八十八年度科技研究發展計畫
成果報告書

計畫名稱：恩慈療法臨床試驗之可行性研究

計畫編號：DOH 88-TD-1067

執行機構：台灣大學醫學院附設醫院

計畫主持人：黃俊升

計畫主持人服務單位：台灣大學醫學院附設醫院外科部

主持人職稱：主治醫師

執行期限：87 年 7 月 1 日至 88 年 6 月 30 日止

目錄

封面

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壹、摘要

中文關鍵詞：恩慈療法，專案申請、另類療法

英文關鍵詞：Treatment IND、Compassionate Use、Alternative Medicine

新藥常為重症及有生命危險的病人帶來希望，但研發過程耗時甚久，為了使無有效療法的重症病人及早使用安全及已初步證實療效的試驗中新藥治療。

國內至今尚無 Treatment IND 管理法規，為少數特殊重症之專案進口新藥辦法，並不周延，適用醫師、病患人數皆受限制頗多，為免國內重症絕望病人急病亂投醫，使用療效不確實之各種偏方，不如儘速建立國內 Treatment IND 管理法規，導入正軌。

本計劃將收集 FDA Treatment IND 相關法，擬定台灣 Treatment IND 管理法規，其中將亦含概原產國已上市，國內未上市及以往以專案進口之新藥。

貳、前言

新藥的研發，常為許多重症的絕望病人帶來希望，但是為了確保藥物的安全性及有效性，各國莫不規定藥物上市要符合許多繁複要求及審查，至使新藥的研發平均費時 15.3 年，耗費 3.6 億美元(1990-1995 統計)。其中臨床試驗即佔 6.9 年，上市審核要 2.3 年。這對重症絕望的病人等待新藥，常是緩不濟急。無怪乎許多癌症病人在已上市抗癌藥物治療成效不佳時，常會急病亂投醫，轉而服用各種道聽途說，療效未經證實的偏方，禁之不絕。與其如此，不如建立一套 "恩慈療法"(compassionate use)的管理規則，導入正軌。

恩慈療法英文名為 Compassionate Treatment，此為一描述對於重症病人以治療為目的，施予尚未經主管單位正式核准的療法。此為一概念性描述的普通名詞，其中重症並未定義，其療法廣義而言，可包含另類療法(alternative medicine)及 Treatment IND 中所定義的療法。Office of Alternative Medicine 乃成立於 NIH 中，負責資助 Alternative Medicine 之相關研究(含臨床試驗)計劃。目前 FDA 並無對 Alternative Medicine 定出管理辦法，因此所收集 FDA 資料及本計劃目的，均未含廣義恩慈療法中所含蓋的 Alternative Medicine。

如何儘速建立國內恩慈療法的管理規則，以嘉惠重症的絕望病人，既可杜絕不肖廠商販賣偏方謀利，亦可促進醫學的發展，應是當務之急。

FDA 對核准 Treatment IND 的使用，一般有下列條件：

(1)此 IND 新藥正進行證實安全性、有效性之嚴格設計的臨床試驗，且已有足夠病人收錄。

(2)Treatment IND 廠商不得以申請 Treatment IND 做為新藥上市前的商業行銷。

(3)此藥不得進行商業推廣或廣告。

(4)廠商正積極研發此藥，預備提出上市許可申請。

廠商提出 Treatment IND 申請後 30 天，如未接獲 FDA 回答，即表示自動通過申請，申請內容應提出①欲治療的重症或有生命危險的病人適應症②此藥安全性及可能有效性的科學證據③訓練合格之臨床醫師如何獲取此藥以治療病人。

