出國報告（出國類別：其他）

參加「第四十一屆藥品資訊協會年會」

（The 41th Annual Meeting of Drug Information Association）

出國報告

服務機關：行政院衛生署中醫藥委員會

姓名職稱：康翠秀技正

派赴國家：美國

出國期間：民國九十四年六月二十五日至七月三日

報告日期：民國九十四年九月二十三日

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C09402445

公務出國報告提要

出國報告名稱：　　頁數：312 含附件：☑是□否

參加「第四十一屆藥品資訊協會年會（The 41th Annual Meeting of Drug Information Association）」

出國計畫主辦機關／聯絡人／電話

中醫藥委員會 洪翠英 02-25872828 ext267

出國人員姓名／服務機關／單位／職稱／電話

康翠秀 中醫藥委員會 研究發展組 技正 02-25872828 ext281

出國類別：□1 考察□2 進修□3 研究□4 實習☑5 其他

出國期間：民國九十四年六月二十五日至七月三日 出國地區：美國

報告日期：民國九十四年九月二十三日

分類號／目：J0／綜合　J3／醫療（醫藥類）

關鍵詞：藥品資訊、DIA、天然健康產品、植物藥

內容摘要：

雖現科技發達但西醫在治療疾病上仍有些瓶頸，且西藥爲化學藥物，副作用較

大，西藥新藥開發上遇到困境，促使國際間掀起天然藥物熱潮，回歸自然療法仰賴傳統醫學的醫療，鑒此，世界衛生組織(WHO)、美國藥物食品管理局（FDA）及歐盟陸續訂定傳統醫藥相關法規及成立相關管理單位，以利推動傳統醫藥及確保被適當安全且有效使用。行政院衛生署中醫藥委員會爲全國最高中醫醫政、中藥藥政最高主管機關，有必要瞭解國際間對植物藥及天然健康產品之發展策略包括：產品研發、管理政策及法規訂定..等最新資訊，俾利推動重要政策時將國際發展趨勢融入，另更加將我國推動中醫藥相關政績，如：執行迄今已成立 13 家「中藥臨床試驗中心」，並以類似美國 FDA 審核方式通過及核發新藥（中藥）藥證；建立中醫醫院訪查制度；傳統中藥廠全面實施 GMP；及公告出版台灣首部「臺灣傳統藥典」..等，與國際人士經驗交流。爰派員參加於美國華盛頓 DC 會議中心舉辦「第 41 屆藥品資訊協會年會」會期自 94 年 6 月 26 日至 30 日止爲期 5 天。藥品資訊協會（Drug Information Association；DIA）年會係討論全球藥品（含植物藥）及天然健康產品的研發、藥品安全的監測與流行病學等重要的主題，與會人士包括有歐、美、日各國產、官、學及研各方面領域專家代表；本次包括 30 個子題，300 個議題討論，除議題討論外，另有展覽場及壁報論文發表等。主要參加議題以天然健康產品（含植物藥）爲主，該議題主要討論各國對天然健康產品、飲食補充品及植物藥等法規規範及執行成效，藉由參與國際會議之機會，瞭解世界各國藥品及天然健康產品（含植物藥）研究動態與藥政管理，作爲未來推動台灣中醫藥產業發展之依據與參考，對我國中醫藥之現代化及國際化實有所助益。

本文電子檔已上傳至出國報告資訊網(http:// open.nat.gov.tw/reportwork)

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附錄二　Guidance for Industry Botanical Drug Products

附錄三　Directive 2004/24/EC

附錄四　HMPWP/31/99(Working Party on Herbal Medicinal Products)

壹、目的

行政院衛生署中醫藥委員會爲全國最高中醫醫政、中藥藥政最高主管機關，爲掌握國際對植物藥及天然健康產品之發展策略，包括：產品研發、管理政策及法規訂定..等最新資訊，俾利推動重要政策時將國際發展趨勢融入，另更加將我國推動中醫藥相關政績，如：執行迄今已成立 13 家「中藥臨床試驗中心」，並以類似美國 FDA 審核方式通過及核發新藥（中藥）藥證；建立中醫醫院訪查制度；傳統中藥廠全面實施 GMP；及公告出版台灣首部「臺灣傳統藥典」..等，與國際人士經驗交流，爰派員參加本次會議，藉由參與國際會議之機會，除與與會專家學者交流外，並瞭解世界各國藥品及天然健康產品（含植物藥）研究動態與藥政管理，作爲未來推動台灣中醫藥產業發展之依據與參考，對我國中醫藥之現代化及國際化實有所助益。

貳、過程

一、行程

日期	行程內容
6 月 25 日	台北---美國華盛頓 DC（於 Newark 轉機）
6 月 26 日-30	註冊及參加「第四十一屆藥品資訊協會年會」
7 月 1-3 日	美國華盛頓 DC--台北（於 Newark 轉機）

二、DIA 簡介

藥品資訊協會(DIA, Drug Information Association) 1964 年成立於美國馬里蘭州(Maryland)，至今已有四十年歷史，會員約有 30,000 人，每年舉辦超過 100 場次研討(或訓練)會議，其創會之宗旨，提供全球會員經驗分享、教育訓練等之平台，亦可將最新相關資訊透過年會、地區論壇及網路，提供會員在其領域中不斷吸收新知繼續成長。每年召開年會，討論有關生物技術、藥品及健康產品等，包括：藥品之研究開發、臨床試驗研究、資料管理、化學製造管制(CMC)、風險管理、法規事務、到藥品上市後之品質安全監測、不良反應等醫藥、技術、法規之議題，以利產、官、學及研界共同討論之全球性論壇，其成員來自歐洲、美國、日本、加拿大、東南亞、印度等國，屬於國際性之協會。

三、會議內容節錄

2005年第四十一屆藥品資訊協會年會於94年6月26日至6月30日在美國華盛頓DC國際會議中心舉行，參加人數約達4,400人，500多家廠商參展。大會內容相當豐富，包括：生物科技（Biotechnology）；研發策略（R&D Strategy）；天然健康產品（Natural Health Products）；廣告（Advertising）；法規事務（Regulatory Affairs）；GCP（Good Clinical Practices）；臨床試驗管理（Clinical Trial Management）；臨床資料管理（Clinical Data Management）；統計（Statistics）；訓練（Training）….等三十個議題，報告人主要參加之場次以天然健康產品（Natural Health Products）主題爲主，因此主題介紹植物藥及天然健康產品各國法規及品質管控，與本會業務較爲相關，本次年會總計約1100場口頭報告。報告人茲就與會內容節錄重點如

下：

開幕典禮

過程簡介：

會長致詞內容摘要：

大會由 DIA 會長 Dr. Fitzmartin 致歡迎詞及頒獎，頒發優良事業獎、傑出服務獎、特殊貢獻獎及研究優勝獎，受獎者大都爲對於 DIA 有極大貢獻之政府官員、學術界及產業界之精英等，頒獎後安排由美國白宮顧問 Dr. Healy 進行演說，於會中一再聲明，藥廠應以病人立場研發新藥，另藥價一定要透明化，才能助益於醫藥產業的正面發展；大會活動分爲三部份：議題討論、壁報論文發表及展覽，而天然健康產品此議題約分 10 個場次進行研討，報告人就以議題彙總重點節錄說明如下：

美國植物藥及天然健康產品相關法條規範：

近年來醫學科技發達，但西醫對一些疾病治療仍有些瓶頸，使得歐美對於「傳統醫學」的態度逐漸開放，有鑑於民眾仰賴傳統醫學的醫療日益增加，美國藥物食品管理局（Food & Drug Administration ；FDA）考量植物藥之藥品特殊性及具有悠久臨床使用經驗，在2000年公布植物藥規範草案，而2004年6月將此草案修正爲正式法案「植物藥品審查準則（Guidance for Industry Botanical Drug Products）」（如附錄二），並由FDA下藥物檢驗及研究中心（Center for Drug Evaluation and Research；CDER）執行此規範，FDA立該規範目的希望藉此賦予植物藥與其他藥

物的品質及臨床效用的保證，而將植物藥導入主流用藥之中，爲利審查作業，訂定「植物藥審查方針及程序手冊（Manual of policies and procedures for review of botanical drug products）」。

而美國FDA公佈植物藥品審查準則，針對具有潛力的傳統經驗方之草藥建立新的法規標準，如：具有廣泛人體使用經驗的植物藥品，可以減少或者延緩非臨床性測試，而證明過去人體使用經驗的相關文件中，提及過去的銷售歷史金額，相關文獻資料，在申請文件中，若明確記載人類過去使用狀況，這樣的植物藥可以不需動物毒性試驗而直接進入臨床，反之，若沒有過去豐富使用經驗，其成分毒性不瞭解者，則需進行動物毒性試驗，故對於中草藥而言可以縮短新藥開發時間，由西藥新藥開發時間約十年以上，將縮短約3-5年，其經費亦可大幅降低，因植物藥品審查準則公佈施行等於承認中藥可以當作藥品來用，只要依照準則進行臨床試驗，雖前置作業動物試驗可省略，放寬審核標準，但其臨床試驗一樣要比照西藥模式嚴謹，仍要求需科學驗證。DIA會中美國FDA官員 Dr.Vaccari及Dr.Chen表示，截至2005年6月1日止向美國FDA申請植物藥有242件，其中192件IND，50件PreIND，192件是在1999年至2005年申請；50件是在1990年至1998年申請，最近每個月約2-3件，約三分之二單方，三分之一爲複方，目前IND進行到PhaseⅢ很稀少，且目前未有NDA核准案，會中美國官員建議進行臨床試驗最好藥材同一批次，若無法則進行多批次，但批次間需收集相關數據，以作爲分析比較，且進行劑量評估，不要只進行單一劑量，最好有個範圍，另中藥複方加減方，未必減方就安全，中藥分君、臣、佐、使，因傳統中藥如此區分且使用千年應有其道理。

