are:

Effect	NOAEL
hypoactivity	<21 X
dyspnea	<21 X
chewing	21 X
salivation	21 X
rearing/pawing	21 X
tremors	21 X
convulsions (in dying animals)	21 X
lethality	21 X

Further data (for example, measured C_{max} in humans) would probably raise the expressed safety margins.

44. Title: An Acute Toxicity Study of MP-1177/10T in the Dog via Intravenous Injection
Study #: 1101/05/91/032
Species/Strain/Source: dog/Beagle/
Sex/age/body weight: ♂ and ♀/5-6 months/♂s 8.1-9.6,♀s 6.4-8.1
Dose information:

Formulation: MP-1177/10T (controls received sterile saline)
Concentration(s): 0.5 M
Dosages: 0, 3, 6, and 12 mmole/kg
Route of administration: iv
Volume of administration: 24, 6, 12, and 24 ml/kg respectively
Rate of administration: 1 ml/min

Study design:

Single Dose Study Design in Dogs (1101/05/91/032)				
Dose (mmole/kg)	Dose as multiple of Human dose*	number of males	number of females	Termination Time
0	0	2	2	14 days post dosing (no interim sac)
3	15	2	2	
6	30	2	2	
12	60	2	2	
*based on body surface area comparison				

Study Schedule:

PROCEDURE	TIME OF PROCEDURE /DATA COLLECTION
acclimated	for 28 days before dose administration
dosed iv	time 0
observed for mortality and clinical signs	minimum 2 times daily
physical exam	pretest and weekly thereafter
body weight	1 week pretest, the day before dosing, 5,12, and 14 days post dosing
hematology	pretest and 14 days after dosing
clinical chemistry	pretest and 14 days after dosing
termination by exsanguination under sodium pentobarbital anesthesia	14 days after dosing
gross pathologic exam	after termination

Results:

Mortality: no effect

Clinical signs and physical exams: no effects

Hematology: no effects

Clinical chemistry:

-10-50% increase in alkaline phosphatase over controls, dose response not apparent, however, values are within historical control values
-up to 20% decrease in phosphorus compared to controls, dose response relationship, however all values within historical control values.

Dose Group (mmole/kg)	An #	ALK PHOS (IU/L)			PHOS (mg/dl)		
		Pretest	14 days	Percent Change	Pretest	14 days	Percent Change
0	1275M	91	80	-12	6.0	5.9	-2
	1276M	172	158	-8	5.8	5.9	+2
	1775F	125	108	-14	6.5	6.2	-5
	1776F	89	99	+11	6.2	6.1	-2
3	2275M	72	82	+14	6.3	6.5	+3
	2276M	201	221	+10	6.6	6.7	+1
	2775F	182	196	+8	5.9	6.7	+12
	2776F	146	149	+2	6.2	5.7	-9
6	3275M	75	90	+20	7.2	6.2	-16
	3276M	84	114	+36	6.1	4.8	-27
	3775F	110	134	+22	6.3	5.5	-15
	3776F	117	152	+30	6.5	5.1	-27
12	4275M	141	186	+32	6.7	4.5	-49
	4276M	137	166	+21	6.7	5.0	-34
	4775F	112	141	+26	6.3	5.1	-24
	4776F	130	151	+16	5.4	4.5	-20

Historical control values-Beagle dog				
	Male		Female	
	mean	range	mean	range
ALK PHOS	114	39-191	119	47-186
PHOS	5.89	4.08-7.77	5.76	3.81-7.33

Gross pathology: no effects

Reviewer comments:

The Sponsor concluded that slight increases in serum alkaline phosphatase and slight decreases in serum phosphorus were suggestive of a treatment-related effect. However, they did not speculate on what the effect may mean. The dose of 3.0 mmole/kg was considered to be a no effect level by the Sponsor. The Sponsor also

concluded that since the effects were within historical control ranges for the laboratory, they were not considered of biological significance.

Since measurements were only made at 14 days, it is not possible to know if values were more extreme at an earlier time points (such as 3 days post-dosing). If there were greater effects at earlier time points, it appears they were reversible.

Increased alkaline phosphatase and decreased serum phosphorus can be suggestive of liver or bone pathology.