FDA 對“有生命危險疾病”定義為(1)可能在數個月死亡的疾病狀態，或(2)如果未早期治療，可能突然死亡。例如嚴重的鬱血性心臟衰竭庖疹病毒、(herpes simples)腦炎、無法治癒之末期癌症、嚴重肺氣腫、細菌性心內膜炎、蜘蛛網膜下腦出血、嚴重之 AIDS、無法控制之心律不整等。而“嚴重疾病”則例如老年癡呆症、嚴重的多發性硬化症(Multiple Sclerosis)、嚴重的巴金森症、短暫缺血性腦中風、進行性強直性脊椎關節炎、嚴重的紅斑性狼瘡，及某些形態的癲間及糖尿病等。

Treatment IND 或相關治療的花費，可以經 FDA 核准後向病人收費，惟收費金額不得超過此藥製造、研發、交運處理的合理價格，必要時 FDA 得撤銷廠商收費權利。各醫療機構 Treatment IND 的使用及收費標準亦需經人體試驗委員會(IRB)評估(1)合理否，(2)注意此收費是否使經濟情況較差或未保險病人不易參與新藥試用。病人同意書中，亦要加註收費範圍。國內對國外已上市但台灣尚未上市的新藥，目前是由醫師以專案方式申請進口使用，但對原廠國尚未上市新藥，則仍無 Treatment IND 管理規則可適用。以上兩者對國內重症絕望患者，皆是恩慈療法管理規則的適用對象。但由以上討論可知其可行性的建立，有賴醫師(或學會)，IRB、廠商、衛生主管當局的通力合作，以重症、絕望病人福祉為依歸，才可順利完成。

參、材料與方法

A.法規收集：

1. 收集 FDA Treatment IND 法規。
2. 收集亞太地區各國相關法規供修法參考。
3. 收集 FDA 其他相關法規[2]，(1)如 AIDS 用藥"parallel tract"，(2)孤兒藥，(3)特許 NCI open protocol 優先供給腫瘤科醫師使用 IND 藥物的"Group C" Treatment IND，(4)Emergency IND 等。

B. 擬出草案：

1. 對原產國研發中新藥(IND Stage)，以 FDA Treatment IND 管理法規精神，擬定台灣 Treatment IND 管理法規，例如①抗癌藥品 Treatment IND，可由 TCOG 或醫學中心主人擬定 open protocol（無對照組），先經 Joint IRB 或 Local IRB 同意後，向衛生署提出申請，一旦通過後，訓練合格之腫瘤科醫師皆可援用此 Protocol 以治療病人(似 Group C Treatment IND)，但要定期彙報 IRB 及衛生署個案治療成效及副作用。②美國已核准在案 Treatment iND 藥物，由廠商提出申請，經衛生署評估後，核定限制使用單位資格（如醫學中心或專科醫院）及使用適應症，有限度開放使用，廠商應隨時報告此藥研發進度給衛生署，監控其使用。
2. 對原產國已上市，台灣未上市者，如確為重症或危及生命危險之突破性新藥，除應另訂加速其查驗登記之流程、法規要求外，應在核准上市前，以 Treatment IND 方式，引進國內使用，而非如現行專案申請方式，每個使用醫師皆要屢次申請少量定額藥品，行政手續繁複。
3. Treatment IND 之收費標準，應經衛生署核可，並經 IRB 評估，列於受試者同意書中。

B. 和癌症醫學會、TCOG(台灣癌症合作組織)、IRPMA、Joint IRB(聯合人體試驗委員會)、藥政處藥物審議委員會等團體定期討論所擬出草案可行性。

C. 對已認定之 Treatment IND(1987~1994)29 種，進行個案分析，了解此法規受惠多少各類重症病人，上市流程，其中所引發相關問題，提出優先試辦新藥種類。

肆、結果

1. 各國對 Treatment IND 的定義不同，通過的流程也不盡一致，例如提出申請可能是醫師／醫院或廠商；病患必須付費與否等。
2. Treatment IND 藥品，廠商對供藥與否十份謹慎，為增加台灣獲取 Treatment IND 機會，建議一旦日後能證實藥品的有效性、安全性後，能適度減少屆時申請上市的 FSC 要求，將該藥品以 Treatment IND 的使用經驗，視為申請上市的重要參考依據。
3. 目前的申請程序：

   目前對國內未上市的藥品提出專案申請流程是，由臨床主治醫師提出：1)治療計畫(Treatment plan)；2)個別病患的病歷摘要；3)病人同意書，經過醫院人委會同意後，以醫院名義向藥政處提出申請。
4. 藥政處對專案申請的處理流程是：

   1)專案申請使用的適應症若是與原產國一致者，三天內（不經委員審查）即發文同意；若與原廠國適應症不同，則由委員審查。

   2)藥品使用後，須由臨床醫師撰寫簡要使用經驗報告。?