美國管理天然健康產品相關單位包括：食品藥物管理局（Food & Drug Administration ；FDA） ；聯邦貿易委員會（Federal Trade Commission；FTC；http://www.ftc.gov/） ；環境保護署（Environmental Protection Agency；EPA；http://www.epa.gov/ ；美國農業部（US Department of Agriculture ；USDA；http://www.usda.gov/)；藥物管制局（Drug Enforcement Administration ；DEA；http://www.usdoj.gov/）等單位，美國 1994 年公佈「飲食補充品健康和教育法案（Dietary Supplement Health and Education Act；DSHEA）」，明確地將飲食補充品（Dietary Supplement）與食品之間的差異加以區分，並明白地將「食品」、「飲食補充品（Dietary Supplement）」、「藥品（Drug）」三大類產品的管理範疇清楚地界定之。根據 DSHEA 的定義，飲食補充品是某一類特定的口服物品，可以作爲一般飲食的補充品之用。其種類包括維他命、礦物質、草藥及其他植物、胺基酸、可作爲補充日常飲食攝取總量不足之用的他類可供膳食之用的物質、及任何前述的濃縮品、代謝物、組成物、萃取物、或是組合。飲食補充品可以用錠劑（tablet）、膠囊（capsule）、粉末狀（powder）、軟膠囊（softgel）、膠囊錠（gelcap）、口服液（liquid）等形態出現，供食用者口服之用。飲食補充物僅能宣稱可以增強身體的構造或功能，並不能宣稱療效。而飲食補充品之特性包括：不以患者訴怨管理；不需要臨床資料；不在 FDA 檢查；不生產管理；批次間不一致性；不設最低品質限度。依 DSHEA 製造業者在飲食補充品上市前有責任保證它的安全性，通常製造業者在生產或銷售飲食補充品前不用在 FDA 註冊也不需 FDA 批准，飲食補充品上市後的安全性則 FDA 有權負責。

在美國藥物食品申請審核及廣告隸屬不同政府單位，藥物食品上市廣告由聯邦

貿易委員會（Federal Trade Commission；FTC）管理，其中最主要的兩個單位 (FDA及FTC) 之工作分工：

藥物食品管理局 Food & Drug Administration (FDA)	聯邦貿易委員會 Federal Trade Commission (FTC)
食物 OTC 藥品 醫學設備 飲食補充品 化妝品 處方藥品標記和 DTC(Direct-to-Consumer) 廣告 **上述相關的標籤**	食物 OTC 藥品 醫學設備 飲食補充品 化妝品 **上述相關的廣告**

爲讓廠商再刊登廣告可參考依據，美國政府將不能用之廣告用語刊登在FDA網站（www.fda.gov/cder/warn）上，供業者查詢參考。

加拿大天然健康產品相關法條規範：

會中Dr. Goldberg介紹加拿大對中草藥相關規範，屬於天然健康產品，他表示：在加拿大有40%以上成人使用替代醫療（包括傳統中醫藥），有50%以上成人使

用天然健康產品，其中30％爲草藥（包括中藥），因天然健康產品的性質介於藥物及食物間，成爲灰色地帶，政府管理複雜且不易，有鑑於此，加拿大特別設立天然健康產品理事會（Natural Health Products Directorate；NHPD），負責該產品相關事務[http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/nhpd-dpsn/index_e.html]，也於2004年1月公布施行天然健康產品規範（Natural Health Products Regulations），該法適用於天然健康產品之販售、製造、包裝、標示、進口、批發及儲存，若產品成分受食品及藥物法管制時，則不被視爲天然健康產品，該產品類型應由下列成分之一組成或混和而成，包括：1.植物或植物原料、藻類、細菌、真菌或非人類之動物原料；2.前述萃取或分離出的物質；3.本法所規定之任一種維他命；4.氨基酸、必需脂肪酸；5.前述第二項至第四項的人工合成物；6.礦物質或對人類有益之微生物（Probiotic）；7.前述任一物質之混合物；8.其他本法所規定之範圍。

在加拿大所有天然健康產品(NHPs)都必須取得"生產證明號(Drug Identification Number；DIN)"讓使用者得知該產品的配方、標籤及使用說明已經過及通過檢查，而最重要是讓使用者知道該產品是安全而且有功效。所有加拿大的天然健康產品(NHPs)的生產商，必須依照優良生產模式(GMP)的指引，由於加拿大政府准許天然健康產品可宣稱預防或治療疾病效果，故需進行臨床試驗，提出科學證據，臨床試驗需符合臨床試驗規範（GCP）。

Dr.Lui會中表示：中草藥在加拿大發展潛力大，在加拿大已超過3500種中醫藥產品上市（但97％進口中醫藥產品沒有DIN或天然健康產品號碼），因而成立加拿

大中醫藥研究學會(Canadian Institute of Chinese Medicinal Research) (CICMR)，對中醫藥進行研究。

歐洲植物藥相關法條規範：

因歐美崇尚自然療法，草藥逐漸在全球蔚爲風潮，爲此歐盟設立 Marketing Authorizations for herbal medicinal products (HMPs)審核草藥上市單位，於2004年4月30日公告「歐盟傳統植物藥註冊程序指令2004/24/EC」，並於2005年10月30日執行，並規定2004年4月30日以前無證照產品需在7年內符合該法條相關規定（2011年4月1日）。

目前只有少數中成藥獲得歐盟上市保健食品許可證，歐盟公布第2004/24/EC號指令對中藥以傳統植物藥品之名義進入歐盟的可行性增加。就傳統草藥產品事宜修訂原規定要在歐盟銷售任何藥品，生產商或銷售商須先通過測試及試用證明藥品的特性、成效和安全性，此舉會爲業者帶來沉重的財政負擔。生產商若能提出詳細的科學文獻資料證明有關藥品的效用，則可獲豁免。可是，即使推出已久的藥品，亦未必有足夠科學文獻資料證明其效用。有鑒於此，第2004/24/EC號指令提出一項特別的簡化藥品登記程序，即「傳統用途登記」，不過產品必須符合以下規例，方可在歐盟銷售：1. 必須是草藥製品(即主要成份包括一種或以上草藥物質或藥劑)；2.在歐盟成員國境內使用30年以上的傳統植物藥產品，或在歐洲已使用15年以上，且能提供該產品在歐盟以外的國家或地區應用30年以上證明，才能通過登記註冊，以傳統植物藥產品形式在歐洲銷售使用，否則廠商需進行藥理毒理及

臨床試驗，以證實符合歐盟相關規範，3.符合標籤要求供應商須在標籤上說明，該草藥的安全性和功效僅依賴長期應用和經驗所獲得等字樣，4.歐盟市場上從事藥品批發的廠商，必須要申請藥品批發營業執照，出口藥品的生產廠商必須通過歐盟GMP審查，且出口藥品的品質必須符合歐盟藥典標準。此外，只有在歐盟的業者(例如進口商)方可爲產品進行「傳統用途登記」。雖然登記程序已經簡化，但業者仍須提交多項資料，包括草藥製品成份的特性和數量資料；製造方法；治療指示和副作用；警告說明或風險；以及製造商獲准在原產地生產有關草藥製品的證明。另歐盟於2004年9月23日成立草藥產品委員會，負責確認傳統植物藥的作用及毒副作用，並將選擇一部份草藥，列出適應適應證、劑量、用藥途徑及安全資訊等。

在歐洲藥典收載114種植物；美國藥典收載27種植物，其中有16種重複，波蘭藥典收載65種植物，而人參及銀杏都有被摘錄，會中以印度大麻爲例，已在荷蘭被列爲合法處方藥，也進行2年品質管制研究，從GAP、CMC等進行相關研究，如何可重複生產及其再現性，此方法亦可適用於其他植物，而影響植物成分因素很多，包括：日月照差異；植物品種差異；肥料、栽種密度、收割時間、成長過程差異…等。

WHO鑑於藥用植物使用率增加，其品質控管日趨重要，故於2003年公佈「藥用植物優良栽種及採集規範(Good agricultural and collection practices(GACP)for medicinal plants)」，公佈此規範主要目的希望以科學方法來進行藥用植物的栽種與採集等過程，能被良好控管，以確保藥用植物的品質、安全及有效性，避免被污染等，此規範促使藥用植物品質提昇，提供極大保障，而源頭品質控制，對於後續臨床試驗等才能得到良好均一性。

目前有執行GAP國家包括：美國、加拿大、歐盟、日本及中國大陸等，也陸續公佈GAP相關規範，如：EMEA(European Medicines Evaluation Agency) [http://www.emea.eu.int/]公布HMPWP/31/99(Working Party on Herbal Medicinal Products)法規，規範重點包括：植物種類（確認品種），生長環境、收割時間、處理植物過程、貯存及運輸條件、品質管制等。

中國大陸中草藥相關法條規範：

眾所周知中國大陸爲全球中草藥栽種及使用最多之國家，而在草藥熱潮各國一致提出品質管制之重要性，冀能達到安全、均一及再現性，爲此中國大陸推動執行 GAP，公佈於 2002 年 6 月起實施「中藥生產質量管理規範（試行）」，該規範包括：產地生態環境、種質和繁植材料、栽培與養殖管理、採收與加工、運輸與貯藏、質量管理、人員和設備及文件管理等項，並在 2004 年國家食品藥品監督管理局公佈「中藥材檢查公告（2 號）」，會中 Dr. Hu 表示在大陸 GAP 執行者（農夫），大多只有小學畢業且大多爲個體戶，故在品質上較難控管，此爲執行 GAP 困難處，並介紹目前在大陸執行 GAP 成功個案爲匯仁集團，從 GAP、GMP 至 GLP 其相關控管機制，並制訂檢核表，以利能達到所謂安全、均一及再現性，另中國大陸依據「中華人民共和國藥品管理法」及「中華人民共和國藥品管理法實施條例」，於 2005 年 5 月 1 日起公佈實施「藥品註冊管理辦法」，由國家食品藥品監督管理局執行，該局主管全國藥品註冊工作，負責對藥物臨床試驗、藥品生產和進口進行審批。