   3)自民國八十二年至八十八年二月，國內醫院提出專案進口品項有 52 項，共計 317 次申請。

伍、討論

1.對於國內未上市的藥品，以專案申請的藥品類別，涵蓋：

A.國外未上市，而國內需要者；

B.國外已上市，但國內未提出新藥申請表未上市者；

C.國內臨床試驗已結束，對於治療有效的病患，在廠商未取得藥品進口前的空窗期，目前專案申請管道通暢，但規範稍嫌簡略，建議配。

2.建議方案：

1)現行專案申請及日後 Treatment IND 案，委託查驗中心建立送審的 checking list 及審查流程，例如藥政處接案後轉交查驗中心審查於一周內審查完畢。並要求適當的追蹤、評估計畫及計畫完成後繳交治療經驗報告。

2) 由某類藥品或個案為例，(如毒蛇血清或罕見疾病用藥）事先擬定計畫書報備，針對特定適應症並限定國內某些適用醫師；確定藥品數量、註明分批進口及期限，待病患需要可以立即於國內使用。

3)由 IRPMA 成立 Treatment IND Working group，協助醫師、會員公司、病人了解申請流程格式。

陸、結論與建議

1.現行專案申請及日後 Treatment IND 案，委託查驗中心建立送審的 checking list 及審查流程，例如藥政處接案後轉交查驗中心審查於一周內審查完畢。並要求適當的追蹤、評估計畫及計畫完成後繳交治療經驗報告。

2.由某類藥品或個案為例，(如毒蛇血清或罕見疾病用藥) 事先擬定計畫書報備，針對特定適應症並限定國內某些適用醫師；確定藥品數量、註明分批進口及期限，待病患需要可以立即於國內使用。

3.由 IRPMA 成立 Treatment IND Working group，協助醫師、會員公司、病人了解申請流程格式。

柒、附錄

一、與產官學界定期討論之會議紀錄

二、美國 FDA 對 Treatment IND 的法規

1.Title 21, Volume 5, Sec. 312.34: Treatment use of an investigational new drug

2.Treatment IND Update

3.Title 21, Volume 5, Sec. 312.35: Submission for Treatment use

附錄一：與產官學界定期討論之會議紀錄

Treatment IND
第一次會議　會議紀錄

一・日期：民國 88 年 1 月 7 日（四）下午 3 時

二・地點：醫藥品查驗中心

三・出席：陳恆德　郭英調

IRPMA 代表：陳璧榮　楊勝仁　李喜鳳　王茂林　程馨　呂秀姥

紀錄：許茜甯

四・討論事項：

(一)Treatment IND。

說明：見(附件一)FDA Treatment IND

決議：Treatment IND 定義：

A指原產國（或國外）未上市的藥品。

B IRPMA 進行國內外資廠調查。

1. 了解總公司對藥品取得 Treatment IND 的條件及該國法規。
2. 國外現有那些 Treatment IND 藥品名單。

C IRPMA 組一 Working group，協助現有外國 Treatment IND 個案引入國內使用。

(二)Bridging Study。

說明：見(附件二)日本 Q & A

決議：1)CDE 審查中，Consideration for Bridging Study 項，建議以 Checking List 方式，綜合 ICH-E5 中，Ethnic factor sensitivity 和本地 Disease Epidemiology，供業界送件參考。

2)請 IRPMA 收集總公司及各國對 Bridging Study 對策及處理經驗。

3)建議廠商在藥品研發過程中，即將人種差異問題列入試驗計劃中（i.e. pivotal study 收集不同人種的病患）

(三)確定定期會議時間及議題。

決議：1)定期每月 IRPMA 代表及學界代表開會一次，必要時得召集臨時會(針對不同研究主題)或由代表人聯絡。

2) 查驗中心代表：陳恆德。

IRPMA 代表：陳璧榮。

學界代表：除郭英調醫師外，包括鄭安理及楊志新醫師。

五・下次會議時間：民國 88 年 2 月 4 日下午 3 時於醫藥品查驗中心。

Treatment IND
第二次會議　會議紀錄

一・日期：民國 88 年 2 月 4 日（四）下午 3 時
二・地點：醫藥品查驗中心
三・主席：陳恆德副執行長
　醫界代表：郭英調　楊志新
　衛生署代表：葉宏一　王兆儀　林建良
　IRPMA 代表：陳璧榮　李喜鳳　鮑力恆　呂秀姣
　請假：鄭安理
　記錄：許茜甯
四・確定前次議錄。
五・報告：

I　. ***Treatment IND***

(一) IRPMA 代表報告：

4.各國對 Treatment IND 的定義不同，通過的流程也不盡一致，例如提出申請可能是醫師／醫院或廠商；病患必須付費與否等。

5.IRPMA 繼續負責調查各國的原廠該類藥品名單及獲准的理由、流程，並進一步取得其使用經驗資料。

6.Treatment IND 藥品，廠商對供藥與否十份謹慎，為增加台灣獲取 Treatment IND 機會，建議一旦日後能證實藥品的有效性、安全性後，能適度減少屆時申請上市的 FSC 要求，將該藥品以 Treatment IND 的使用經驗，視為申請上市的重要參考依據。

(二) 臨床醫師代表意見：

1.目前對國內未上市的藥品提出專案申請流程是，由臨床主治醫師提出：1)治療計畫(Treatment plan)；2)個別病患的病歷摘要；3)病人同意書，經過醫院人委會同意後，以醫院名義向藥政處提出申請。

(三)藥政處對專案申請的處理流程是：

4) 專案申請使用的適應症若是與原產國一致者，三天內（不經委員審查）即發文同意；若與原廠國適應症不同，則由委員審查。

5) 藥品使用後，須由臨床醫師撰寫簡要使用經驗報告。?

6) 自民國八十二年至八十八年二月，國內醫院提出專案進口品項有 52 項，共計 317 次申請。

(四)結論：

3.對於國內未上市的藥品，以專案申請的藥品類別，涵蓋 1)國外未上市，而國內需要者。2)國外已上市，但國內未提出新藥申請表未上市者；3)國內臨床試驗已結束，對於治療有效的病患，在廠商未取得藥品進口前的空窗期，目前專案申請管道通暢，但規範稍嫌簡略，建議配合 Treatment IND 擬定流程，一併檢討。

4.建議方案：

4) 現行專案申請及日後 Treatment IND 案，委託查驗中心建立送審的 checking list 及審查流程，例如藥政處接案後轉交查驗中心審查於一周內審查完

畢。並要求適當的追蹤、評估計畫及計畫完成後繳交治療經驗報告。

5) 由某類藥品或個案為例，(如毒蛇血清或罕見疾病用藥）事先擬定計畫書報備，針對特定適應症並限定國內某些適用醫師；確定藥品數量、註明分批進口及期限，待病患需要可以立即於國內使用。

6) 由 IRPMA 成立 Treatment IND Working group，協助醫師、會員公司、病人了解申請流程格式。

II. *Bridging Study*

(一) IRPMA 報告：

負責取得日本目前對 Bridging study 的要求標準及其處理流程。

(二) 結論：

1) 建議由查驗中心受理國內銜接性試驗是否需要執行的諮詢業務，以可能的 ethnic factor 問題為導向來決定試驗執行與否。

2) 建議可由已知同類類似藥品事先進行 Drug-food 交互作用、HbsAg carrier 的 PK study 或由已知代表性藥品提出可能的 ethnic factor 解釋或試驗計畫。