其他國家草藥發展：

DIA會中Dr.Gupta及Dr.Mukherjee介紹現全球其他較爲風靡的草藥，如：拉丁美洲草藥及印度醫學..等，拉丁美洲草藥亦很盛行，因其需求量大，而大量栽種，未控制栽種品質，且缺乏物種資訊及知識，對栽種植物的真正特性不瞭解，只有傳統的認知，此部分是該單位需加強的，因該草藥使用多年，有多年使用經驗，故申請健康產品上市較易，若要以藥的身份申請則需通過較嚴謹法規，拉丁美洲草藥其申請專利遍及各國，申請日本有592件；美國254件；世界智慧財產權組織（World Intellectual Property Organization；WIPO）94件；歐洲36件。

印度醫學起掘於西元前900年，約有2000多種類的藥，1800種植物，85％是複方，17000植物花，2000種常被用；4500-5000種常被鄉村人民使用；8000種其他部落使用，目前印度醫學歸「健康及家庭福利署（Ministry of Health and Family Welfare Government）」管，而Dr.Mukherjee認爲發展印度醫學所面臨挑戰包括：1.缺乏有效之實證背景；2.缺乏分析方法；3.缺乏國際國家標準，以確保安全有效；4.缺乏品質控制。

其他綜論：

Dr.Smith會中表示：33%的飲食補充品使用者不使用藥品，25%民眾感覺藥品是不安全，而會使用天然產品。

化學藥產品與植物用藥產品之差異：

化學產品	植物用藥產品
界限分明的組成 非傳統使用 通常專利保護的物質 專利保護的指示 保護的臨床資料(有 5 年)在美國 OTC	擷取，粉狀物，… 可長期傳統使用 罕有專利保護的擷取物 罕有專利保護的指示 保護的臨床資料是問題 （可能無此資料）

飲食補充品、天然健康產品及藥品銷售路徑：

醫生	**大賣場**(食物，藥品和 Wal-Mark/目標)	**天然健康產品專賣店**	**多層次傳銷**
實質上全部處方藥品 販賣其他產品最少	實質上全部 OTC ~40% 的飲食補充品	40%的飲食補充品 非藥品	12%的飲食補充品 非藥品

中草藥取得專利有其障礙，相較於西藥專利申請案，中草藥申請較不亦獲准專利，因其是天然物。

參、心得

參加此次國際會議，更加實際瞭解現各國對植物藥及天然健康產品熱潮，如：加拿大史無前例全球僅有，開放天然健康產品可宣稱具醫療效果，在符合天然健康產品規範下，只要廠商能證明其產品具有預防或治療某種疾病即可申請上市（但須提出科學證據），歐美各國已警覺到天然健康產品及中草藥市場潛力無窮，紛紛制訂或修改相關法規，以達到除能確保民眾健康外，亦能促進產業發展，而台灣中草藥具有悠久歷史，在歐美各國對此法規較寬鬆，而植物藥的研發應是契機，可針對目前西藥較無治療效果的疾病進行研發，如癌症、免疫疾病..等，且要選對市場而非侷限在台灣市場，需放眼國際，應是將台灣中草藥打入國際市場的大好時機，迎合趕上此優勢，可達到事半功倍。

台灣在政府大力推動下，特別是行政院衛生署中醫藥委員會，已有產品通過及核發新藥（中藥）藥證，而台灣市場小，且需面臨中西醫使用之爭議及健保未給付等問題，相關配套措施並未很完善，像德國其草藥研發及制度都有不錯配套措施，如草藥有 54%被列入健保給付，46%爲成藥，亦有草藥被列爲處方用藥，如銀杏銷售連續佔全球之冠等都值得我國借鏡。台灣應與國際公司合作，在 DIA 會中 Dr. Pittner 表示在歐洲對中草藥部分極度興趣，但他們極度缺乏具臨床試驗經驗之中醫師參與合作，故我國若能以此切入與國際性公司合作，將能獲得很好機會。

本次行程收穫豐碩，除了見識到所謂國際會議外，透過豐富專題研討，了解全球對植物藥熱潮，同時藉由大會開闢許多不同領域的小型討論會及晚宴之機會，與世界各國的專家交換經驗，報告人攜帶本會之英文簡介、VCD 及英文簡報

資料，予與會人士，在會中與演講者 Dr.Smith 交換意見及名片時，他很贊同中醫所提陰陽調和，故在公司 Logo 上亦有陰陽太極符號，2-3 位學者專家建議本會在下屆 DIA 年會上發表台灣在中草藥方面努力成果，或許可透過本會，協助我國業者與各國進一步有合作之機會。

會中 Dr.Smith 建議草藥可先以飲食補充品的身份申請上市，因申請植物藥至少約 5 年，方能上市，而飲食補充品只要 1 年即可，且植物藥進行 PhaseⅢ需花費 30-50 百萬美金；而飲食補充品只要 10 萬美金即可。

綜合本次 DIA 會議中有關各國對天然健康產品相關法規如下：

國別	法條
美國	植物藥品審查準則（Guidance for Industry Botanical Drug Products）(http://www.fda.gov/cder/guidance/4592fnl.pdf) 植物藥審查方針及程序手冊（Manual of policies and procedures for review of botanicals）http://www.fda.gov/cder/mapp/6007.1.pdf 飲食補充品健康和教育法案（Dietary Supplement Health and Education Act；DSHEA） （http://www.fda.gov/opacom/laws/dshea.html）
加拿大	天然健康產品規範（Natural Health Products Regulations）

	（http://laws.justice.gc.ca/en/F-27/SOR-2003-196/）
世界衛生組織	藥用植物優良栽種規範(Good agricultural and collection practices(GACP)for medicinal plants) http://whqlibdoc.who.int/publications/2003/9241546271.pdf
歐盟	歐盟草藥指令 Directive 2004/24/EC 第 2001/83/EC 號指令 http://medicines.mhra.gov.uk/ourwork/licensingmeds/herbalmeds/thmpd_final.pdf HMPWP/31/99(Working Party on Herbal Medicinal Products [http://www.emea.eu.int/pdfs/human/hmpwp/003199en.pdf]
中國大陸	中藥材生產質量管理規範（試行） 中華人民共和國藥品管理法 藥品註冊管理辦法

肆、建議事項

一、 積極參與國際性研討會及組織，除有助於提昇能見度，與各國專家學者作良好之互動，以建立日後交流互訪之基礎外，並可獲得更多管理、法規及最新動向等資訊，以掌握世界趨勢及培養國際觀。

二、 建議我國參與相關國際會議，以產、官、學、研代表共同組團，用有組織有計畫方式參與相關會議，國際會議大多是各國產官學研菁英參與，參與人員除想得新知外，亦是想尋找合作機會，故以組團方式前往，可有效率達到合作契機，如：即時就可談論產官學研如何配合，以達到事半功倍，並向國際舞台展現我國的企圖心及競爭力。

三、 在擬訂我國中醫藥產品查驗登記之相關法規建議多參採國際相關規定，以瞭解掌握其趨勢能與國際同步，使我國中草藥之法規國際化、管理與全球一致性，利業者遵循，提昇我國製藥業之競爭力，使我國中醫藥能達到國際水準。

四、 台灣生技產業蓬勃發展，生技公司如雨後春筍般成立，而部分生技公司從事中草藥產品之研發，但公司規模較小，若要將產品成功打入國際市場，應策略聯盟，並將中藥先以保健食品先上市打入國際，再以植物藥產品，最後甚至爲藥品，而政府單位對於國際間有關中草藥法規，如植物藥及健康產品等譯文宣導至業界，讓其更瞭解國際法規，以利長遠發展，政府應提供業界策略聯盟之平台。

五、 綜合上述，國際間掀起天然藥物熱潮，世界衛生組織(WHO)、美國 FDA 及歐盟陸續成立相關管理單位，各國致力推動傳統醫藥，以確保適當安全且有效使用，在世界衛生組織及國際積極發展傳統醫藥、中醫藥生物科技蓬勃發展及爲國人使用中草藥安全把關，應順應世界潮流，在政府組織改造之際建議維持中醫藥委員會位階之專責機構，以利臺灣中醫藥發展，促進中

醫藥現代化及國際化，並落實 WHO 對傳統醫藥之全球策略，以確保民眾就醫及用藥安全，使民眾得到更優質的中醫藥服務。

伍、誌謝

感謝行政院衛生署中醫藥委員會提供經費補助，以及本會林主任委員宜信、羅主任秘書淑慧及謝伯舟組長給予機會，從參與本次國際會議中亦學習到不少寶貴的經驗及具國際觀。

陸、附錄

附錄一　第四十一屆藥品資訊協會年會議程

附錄二　Guidance for Industry Botanical Drug Products

附錄三　Directive 2004/24/EC

附錄四　HMPWP/31/99(Working Party on Herbal Medicinal Products)

Guidance for Industry

Botanical Drug Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
June 2004

Chemistry

Guidance for Industry

Botanical Drug Products

Copies of this Guidance are available from:

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Internet at http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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Chemistry

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Contains Nonbinding Recommendations

Guidance for Industry[1]
Botanical Drug Products

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance explains when a botanical drug may be marketed under an over-the-counter (OTC) drug monograph and when FDA regulations require approval for marketing of a new drug application (NDA), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 355(b). In addition, this document provides sponsors with guidance on submitting investigational new drug applications (INDs) for botanical drug products, including those botanical products (or *botanicals*) currently lawfully marketed as foods (including conventional foods and dietary supplements) in the United States.