III. *Registration trial waiving*

結論：由 IRPMA 負責各會員意見整合，除依 Therapeutic index 考量（如前三次公告內容）外，擴大至依全國需要程度或其他需求性考量後，於 2/24 日前將意見交給查驗中心彙整，向藥政處提出草案。

六、下次會議日期：二月二十四日下午二時。

附錄二、美國 FDA 對 Treatment IND 的法規

1.Title 21, Volume 5, Sec. 312.34: Treatment use of an investigational new drug

2.Treatment IND Update

3.Title 21, Volume 5, Sec. 312.35: Submission for Treatment use

[Code of Federal Regulations]
[Title 21, Volume 5, Parts 300 to 499]
[Revised as of April 1, 1998]
From the U.S. Government Printing Office via GPO Access
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TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES--C

PART 312--INVESTIGATIONAL NEW DRUG APPLICATION--Table of Contents

Subpart B--Investigational New Drug Application (**IND**)

Sec. 312.34 **Treatment** use of an investigational new drug.

(a) General. A drug that is not approved for marketing may be under clinical investigation for a serious or immediately life-threatening disease condition in patients for whom no comparable or satisfactory alternative drug or other therapy is available. During the clinical investigation of the drug, it may be appropriate to use the drug in the **treatment** of patients not in the clinical trials, in accordance with a **treatment** protocol or **treatment IND**. The purpose of this section is to facilitate the availability of promising new drugs to desperately ill patients as early in the drug development process as possible, before general marketing begins, and to obtain additional data on the drug's safety and effectiveness. In the case of a serious disease, a drug ordinarily may be made available for **treatment** use under this section during Phase 3 investigations or after all clinical trials have been completed; however, in appropriate circumstances, a drug may be made available for **treatment** use during Phase 2. In the case of an immediately life-threatening disease, a drug may be made available for **treatment** use under this section earlier than Phase 3, but ordinarily not earlier than Phase 2. For purposes of this section, the ``**treatment** use'' of a drug includes the use of a drug for diagnostic purposes. If a protocol for an investigational drug meets the criteria of this section, the protocol is to be submitted as a **treatment** protocol under the provisions of this section.

(b) Criteria. (1) FDA shall permit an investigational drug to be used for a **treatment** use under a **treatment** protocol or **treatment IND** if:

(i) The drug is intended to treat a serious or immediately life-threatening disease;

(ii) There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the

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disease in the intended patient population;

(iii) The drug is under investigation in a controlled clinical trial under an **IND** in effect for the trial, or all clinical trials have been completed; and

(iv) The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.

(2) Serious disease. For a drug intended to treat a serious disease, the Commissioner may deny a request for **treatment** use under a **treatment** protocol or **treatment IND** if there is insufficient evidence of safety and effectiveness to support such use.

(3) Immediately life-threatening disease. (i) For a drug intended to treat an immediately life-threatening disease, the Commissioner may deny a request for **treatment** use of an investigational drug under a **treatment** protocol or **treatment IND** if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the

drug:

(A) May be effective for its intended use in its intended patient population; or

(B) Would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury.

(ii) For the purpose of this section, an ``immediately life-threatening'' disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early **treatment**.

(c) Safeguards. **Treatment** use of an investigational drug is conditioned on the sponsor and investigators complying with the safeguards of the **IND** process, including the regulations governing informed consent (21 CFR part 50) and institutional review boards (21 CFR part 56) and the applicable provisions of part 312, including distribution of the drug through qualified experts, maintenance of adequate manufacturing facilities, and submission of **IND** safety reports.

(d) Clinical hold. FDA may place on clinical hold a proposed or ongoing **treatment** protocol or **treatment IND** in accordance with Sec. 312.42.