This guidance also discusses several areas in which, because of the unique nature of botanicals, FDA finds it appropriate to apply regulatory policies that differ from those applied to synthetic, semisynthetic, or otherwise highly purified or chemically modified drugs (including antibiotics derived from microorganisms). This latter group of drug substances is referred to in this guidance as synthetic or highly purified drugs. Therefore, when the recommendations on a specific topic discussed in this guidance differ from those in other existing guidances (e.g., *Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances*, 1987),[2] this guidance takes precedence. In particular, this guidance states that applicants may submit reduced documentation of nonclinical (preclinical) safety and of chemistry, manufacturing, and controls (CMC) to support an IND for initial clinical studies of

[1] This guidance has been prepared by working groups in the Medical Policy, Pharmacology and Toxicology, and Complex Drug Substances Coordinating Committees in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

[2] FDA has issued a draft guidance entitled *Drug Substance: Chemistry, Manufacturing, and Controls Information*, which, when finalized, will replace the 1987 guidance (see 69 FR 929, January 7, 2004).

botanicals that have been legally marketed in the United States and/or a foreign country as dietary supplements without any known safety concerns.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Botanical products are finished, labeled products that contain vegetable matter as ingredients.[3] A botanical product may be a food (including a dietary supplement), a drug (including a biological drug), a medical device (e.g., gutta-percha), or a cosmetic under the Act. An article is generally a food if it is used for food (21 U.S.C. 312(f)(1)). Whether an article is a drug, medical device, or cosmetic under the Act turns on its "intended use" (21 U.S.C. 312(g)(1)(B) and (C), (h)(2) and (3), (i)). "Intended use" is created by claims made by or on behalf of a manufacturer or distributor of the article to prospective purchasers, such as in advertising, labeling, or oral statements.

For the purposes of this document, the term *botanicals* includes plant materials, algae, macroscopic fungi, and combinations thereof. It does not include:

- Materials derived from genetically modified botanical species (i.e., by recombinant DNA technology or cloning).
- Fermentation products (i.e., products produced by fermentation of yeast, bacteria, and other microscopic organisms, including when plants are used as a substrate, and products produced by fermentation of plant cells), even if such products are previously approved for drug use or accepted for food use in the United States (e.g., antibiotics, amino acids, and vitamins).
- Highly purified substances (e.g., paclitaxel) or chemically modified substances (e.g., estrogens synthesized from yam extracts) derived from botanical sources.

This guidance addresses all botanical drug products (in all dosage forms) that are regulated under the Act, except those also regulated under section 351 of the Public Health Service Act (42 U.S.C. 262). Although this guidance does not address drugs that contain animals or animal parts (e.g., insects, annelids, shark cartilage) and/or minerals, either alone or in combination with botanicals, many scientific principles described in this guidance may also apply to those products. When a drug product contains botanical ingredients in combination with either (1) a synthetic or highly purified drug or (2) a biotechnology derived or other naturally derived drug, this guidance only applies to the botanical portion of the product.

[3] *Botanical product* and other terms used in this guidance are defined in the Glossary for use in this guidance only; these definitions may not be appropriate in other contexts.

III. GENERAL REGULATORY APPROACHES

Many botanical products are used widely in the United States. Depending on its labeling and intended use, a botanical product can be a food, a dietary supplement, and/or a drug. Botanicals used for food and consumed primarily for their taste, aroma, or nutritive value (e.g., lettuce, herbs used as seasonings) are regulated as foods. Botanicals can also be dietary supplements if they are labeled as dietary supplements and otherwise meet the dietary supplement definition in section 201(ff) of the Act (21 U.S.C. 321(ff)).

If a botanical product is intended for use in diagnosing, mitigating, treating, or curing disease, it is a drug under section 201(g)(1)(B) of the Act and is subject to regulation as such. If a botanical product is intended to prevent disease, it is also a drug under section 201(g)(1)(B), except that a product that bears a health claim authorized in accordance with section 403(r) of the Act (21 U.S.C. 343(r)) is not a drug solely because its labeling contains such a claim. If the intended use of a botanical product is to affect the structure or function of the human body, it may be regulated either as a dietary supplement or as a drug, depending on the circumstances.

Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), an orally ingested product that meets the definition of a "dietary supplement" under section 201(ff) of the Act may be lawfully marketed with a statement that (1) claims a benefit related to a classical nutrient deficiency disease (and discloses the prevalence of the disease in the United States), (2) describes how the product is intended to affect the structure or function of the human body, (3) characterizes the documented mechanism by which the product acts to maintain such structure or function, or (4) describes general well-being from consumption of the product (section 403(r)(6)(A) of the Act).[4] A dietary supplement statement of the type described above may not claim to diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases (section 403(r)(6) of the Act).[5]

If a botanical product is intended to affect the structure or function of the body but does not meet the definition of a dietary supplement, or does not meet the requirements for making a structure/function claim under section 403(r)(6) of the Act, it is subject to regulation as a drug under section 201(g)(1)(C) of the Act. As noted above, a botanical product is subject to regulation as a drug under section 201(g)(1)(B) of the Act if it is intended for use in diagnosing, mitigating, treating, curing, or preventing disease (except for a product marketed with certain health claims authorized under section 403(r) of the Act). Under section 505(b) of the Act, a

[4]The manufacturer must have substantiation that such statement is truthful and not misleading (section 403(r)(6)(B) of the Act) and must notify FDA that the statement is being used no later than 30 days after the first marketing of the dietary supplement with the statement (section 403(r)(6) of the Act). In addition, the statement must be accompanied by the following disclaimer: "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease" (section 403(r)(6)(C) of the Act). FDA regulations at 21 CFR 101.93(b)-(e) prescribe the required format and placement of the disclaimer in dietary supplement labeling.

[5]FDA regulations at § 101.93(g) define *disease* for purposes of this provision and set forth what types of statements FDA will consider to be claims to diagnose, mitigate, treat, cure, or prevent disease.

drug must be marketed under an approved NDA[6] unless the product is excluded from the definition of a new drug under section 201(p) of the Act. Certain products that FDA determines are generally recognized as safe and effective in accordance with section 201(p) may be marketed under FDA′s OTC drug monograph system.

A. Marketing Under OTC Drug Monograph Versus Approved NDA

A botanical drug product may be marketed in the United States under (1) an OTC drug monograph or (2) an approved NDA or ANDA. A botanical product that has been marketed in the United States for a material time and to a material extent for a specific OTC drug indication may be eligible for inclusion in an OTC drug monograph codified in
21 CFR parts 331-358. The manufacturer would need to submit a petition in accordance with 21 CFR 10.30 to amend the monograph to add the botanical substance as a new active ingredient.

Under current regulations, if there is no marketing history in the United States or a foreign country for a botanical drug product,[7] if available evidence of safety and effectiveness does not warrant inclusion of the product in an OTC drug monograph, or if the proposed indication would not be appropriate for nonprescription use, the manufacturer must submit an NDA to obtain FDA approval to market the product for the proposed use (sections 201(p) and 505 of the Act). An NDA for a botanical drug could seek approval for either prescription or OTC use, depending on the indication and characteristics of the product and whether it is safe for use outside of the supervision of a practitioner licensed by law to administer it. If existing information on the safety and effectiveness of a botanical drug product is insufficient to support an NDA, we recommend that new clinical studies be conducted to demonstrate safety and effectiveness.[8]

When a final OTC drug monograph is published for a specific use of a botanical drug, any person may market a product containing the same substance and for the same use, provided the labeling and other active ingredients (if present) are in accord with all relevant monographs and other applicable regulations. In contrast, when a product is approved under an NDA, the approval is specific to the drug product that is the subject of the application (the applicant's drug product), and the applicant may be eligible for

[6]Under section 505(j) of the Act, a botanical drug product may also be marketed as a generic drug under an abbreviated new drug application (ANDA). The *generic* version of the previously approved drug would have to be both pharmaceutically equivalent and bioequivalent to such drug. For information on the submission of ANDAs, see FDA regulations in 21 CFR parts 314 and 320 as well as Agency guidance documents.

[7]FDA has issued a final rule that establishes criteria and procedures by which conditions may become eligible for inclusion in the OTC drug monograph system (67 FR 3060, January 23, 2002). Among other things, the final rule addresses how FDA considers *foreign* marketing data in determining whether a drug has been used under particular conditions to a material extent and for a material time (as required under section 201(p) of the Act) to qualify for inclusion in an OTC drug monograph.

[8]See 21 CFR 312.20 (concerning requirement for an IND).

marketing exclusivity for either 5 years (if it is a new chemical entity) or 3 years from the time of approval, even in the absence of patent protection. A new botanical drug (containing multiple chemical constituents) may qualify as a new chemical entity under § 314.108(a). If a product qualifies as a new chemical entity, during the period of exclusivity, FDA will not approve, or in some cases even review, certain competitor products unless the second sponsor conducts all studies necessary to demonstrate the safety and effectiveness of its product and submits a 505(b)(1) application. Therefore, if a person wishing to market a botanical drug product that is not included in an existing OTC drug monograph desires marketing exclusivity for the product, the person should seek approval of an NDA rather than petition the Agency to amend a monograph. Attachment A contains a schematic showing different regulatory approaches that can be taken for marketing botanical drug products in the United States, including OTC drug monograph and NDA procedures.