[52 FR 19476, May 22, 1987, as amended at 57 FR 13248, Apr. 15, 1992]

Answers 03/20/1990

≤TREATMENT≥ ≤IND≥ UPDATE

The following may be used to answer inquiries about FDA's "**≤treatment≥ ≤IND≥**" program:

Under the FDA **≤treatment≥ ≤IND≥** (investigational new drug) regulations enacted in 1987, drugs that are in controlled clinical trials can be provided outside these trials to treat patients with serious or immediately life-threatening diseases for which no comparable or satisfactory alternate therapy exists.

Certain safeguards must be observed, including requirements:

-- That the patient is fully informed of the risks and expressly consents.

-- That the drug is not promoted or otherwise "commercialized," though drug companies can charge patients to recover the cost of the drug's manufacture, research, development and handling.

-- That clinical trials are underway and continue unimpeded, and the sponsor of the drug actively pursues marketing approval of the drug with "due diligence."

FDA has approved 18 drugs for use under its **≤treatment≥ ≤IND≥** program.

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The most recent approval, baclofen for infusion into the spinal canal (intrathecal infusion) using the Medtronic SynchroMed Infusion System, was approved for those multiple sclerosis and spinal cord injury patients with severe and chronic spasticity who cannot tolerate or do not respond to oral baclofen. The drug has been available in an oral form for treating spasticity for 12 years. But about 20,000 patients who suffer painful chronic spasticity either do not experience sufficient benefit from the oral preparation or suffer unacceptable side effects.

One study has indicated that intrathecal baclofen can have a dramatic clinical effect in some patients who had not responded to oral baclofen.

The SynchroMed Infusion System, an infusion pump containing baclofen, is placed beneath the skin in the patient's abdomen. It can be programmed via radio signals to dispense the drug through a small catheter inserted into the spinal canal. The device is refilled every four to eight weeks by injection with a hypodermic needle through the skin and a self-sealing rubber cover on the pump.

Although there has been significant benefit from intrathecal baclofen in some patients, overall exposure of patients is small to date, and there is need for caution and careful patient monitoring. At least one death not explained by any other cause has occurred with the intrathecal infusion of baclofen. The informed consent obtained from patients in the **≤treatment≥ ≤IND≥** will make note of this, and FDA will require that doctors using the device call each patient under their care every week for at least the first six months of treatment and that the **≤treatment≥ ≤IND≥** sponsor call each doctor each week to ascertain the status of all patients.

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Physicians treating patients with severe spasticity who have failed oral antispastic medications can contact Medtronic Inc. at 800-328-0810 or 612-572-5000 for detailed information about enrollment in the treatment protocol and the drug's distribution.

A list of previously approved **≤treatment≥ ≤IND≥**'s and their status follows.

≤TREATMENT≥ ≤IND≥ LIST

Drug: Cytomegalovirus immune globulin (CMV-IG)
≤Treatment≥ ≤IND≥ Granted: October 1987

Indication: Prevention of cytomegalovirus infections in renal transplant patients.
Sponsor: Comonwealth of Massachusetts, Department of Public Health.
Market Approval Date: Not yet approved.

Drug: Ifosfamide & Mesna
≤**Treatment**≥ ≤**IND**≥ Granted: December 1987
Indication: Germ cell carcinoma.
Sponsor: National Cancer Institute.
Market Approval Date: December 31, 1988.

Drug: Trimetrexate
≤**Treatment**≥ ≤**IND**≥ Granted: February 1988
Indication: AIDS patients with Pneumocystis carinii pneumonia who are intolerant to standard forms of therapy.
Sponsor: National Institute of Allergy and Infectious Diseases.
Market Approval Date: Not yet approved.

Drug: Anafranil (clomipramine HCl)
≤**Treatment**≥ ≤**IND**≥ Granted: June 1988
Indication: Severe cases of Obsessive Compulsive Disorder.
Sponsor: Ciba-Geigy.
Market Approval Date: December 29, 1989.

Drug: Eldepryl (selegiline HCl)
≤**Treatment**≥ ≤**IND**≥ Granted: June 1988
Indication: Severe Parkinson's Disease.
Sponsor: Somerset Pharmaceuticals.
Market Approval Date: June 5, 1989.

Drug: Pentostatin
≤**Treatment**≥ ≤**IND**≥ Granted: July 1988
Indication: Hairy cell leukemia refractory to alpha interferon.
Sponsor: National Cancer Institute.
Market Approval Date: Not yet approved.

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Drug: Teniposide
≤**Treatment**≥ ≤**IND**≥ Granted: October 1988
Indication: Relapsed or refractory acute lymphoblastic leukemia.
Sponsor: National Cancer Institute.
Market Approval Date: Not yet approved.

Drug: Ganciclovir
≤**Treatment**≥ ≤**IND**≥ Granted: November 1988
Indication: CMV retinitis in AIDS patients.
Sponsor: National Institute of Allergy and Infectious Diseases.
Market Approval Date: June 23, 1989.

Drug: Pentamidine Isethionate Aerosol
≤**Treatment**≥ ≤**IND**≥ Granted: February 1989
Indication: Prevention of Pneumocystis carinii penumonia (PCP) in AIDS patients who have recovered from an episode of PCP.
Sponsor: LyphoMed.
Market Approval Date: June 15, 1989.

Drug: Levamisole hydrochloride
≤**Treatment**≥ ≤**IND**≥ Granted: May 1989
Indication: For use (with 5-fluorouracil) as an adjuvant treatment for Dukes C adenocarcinoma of the colon.
Sponsor: National Cancer Institute.
Market Approval Date: Not yet approved.

Drug: Erythropoietin (EPO)
≤**Treatment**≥ ≤**IND**≥ Granted: June 1989
Indication: Treatment of AZT related anemia in HIV positive patients.
Sponsor: Ortho.
Market Approval Date: Not yet approved.

Drug: Exosurf (synthetic pulmonary surfactant)
≤**Treatment**≥ ≤**IND**≥ Granted: July 1989
Indication: Prophylactic treatment of newborns likely to develop respiratory distress syndrome and rescue treatment of newborns with confirmed RDS.
Sponsor: Burroughs Wellcome.
Market Approval Date: Not yet approved.

Drug: 2'3' dideoxyinosine (ddI)
≤**Treatment**≥ ≤**IND**≥ Granted: September 1989
Indication: Treatment of AIDS patients intolerant to AZT.
Sponsor: Bristol Myers.
Market Approval Date: Not yet approved.

Drug: Survanta (bovine pulmonary surfactant)
≤**Treatment**≥ ≤**IND**≥ Granted: October 1989
Indication: Prevention and treatment of respiratory distress syndrome in premature infants.
Sponsor: Ross Labs.
Market Approval Date: Not yet approved.

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Drug: zidovudine
≤**Treatment**≥ ≤**IND**≥ Granted: October 1989
Indication: Treatment of children under the age of 13 who have AIDS or are suffering from symptoms of advanced infection with the AIDS virus.
Sponsor: Burroughs Wellcome.
Market Approval Date: Not yet approved.

Drug: mannose terminated beta-glucocerebrosidase
≤**Treatment**≥ ≤**IND**≥ Granted: November 1989
Indication: Treatment of patients with chronic Gaucher's disease.
Sponsor: Genzyme Corporation.
Market Approval Date: Not yet approved.

Drug: fludarabine phosphate
≤**Treatment**≥ ≤**IND** Granted: November 1989
Indication: Chronic Lymphocytic Leukemia
Sponsor: National Cancer Institute
Market Approval Date: Not yet approved.

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[Title 21, Volume 5, Parts 300 to 499]
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TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES--C

PART 312--INVESTIGATIONAL NEW DRUG APPLICATION--Table of Contents

Subpart B--Investigational New Drug Application (**IND**)

Sec. 312.35 Submissions for **treatment** use.