B. CMC Information for Botanical Drug Products

Botanical drug products have certain unique characteristics that should be taken into account in the application of FDA regulations and guidance. Botanical drugs are derived from vegetable matter and are usually prepared as complex mixtures. Their chemical constituents are not always well defined. In many cases, the active constituent in a botanical drug is not identified, nor is its biological activity well characterized. Therefore, the CMC documentation that should be provided for botanical drugs will often be different from that for synthetic or highly purified drugs, whose active constituents can be more readily chemically identified and quantified. For example, FDA would expect an NDA for a synthetic or highly purified drug to identify the active ingredient. However, it would not be essential for the sponsor of a botanical drug to identify the active constituents (although FDA recommends that this be done if feasible). Even if the sponsor were to eventually identify the active constituents in the NDA, the active constituents might not be identified during the IND stage.

Because of the complex nature of a typical botanical drug and the lack of knowledge of its active constituent(s), FDA may rely on a combination of tests and controls to ensure the identity, purity, quality, strength, potency, and consistency of botanical drugs. These tests and controls include (1) multiple tests for drug substance and drug product (e.g., spectroscopic and/or chromatographic fingerprints, chemical assay of characteristic markers, and biological assay), (2) raw material and process controls (e.g., strict quality controls for the botanical raw materials and adequate in-process controls), and (3) process validation (especially for the drug substance).

C. CMC and Toxicology Information to Su pport Initial Studies

Many botanical products are legally available in the United States as dietary supplements. Given the wide availability of such products outside of clinical trials, it is important to assess the effectiveness of such products. To support initial clinical trials, the nonclinical pharmacology and toxicology information that must be provided under 21 CFR 312.22(b) for legally available botanical products with no known safety issues (see

section VI.A) may be markedly reduced compared to that expected for synthetic or highly purified new drugs that are not legally marketed and for which there is no prior human experience. In most cases, additional toxicology and CMC data will not be required for such initial trials.

D. Applicability of Combination Drug Regulations

Botanical drug products that are derived from a single part of a plant (e.g., leaves, stems, roots, or seeds), or from a single species of alga or macroscopic fungus (e.g., a mushroom), are not considered to be fixed-combination drugs within the meaning of 21 CFR 300.50 and 330.10(a)(4)(iv). Consequently, they do not have to meet the requirements for combination drugs, principally the need to demonstrate that each component or active ingredient makes a contribution to claimed effects.

Botanical drugs composed of multiple parts of a single species of plant, alga, or macroscopic fungus, or of parts from different species of plants algae, or macroscopic fungi, currently are subject to the combination drug requirements. However, FDA is considering revising its regulations to allow for the exemption of such botanical drugs from application of the combination drug requirements under certain circumstances.

IV. MARKETING A BOTANICAL DRUG UNDER AN OTC DRUG MONOGRAPH

A botanical product that has been marketed in the United States for a material time and to a material extent for a specific OTC indication may be eligible for consideration in the OTC drug monograph system. Currently, there are several botanical drugs, including cascara, psyllium, and senna, that are included in the OTC drug review. For a botanical drug substance to be included in an OTC drug monograph, there must be published data establishing general recognition of safety and effectiveness, usually including results of adequate and well-controlled clinical studies (see §§ 314.126(b) and 330.10). Requirements related to safety, effectiveness, and labeling for drugs to be included in an OTC drug monograph are set forth in 21 CFR part 330.

A request to amend an OTC drug monograph to include a botanical substance must be submitted by citizen petition in accordance with §§ 10.30 and 330.10(a)(12). There should be publicly available quality standards for such a botanical drug substance in the drug section (i.e., not in the National Formulary or other nondrug sections) of the *United States Pharmacopeia* (USP).[9] In the absence of a USP drug monograph, the petitioner should include suitable quality standards for the botanical drug substance in its citizen petition and simultaneously propose adoption of those standards in the USP. Additional criteria and procedures by which a botanical drug substance may become eligible for inclusion in the OTC drug monograph system are set forth in § 330.14. FDA regulations on current good manufacturing practices (CGMPs) apply to all OTC drug monograph products, including any listed botanical drug products (see § 330.1(a)).

[9]However, a botanical drug's conformance to the standards of the USP or any other official compendium does not establish that the botanical is safe, effective, and not misbranded for its intended use as a drug.

For further information on the OTC drug monograph approach to marketing a botanical drug product, sponsors are encouraged to contact CDER′s Division of Over-the-Counter Drug Products (HFD-560).

V. MARKETING A BOTANICAL DRUG UNDER AN NDA

A botanical drug product that is not generally recognized as safe and effective for its therapeutic claims is considered a new drug under section 201(p) of the Act. Section 505(a) of the Act requires any person wishing to market a botanical drug product that is a new drug to obtain FDA approval of an NDA or ANDA for that product. According to section 505(d) of the Act and § 314.50, an NDA must contain substantial evidence of effectiveness derived from adequate and well-controlled clinical studies, evidence of safety, and adequate CMC information. The format of an NDA submission and the requirements for its various sections are set forth in part 314 and discussed in several CDER guidance documents.

VI. INDS FOR BOTANICAL DRUGS

If available information is insufficient to support an NDA for a botanical drug, the sponsor will need to develop further data. An IND is required under section 505(i) of the Act and 21 CFR part 312 (unless exempt under § 312.2(b)) when a botanical product is studied in the United States for a drug use (see section 201(g) of the Act), even if such study is intended solely for research purposes. Under § 312.22, an IND must contain sufficient information to demonstrate that the drug product is safe for testing in humans and that the clinical protocol is properly designed for its intended objectives.

A. IND Information for Different Categories of Botanicals

Under § 312.22(b), the amount of information that must be submitted in an IND for a particular drug product depends on, among other things, the novelty of the drug, the extent to which it has been studied previously, the drug product′s known or suspected risks, and the developmental phase of the drug. Sections VII and VIII of this guidance describe the information that we recommend a sponsor provide in meeting the requirements in § 312.23 for an IND for initial (i.e., phase 1 and phase 2) clinical studies of a botanical drug. As noted above, for botanicals legally marketed under the DSHEA, there will often be very little new CMC or toxicological data needed to initiate such trials, as long as there are no known safety issues associated with the product and it is to be used at approximately the same doses as those currently or traditionally used or recommended. A botanical drug is considered to have a known safety issue when FDA has evidence that it produces serious and/or possibly life-threatening effects. Nonclinical evaluation to characterize toxicities may be appropriate for products with known safety issues. For example, nonclinical data may be appropriate to help establish safe doses and to determine ways to better monitor potential toxicities in humans. Such nonclinical studies may be needed early in development (see § 312.23(a)(8)).

Properly conducted early clinical investigations, including controlled effectiveness trials in phase 2, will allow a determination of whether there is a clinical effect worth pursuing and will provide a more systematic evaluation of safety than previously available. If a botanical drug product shows promise of effectiveness in such early trials, the potential for wider use for particular purposes will create a need for greater assurance of product quality and consistency and for expanded (i.e., phase 3) clinical studies of safety and effectiveness (§ 312.22(b)). IND information appropriate for expanded clinical studies of botanical drugs is discussed in section IX.

Under § 312.22(b), the IND sponsor of a botanical product that has been previously marketed but *not* in the United States must provide sufficient additional information to assist FDA in determining the safety of the product for use in initial clinical studies (section VII). Such additional information is appropriate under that regulation because these products are not already marketed in the United States and evidence of safety should be provided before patients are exposed to them.

This guidance also addresses the type of information that should be provided under § 312.22 in INDs for initial studies on botanical products that have not been lawfully marketed anywhere or have known safety issues (section VIII). In contrast to botanical products that have been marketed in some form, considerably less information may be available on the safety of a new botanical product that has not been marketed anywhere as a food or dietary supplement and has not been tested as a drug in humans. Consequently, it is appropriate that, under § 312.22(b), sponsors of INDs for initial trials of botanical products that have not previously been lawfully marketed anywhere, or for which there are known safety issues, provide certain additional information to FDA.

The information to be provided in an IND for a botanical drug product is illustrated schematically in Attachment B and discussed in this section and sections VII-IX below. FDA encourages sponsors of INDs for initial studies of botanical drugs to seek input from CDER review divisions (organized based on the therapeutic classes of the drugs) to ensure that the appropriate information is submitted and that the clinical protocols are well designed. Many guidance documents specific to particular indications or dosage forms are also available from the respective review divisions.

FDA may place an IND for initial studies of a botanical drug on clinical hold (i.e., an order issued by the Agency to delay a proposed clinical study) if it finds that the IND does not contain sufficient information required under § 312.23 to assess the risk to subjects of the proposed studies (§ 312.42(b)(1)(iv)). However, the lack of any specific item of information listed in § 312.23 for a phase 1 study will not necessarily justify imposing a clinical hold. Possible grounds for a clinical hold are set forth in § 312.42(b) and discussed in CDER′s guidance for industry on *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products* (November 1995).

B. Basic Format for INDs

The format and general requirements for IND submissions are stated in § 312.23 and discussed in several CDER guidance documents, including the phase 1 guidance referenced above. These requirements are summarized below, with guidance on the specific types of information that we recommend sponsors of botanical drug products provide to meet these requirements:

1. *Cover Sheet (see § 312.23(a)(1))*

2. *Table of Contents (see § 312.23(a)(2))*

3. *Introductory Statement and General Investigational Plan (see § 312.23(a)(3))*

4. *Investigator's Brochure (see § 312.23(a)(5))*

5. *Protocols (§ 312.23(a)(6))*

Section 312.23(a)(6) requires information on protocols for planned studies. In general, clinical evaluation of botanical drug products for safety and effectiveness does not differ significantly from evaluation of synthetic or highly purified drugs. For study results to be interpretable, clinical studies must be well designed and carefully executed (see § 314.126). A sponsor need not differentiate the clinical effects of each molecular entity in a botanical product derived from a single part of a plant (see section III.D, Applicability of Combination Drug Regulations). Even where the components of a combination product must be studied under § 300.50, initial controlled studies could be used to evaluate the entire combination product. For additional information on the clinical development of new drugs, see the CDER guidance *Format and Content of the Clinical and Statistical Sections of an Application* (July 1988) and other guidances related to the submission of applications involving specific drug classes and diseases.

Clinical studies of botanical products may pose special problems associated with the incorporation of traditional methodologies, such as selection of doses and addition of new botanical ingredients based on response, that will need to be resolved. In almost all cases, credible studies will be randomized, double blind, and placebo-controlled (or dose-response) (see § 314.126). Studies with only active controls may be appropriate when it is unethical to use a placebo, as would be the case in serious and life-threatening conditions for which there is established effective therapy. However, active studies pose special difficulties in interpretation and should be used only when a placebo cannot be used and there is good reason to expect the botanical treatment to be effective. With respect to serious illnesses for which there is established effective therapy, we generally encourage sponsors to use an "add-on" design for the initial trials: The botanical product would be compared to a placebo, each being added to the standard treatment. For symptomatic disorders where the use of a placebo poses no ethical problem, placebo-controlled trials should almost always be conducted because active control trials are particularly difficult to interpret in such situations. Having a concurrent active treatment

group in addition to placebo control (e.g., a three-armed study) is advisable in certain cases (as in psychiatric trials) to verify the assay sensitivity of the study. The sponsor is encouraged to consult International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidance *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2000).

For botanical as well as for synthetic or highly purified drugs, absolute safety does not exist for any therapeutic intervention, and FDA must assess risks in light of potential clinical benefits (see § 312.22). For more comprehensive information on safety evaluations, see other CDER guidance documents. As is the case for synthetic or highly purified drugs, the best safety data on newly developed botanicals will be derived from controlled efficacy trials, but for chronic indications, long-term, open-label extensions also will be important. For chronic conditions, exposures of at least 6-12 months' duration are usually appropriate (see ICH guidance *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions* (March 1995)).

Section VII.E of this guidance provides recommendations on the protocol design of initial clinical trials for botanical products legally marketed under the DSHEA. Sections VIII.E and IX.E provide information on the design of initial clinical trials for nonmarketed botanical drug products and for expanded studies on all botanical drug products, respectively.

As with any clinical study, appropriate human research subject protections must be followed, including submission of the protocol to an institutional review board (IRB) and obtaining proper informed consent (see 21 CFR parts 56 and 50). Pursuant to § 50.25, the consent form should describe any procedures that are experimental along with a description of the risks, benefits, and alternatives of taking the product. We recommend that the consent form acknowledge any lack of additional chemical or toxicological characterization.

6. Chemistry, Manufacturing, and Controls (§ 312.23(a)(7))

The requirements for the content and format of the CMC section of an IND are stated in § 312.23(a)(7)(iv)*(a)-(e)*. These regulations require documentation of the drug substance, drug product, placebo, labeling, and an environmental analysis.

Plant materials used in the production of botanical drug products often are not completely characterized and defined or are prone to contamination, deterioration, and variation in composition and properties. In many cases, the active constituent in a botanical drug is not identified, nor is its biological activity well characterized. Therefore, in contrast to the situation with synthetic or highly purified drug products, it may be difficult to ensure the quality of a botanical drug by controlling only the corresponding drug substance and drug product. To ensure that a botanical drug product used in clinical trials is of consistently good quality, and that sufficient information exists to meet the requirements

of § 312.23(a)(7)(iv), the sponsor should have, in addition to final product testing, appropriate quality controls for the botanical raw materials. The manufacturing process should be well defined, with adequate in-process controls, especially for the drug substance.

As noted in section III.C, sponsors of initial clinical trials on botanical products that have been legally marketed as dietary supplements and that do not have safety issues can submit less CMC information than must be provided under §§ 312.22(b) and 312.23(a)(7)) for later studies or for studies on products not previously marketed. Section VII.B describes the CMC information that generally will be necessary under § 312.23(a)(7) for initial trials on previously marketed botanicals without safety issues.

To comply with §§ 312.22(b) and 312.23(a)(7), sponsors must submit additional CMC information for initial studies of nonmarketed botanical products and marketed botanicals with safety issues (see section VIII.B) and for expanded trials on all botanical products (see section IX.B). Additional guidance (not specific to botanical drugs) on the submission of CMC information in INDs and marketing applications can be found in other CDER guidance documents.

In the initial stage of clinical studies of a botanical drug, it is generally not necessary to identify the active constituents or other biological markers or to have a chemical identification and assay for a particular constituent or marker. Identification by spectroscopic and/or chromatographic fingerprinting and strength by dry weight (weight minus water or solvents) can be acceptable alternatives. Attributes for lot or batch release testing should be determined as the clinical study progresses, although appropriate acceptance criteria for batch release need not be established until later in phase 3 studies. Batch analyses on clinical batches should be submitted as they become available, to demonstrate batch-to-batch consistency and to help establish appropriate acceptance criteria for fingerprinting. Identification of active constituents is helpful in optimizing manufacturing procedures, ensuring batch consistency, and contributing to an understanding of the clinical effects of the botanical product. Therefore, when feasible, active constituents should be identified during phase 3 studies.

A single formulation (i.e., one in which the components or ingredients and composition of the drug substance and drug product are kept constant) and a single dosage form should be used throughout the different stages of the clinical trials unless this proves impossible. Screening of a number of sources/batches for product quality is recommended to ensure that the material used in initial trials will yield interpretable results that can be used to guide later development. Once a batch or source of acceptable quality is identified, sufficient quantities should be obtained to sustain the initial clinical trials. This is especially important if the sponsor does not have access to the manufacturing and controls information on the botanical drug substance and finished product. In addition, sufficient quantities of the botanical raw material and drug substance from the same batch should be retained for future chemical characterization and/or pharmacological/toxicological testing. It is also important to obtain the botanical drug product from a source willing to provide FDA with detailed manufacturing and

controls information when needed, or as clinical evaluation of the product progresses. These factors are crucial if the sponsor intends to pursue FDA approval for a new drug application for the botanical product.

Consistency should be maintained when multiple batches are used in the nonclinical and clinical trials. It also is important that the material used in phase 1/2 trials be verified for its authenticity (see VIII.B.1 below). Samples from phase 1/2 studies should be retained for comparison with batches to be used in the phase 3 trials to ensure consistency. Bridging studies (clinical and/or nonclinical) should be performed if the use of batches with different characteristics in different phases cannot be avoided.

Botanical raw materials may sometimes be dispensed at clinics on an as needed or by prescription basis and subsequently prepared by patients themselves at home. We recommend avoiding these practices during clinical trials if at all possible because data related to such use may not be reliable because of variability in preparation by patients. When absolutely necessary, dispensing in such a manner may be considered for initial clinical studies. But as clinical trials are expanded, the botanical drug product should be produced in a controlled manner by an established manufacturer to ensure the validity and reliability of data.

If previously available nonclinical and/or clinical data are provided or referenced in the IND, a comparison should be made of the botanical drug products used in the referenced studies, the products to be used in the proposed trials, and (if appropriate) the products intended for marketing (including their corresponding botanical raw materials, drug substances, and formulations).

If a synthetic or highly purified drug or a biotechnology- or other naturally derived (non-botanical) drug is added to a botanical drug product, the CMC data for this added substance should be described or cross-referenced according to § 312.23(b) and guidances. Under § 312.23(a)(7), animal parts (e.g., insects, annelids, shark cartilage) or minerals that are combined with a botanical in a drug product, must be accompanied by additional manufacturing and controls information specific to these materials because they are part of the drug substance being studied.

CMC information on a botanical raw material, drug substance, and/or drug product may be submitted by the sponsor as part of the IND or by the manufacturer (if different from the sponsor) in a drug master file (DMF). A DMF is a submission from a manufacturer to FDA that may be used to provide confidential information on a human drug (§ 314.420(a)). The information contained in a DMF may be cross-referenced to support an IND or NDA and is reviewed and used by FDA only when authorized by the manufacturer. However, the sponsor relying on information in a DMF should have adequate acceptance testing (e.g., identification test, assay) before accepting the raw material, drug substance, or drug product received from the DMF holder for further processing or for use in humans directly.

7. Pharmacological and Toxicological Information (§ 312.23(a)(8))

The content and format for pharmacological and toxicological information to be provided in an IND are described in § 312.23(a)(8). Nonclinical pharmacology and toxicology studies are useful in guiding early clinical studies and in predicting the potential toxicity of a new drug.

Ordinarily, less nonclinical information will be required to support the initial clinical trials of currently marketed orally ingested botanical products than is expected for synthetic or highly purified drugs. For a botanical product that is not currently lawfully marketed in the United States, but is administered orally and prepared, processed, and used according to methodologies for which there is prior human experience, sufficient information may be available to support initial clinical studies without standard nonclinical testing. However, for a botanical drug with a route of administration other than oral, additional pharmacology/toxicology information may be necessary before initial clinical studies.

After initial clinical studies, further pharmacology and toxicology studies of a botanical drug generally would be needed before later phases of clinical development and before approval for marketing. Sections VII.C, VIII.C, and IX.C provide details on the pharmacological and toxicological information that should be provided for clinical trials on botanical drugs.