(a) **Treatment** protocol submitted by **IND** sponsor. Any sponsor of a clinical investigation of a drug who intends to sponsor a **treatment** use for the drug shall submit to FDA a **treatment** protocol under Sec. 312.34 if the sponsor believes the criteria of Sec. 312.34 are satisfied. If a protocol is not submitted under Sec. 312.34, but FDA believes that the protocol should have been submitted under this section, FDA may deem the protocol to be submitted under Sec. 312.34. A **treatment** use under a **treatment** protocol may begin 30 days after FDA receives the protocol or on earlier notification by FDA that the **treatment** use described in the protocol may begin.

(1) A **treatment** protocol is required to contain the following:

(i) The intended use of the drug.

(ii) An explanation of the rationale for use of the drug, including, as appropriate, either a list of what available regimens ordinarily should be tried before using the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available marketed treatments.

(iii) A brief description of the criteria for patient selection.

(iv) The method of administration of the drug and the dosages.

(v) A description of clinical procedures, laboratory tests, or other measures to monitor the effects of the drug and to minimize risk.

(2) A **treatment** protocol is to be supported by the following:

(i) Informational brochure for supplying to each treating physician.

(ii) The technical information that is relevant to safety and effectiveness of the drug for the intended **treatment** purpose. Information contained in the sponsor's **IND** may be incorporated by reference.

(iii) A commitment by the sponsor to assure compliance of all participating investigators with the informed consent requirements of 21 CFR part 50.

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(3) A licensed practioner who receives an investigational drug for **treatment** use under a **treatment** protocol is an ``investigator'' under the protocol and is responsible for meeting all applicable investigator responsibilities under this part and 21 CFR parts 50 and 56.

(b) **Treatment IND** submitted by licensed practitioner. (1) If a licensed medical practitioner wants to obtain an investigational drug subject to a controlled clinical trial for a **treatment** use, the practitioner should first attempt to obtain the drug from the sponsor of the controlled trial under a **treatment** protocol. If the sponsor of the controlled clinical investigation of the drug will not establish a **treatment** protocol for the drug under paragraph (a) of this section, the licensed medical practitioner may seek to obtain the drug from the sponsor and submit a **treatment IND** to FDA requesting authorization to use the investigational drug for **treatment** use. A **treatment** use under a

treatment IND may begin 30 days after FDA receives the **IND** or on earlier notification by FDA that the **treatment** use under the **IND** may begin. A **treatment IND** is required to contain the following:

(i) A cover sheet (Form FDA 1571) meeting Sec. 312.23(g)(1).

(ii) Information (when not provided by the sponsor) on the drug's chemistry, manufacturing, and controls, and prior clinical and nonclinical experience with the drug submitted in accordance with Sec. 312.23. A sponsor of a clinical investigation subject to an **IND** who supplies an investigational drug to a licensed medical practitioner for purposes of a separate **treatment** clinical investigation shall be deemed to authorize the incorporation-by-reference of the technical information contained in the sponsor's **IND** into the medical practitioner's **treatment IND**.

(iii) A statement of the steps taken by the practitioner to obtain the drug under a **treatment** protocol from the drug sponsor.

(iv) A **treatment** protocol containing the same information listed in paragraph (a)(1) of this section.

(v) A statement of the practitioner's qualifications to use the investigational drug for the intended **treatment** use.

(vi) The practitioner's statement of familiarity with information on the drug's safety and effectiveness derived from previous clinical and nonclinical experience with the drug.

(vii) Agreement to report to FDA safety information in accordance with Sec. 312.32.

(2) A licensed practitioner who submits a **treatment IND** under this section is the sponsor-investigator for such **IND** and is responsible for meeting all applicable sponsor and investigator responsibilities under this part and 21 CFR parts 50 and 56.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910-0014)

[52 FR 19477, May 22, 1987, as amended at 57 FR 13249, Apr. 15, 1992]