8. Previous Human Experience With the Product (§ 312.23(a)(9))

Under § 312.23(a)(9), an IND sponsor must submit information about previous human experience with an investigational drug. Many botanical products have been marketed or tested in clinical studies (often involving few patients). When such studies have been conducted, data from the studies must be included in an IND for a botanical drug to assist FDA in its overall safety assessment. Sections VII.A, VIII.A, and IX.A of this guidance provide additional recommendations on the submission of information on previous human experience with a botanical product.

VII. INDS FOR PHASE 1 AND PHASE 2 CLINICAL STUDIES OF LAWFULLY MARKETED BOTANICAL PRODUCTS WITHOUT SAFETY CONCERNS

This section provides more detailed guidance on the submission of certain types of information for INDs for initial clinical studies on botanical products that have been lawfully marketed and that do not raise safety issues (for drugs with known safety concerns, see section VIII). This section also notes where additional information must be provided under § 312.22(b) when an IND is for a botanical product that has been marketed in one or more foreign countries but not the United States.

A. Description of Product and Documentation of Human Use

1. Description of Botanicals Used (§ 312.23(a)(3)(i))

The following information should be provided for ***each*** of the botanical raw materials used as ingredients in a botanical drug product:

- Common or usual names of the plant, alga, or macroscopic fungus
- Synonyms (e.g., Latin, Greek, English, Spanish, Chinese)
- Name of variety, species, genus, and family, including the name of the botanist who first described the species or variety, if known
- Chemical class of the active constituent (the chemical constituent that is responsible for the claimed pharmacological activity or therapeutic effect) or characteristic marker (a chemical constituent used for identification and/or quality control purposes), if known

2. History of Use (§ 312.23(a)(3)(ii),(a)(9))

The sponsor should include information found in historical sources (e.g., books of medical practice in Ayurveda, traditional Chinese medicine, Unani, Sida) and scientific literature about the prior human use of the botanical product, and each of its ingredients, in traditional foods and drugs. Any literature submitted must be provided in English (and in its original language, if other than English) (§ 312.23(c)).

3. Current Marketed Use (§ 312.23(a)(3)(ii), (a)(9))

The sponsor must include information about the nature and extent of the current worldwide use of the botanical product, and each of its ingredients, in foods and drugs, including evidence concerning its marketing experience in the United States and/or foreign countries. For a foreign-marketed botanical product, the sponsor should provide data that verify its safe human use, including proof of the annual sales volume, an estimate of the size of the exposure population, and the rate of adverse effects.

B. Chemistry, Manufacturing, and Controls

Outlined below is the CMC information that we recommend you submit, in meeting the requirements of § 312.23(a)(7), in an IND to support a phase 1 or phase 2 clinical trial on a botanical product that is currently lawfully marketed without any known safety issues in the United States and/or a foreign country. Literature references and relevant official compendia or published standards should be provided whenever possible.

1. Botanical Raw Material (§ 312.23(a)(7)(i))

The information discussed in section VII.A.1 should be provided for all currently lawfully marketed products. It is important for the safe conduct of clinical trials to

ensure the proper identity of botanical raw materials used in the trials. Since there is no history of U.S. experience for botanical raw materials marketed only outside the United States, a certificate of authenticity of the plant and plant parts should be provided for such materials. A trained professional who is competent to determine authenticity should sign this certificate. This information also should be provided, if available, for a botanical raw material marketed in the United States.

*2. Botanical Drug Substance (§ 312.23(a)(7)(iv)(*a*))*

The general method of preparation (e.g., pulverization, decoction, expression, aqueous extraction, or ethanolic extraction) must be provided under § 312.23(a)(7)(iv)(*a*). This is especially important where more than one process exists in the literature on which the safety of the botanical drug substance is based.

*3. Botanical Drug Product (§ 312.23(a)(7)(iv)(*b*))*

A botanical drug product is manufactured from a botanical drug substance by adding one or more excipients, mixing, blending, granulating, tableting, encapsulating, or performing other dosage-form-specific procedures, followed by packaging. When packaged without further processing, a botanical drug substance is considered the drug product. We recommend that the following information be provided for a botanical drug product:

- A qualitative description of the finished product, including the dosage form, route of administration, names of all ingredients (i.e., botanical drug substance and excipients), and a statement that the product is not adulterated with potent, toxic, or addictive botanical substances, synthetic or highly purified drugs, biotechnology-derived drugs, or other naturally derived drugs.

- The composition or quantitative description of the finished product (i.e., the quantity of the botanical drug substance and each excipient, if any) expressed in terms of amount per dosage unit. We recommend that sponsors provide this information in tabular form.

Example for a single-herb botanical drug product

Component	Amount per tablet	Amount per batch
Senna leaf extract (8:1 powdered aqueous extract)	250 mg	10.0 kg (equivalent to 80.0 kg of dried leaves)
Excipient 1	100 mg	4.0 kg
Excipient 2	10 mg	0.4 kg

The amount may also be expressed on the basis of amount of botanical raw material (e.g., weight of dried leaves).

Component	Amount per tablet	Amount per batch
Senna	250 mg (equivalent to 2000 mg dried leaves)	10.0 kg (equivalent to 80.0 kg of dried leaves)
Excipient 1	100 mg	4.0 kg
Excipient 2	10 mg	0.4 kg

Example for a multi-herb botanical drug product:

Component	Amount per tablet	Amount per batch
A 5:1 powdered, aqueous extract from 1:1 mixture of *Forsythia suspensa* Vahl. flowers and *Lonicera japonica* Thunb. fruits	600 mg	24 kg
Excipient 1	100 mg	4.0 kg
Excipient 2	10 mg	0.4 kg

- The manufacturer′s certificate of analysis for the study product or, if none is available, authorization to allow FDA to cross-reference the manufacturer's previous submission for the relevant CMC information. If this information is unavailable for a foreign-marketed product, the sponsor should perform quality testing on the product according to the recommendations listed under section VIII.B.3. In addition to those tests, heavy metal analysis, and an animal safety test (see below), if applicable, should be performed. The test methods and results should be provided in the IND. The study product should be from a single source and, where feasible, from a single batch. A product sample from the batch to be used in the clinical study should be retained for possible future testing by FDA and/or the sponsor.

4. Animal Safety Test (§ 312.23(a)(8))

An animal safety test (different from the rabbit pyrogen test, USP <151>) is an acute animal toxicity test applied only to injectable drug products. We recommend that this test be performed for crude extracts from natural sources, especially when the raw material, process, and final product cannot be fully characterized and controlled.

5. Placebo (§ 312.23(a)(7)(iv)(c)*)*

The components of any placebo used must be described.

6. Labeling (§ 312.23(a)(7)(iv)(d)*)*

The following labeling information must be provided:

- A copy of the container label and the immediate outer carton label of the marketed product to be used in the clinical study.

- A mock or printed representation of the proposed container label that will be provided to the investigators in the proposed clinical study. It should contain the following information: protocol number; patient number; sponsor′s name; product name or code number; strength and/or potency; recommended storage conditions; lot number; and (as required under § 312.6) the statement, "Caution: New drug -- Limited by Federal law to investigational use." In a placebo-controlled clinical trial, both the study drug and the placebo should be properly labeled to protect the integrity of the blinded study.

*7. Environmental Assessment or Claim of Categorical Exclusion (§ 312.23(a)(7)(iv)(*e*))*

A claim for categorical exclusion from the requirement for preparation of an environmental assessment (EA) ordinarily can be made for an IND (21 CFR 25.31(e)).

C. Pharmacology/Toxicology Information

1. All Marketed Botanical Products

Under § 312.23(a)(8), previous human experience and available animal toxicity data concerning the clinical formulation and the individual botanical ingredients within the formulation must be provided to support initial clinical trials (phase 1 and phase 2) of a botanical drug product for the proposed use. As noted in section VI.A, initial studies for botanical products with no known safety concerns and that have been marketed in the United States as dietary supplements may generally be conducted without further pharmacologic/toxicologic testing. Nevertheless, available information should be provided. A database search should be conducted, when feasible, to identify information relevant to the safety and effectiveness of the following:

- the final formulation of the intended commercial botanical drug product
- the individual botanical ingredients
- the known chemical constituents of the botanical ingredients.

Under § 312.23(a)(8)(ii), an integrated summary of available data from medical and toxicological databases (e.g., Medline, Toxline, TOMES, RTEC) must be submitted for review. Using the information gathered from this literature, the sponsor should address, as appropriate for the proposed study, the following issues concerning the botanical drug product:

- general toxicity
- target organs or systems of toxicity

- teratogenic, carcinogenic, or mutagenic potential of any botanical ingredient in the product
- relationship of dosage and duration to toxic responses
- pharmacological activity.

2. Foreign-Marketed Botanical Products

For the reasons discussed in section VI, additional information must be provided in accordance with § 312.22(b) for a botanical product that has been previously marketed but not in the United States. In addition to the information listed above, the sponsor should provide data that support safe human use and should include the annual sales volume, an estimate of the size of the exposure population, and available data on the rate of adverse effects. The nature of nonclinical pharmacology/toxicology information needed before a sponsor conducts an initial clinical study will be determined on a case-by-case basis, depending on the indications, proposed dose, duration and size of study, and available data supporting safe human experience.

D. Bioavailability

Pharmacokinetic and pharmacodynamic information is helpful in the design and interpretation of clinical studies. Since botanical products often consist of more than one chemical constituent and the active constituents are often unknown, standard pharmacokinetic measurements to demonstrate systemic exposure to a product in animals and/or humans may be difficult to obtain. However, when feasible, sponsors are encouraged to monitor the blood levels of known active constituents, representative markers, or major chemical constituents in a botanical drug product (see section IX.D).

E. Clinical Considerations

The initial clinical trial for a botanical product currently marketed under the DSHEA will ordinarily be a well-controlled study capable of demonstrating effectiveness. Because the product is marketed and the dose that is thought to be appropriate and well tolerated is known, there should be little need for pilot or typical phase 1 studies, and uncontrolled observations are unlikely to be useful. Sponsors are therefore strongly encouraged to initiate more definitive trials early in the development program to determine whether a botanical product has efficacy for one or more claimed indications. Safety data should be collected during the trials. If there is doubt about the best dose of the product tested, a randomized, parallel, fixed-dose, dose-response study may be particularly useful as an initial trial.

Regarding the safety of the drug, a botanical preparation lawfully marketed in the United States will generally be considered acceptable for at least short-term (e.g., up to several months) use in clinical trials. For foreign-marketed botanical products, safety considerations will be based on available CMC, pharmacology, and toxicology information, as well as indications, proposed doses, duration and size of the study, and available data supporting safe human use.

VIII. INDS FOR PHASE 1 AND PHASE 2 CLINICAL STUDIES FOR NONMARKETED BOTANICAL PRODUCTS AND PRODUCTS WITH KNOWN SAFETY CONCERNS

This section discusses the type of information that we recommend be provided in meeting the requirements for INDs for initial trials of botanicals that (1) have not previously been lawfully marketed in the United States or elsewhere or (2) that have been marketed and have known safety issues.

A. Description of Product and Documentation of Human Use

In addition to the information outlined in section VII.A.1-2, the following should be provided in accordance with the listed subsections of § 312.23 for each raw material contained in a botanical product not lawfully marketed in either the United States or other countries:

1. Description of Botanicals Used (§ 312.23(a)(3)(i))

- Morphological and anatomical description (including gender, if applicable) and a photograph of the plant or plant part, alga, or macroscopic fungus used
- Natural habitat and geographical distribution of the plant, alga, or macroscopic fungus
- Current sources of the plant, alga, or macroscopic fungus, including its geographical location and whether it is cultivated or harvested from the wild
- A statement indicating whether the species is any of the following:
  - Determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora;
  - Entitled to special protection under some other Federal law or international treaty to which the United States is a party;
  - The critical habitat of a species that has been determined to be endangered or threatened

2. History of Use (If Any) (§ 312.23(a)(3)(ii), (a)(9))

- Method of preparation, processing, and formulation

- Routes, schedules, and doses of administration
- Medical claims
- Contraindications and adverse events associated with use in humans and animals
- Traditional geographical areas and populations in which such use occurred
- A description of the similarities and/or differences between the traditional preparation and the proposed clinical formulation

3. Current Investigational Use (If Any) (§ 312.23(a)(3)(ii), (a)(9))

- Proposed therapeutic claim and dose regimen (mg/kg/dose and dose/day)
- All available information in the literature that addresses the proposed therapeutic claim, including both positive and negative studies

B. Chemistry, Manufacturing, and Controls

Outlined below is the CMC information that should be submitted, in meeting the requirements of § 312.23(a)(7), in an IND to support a phase 1 or phase 2 clinical trial using a botanical product that is not currently lawfully marketed in the United States or a foreign country, or for which there are known safety issues.

1. Botanical Raw Material (§ 312.23(a)(7)(i))

A botanical drug substance can be derived from one or more botanical raw materials. The following recommendations apply to each individual botanical raw material used.

The botanical raw material should be described as outlined in sections VII.A.1 and VIII.A.1. If the botanical raw material has no documented history of use, the IND sponsor should so indicate. The following information should be provided:

- Identification by trained personnel of the plant, plant parts, alga, or macroscopic fungus used, including organoleptic, macroscopic, and microscopic examination. The identification should be done against a voucher specimen (reference specimen). If more than one variety of a given species is used, each should be specified. A sample of the plant, plant parts, or other botanical materials should be retained and stored under appropriate conditions by the raw material supplier and botanical drug substance manufacturer for each batch. These samples will be used for verification of identity, if needed.
- A certificate of authenticity

- A list of all grower(s) and/or supplier(s) (including names and addresses). The following items should be provided for each grower/supplier, if available:

  – Harvest location

  – Growth conditions

  – Stage of plant growth at harvest

  – Harvest time

  – Collection, washing, drying, and preservation procedures

  – Handling, transportation, and storage conditions

*2. Botanical Drug Substance (§ 312.23(a)(7)(iv)(*a*))*

The following information should be provided for all botanical drug substances, regardless of whether they are prepared from one or more botanical raw materials:

- A qualitative description of the drug substance, including the name, appearance, physical and chemical properties, active constituent (if known), biological activity (if known), and clinical indication (if known) of each botanical raw material. If the active constituent, biological activity, and/or clinical indication is unknown, the IND sponsor should clearly so state. In the case of a multi-herb substance, the sponsor should state whether the drug substance is prepared by combining individually processed botanical drug substances or by processing combined botanical raw materials.

- The quantitative description (strength) of the drug substance. Historically, the strength of a botanical drug substance is expressed simply as the absolute dry weight of the processed substance. The batch size and the yield of the process, relative to the botanical raw material, also should be indicated. Furthermore, where the active constituents or other chemical markers are known and measurable, the amount in which they are present in the botanical drug substance should be declared. For a multi-herb substance, its composition should be expressed in terms of the relative ratio of the individually processed botanical drug substances or of the botanical raw materials before processing, whichever is appropriate.

- The name and address of the drug substance manufacturer (processor).

- A description of the manufacturing process for the botanical drug substance. The description should include the quantity of botanical raw material, solvents, extraction and/or drying, and yield. The yield of the process, expressed as the amount of the original botanical raw material relative to the amount of the extract, also should be

indicated. If more than one botanical raw material is introduced to produce a multi-herb substance, the quantity of each raw material and the sequence of addition, mixing, grinding, and/or extraction should be provided. If a multi-herb substance is prepared by combining two or more individually processed botanical drug substances, the process leading to each botanical drug substance should be described separately.

- The quality control tests performed on each batch of the drug substance, the analytical procedures used, and the available test results. These tests should include, but need not be limited to, the following attributes:

  – Appearance

  – Chemical identification by spectroscopic and/or chromatographic fingerprints. Examples of spectroscopic methods include ultraviolet, infrared, Fourier transformed infrared, and mass spectroscopy. Examples of chromatographic methods include high performance liquid chromatography (HPLC), HPLC with diode array detection, thin layer chromatography (TLC), 2-dimensional-TLC, and gas chromatography.

  – Chemical assay (i.e., assay) for active constituents or characteristic markers. If several botanical raw materials are combined to produce a multi-herb substance and a quantitative determination of each individual active constituent or marker is infeasible, a joint determination can be made for several active constituents or markers. When multiple active constituents or markers are known, they should be chemically characterized and their relative amounts should be defined.

  – Biological assay (when the active chemical constituent(s) are not known or quantifiable), if available. If the botanical drug substance is considered potent (i.e., highly active), toxic, addictive, or has abuse potential (e.g., ephedra or marijuana), an assay for biological activity and/or a chemical assay for the active constituent(s) should be performed.

  – Strength by dry weight (equivalent to botanical raw material)

  – Heavy metals

  – Microbial limits

  – Animal safety test, if applicable

- A description of the container/closure in which the botanical drug substance is to be stored and/or shipped.

- Available stability data on the drug substance. The sponsor should develop stability-indicating analytical methods and conduct stability studies as the IND progresses.

- The container label, which should reflect the qualitative and quantitative description of the botanical drug substance, as discussed above, and recommended storage conditions. Examples of labeling for single-herb and multi-herb substances are shown below:

  Single-herb substance:

  – Expressed in terms of yield:
  Senna, 10 kg, equivalent to 80 kg of dried leaves
  or
  Senna, 10 kg, 8:1 (w/w) powdered extract of dried leaves

  – Expressed in terms of active constituents:
  Senna, 10 kg extract, containing 2 kg of hydroxyanthracene glycosides (sennosides), calculated as sennoside B

  – Expressed in terms of chemical markers:
  Valerian, 10 kg extract, containing 0.1 kg valerinic acid

  Multi-herb substance:

  – Prepared by combining individually processed botanical drug substances:
  Lonicera japonica Thunb. and *Forsythia suspensa* Vahl., 6 kg, containing 3 kg of *Lonicera japonica* Thunb. 4:1 solid extract and 3 kg of *Forsythia suspensa* Vahl. 6:1 solid extract

  – Prepared by processing combined botanical raw materials:
  Lonicera japonica Thunb. and *Forsythia suspensa* Vahl., 6 kg, a 5:1 powdered extract prepared from 15 kg of *Lonicera japonica* Thunb. and 15 kg of *Forsythia suspensa* Vahl

*3. Botanical Drug Product (§ 312.23(a)(7)(iv)(*b*))*

The following information should be provided:

- A qualitative description of the finished product (see section VII.B.3.)

- The composition, or quantitative description, of the finished product (i.e., the name and quantity of the botanical drug substance and of each excipient (if any), expressed in terms of amount per dosage unit and amount per batch). This information should be provided in tabular form. A quantitative description of the drug substance should be provided as described in section VIII.B.2.

Example:

Component	Amount per tablet	Amount per batch
Senna	250 mg (equivalent to 2000 mg dried leaves)	10.0 kg (equivalent to 80.0 kg of dried leaves)
Excipient 1	100 mg	4.0 kg
Excipient 2	10 mg	0.4 kg

- The name and address of the manufacturer of the finished drug product

- A description of the manufacturing process. (If the botanical drug substance is filled and packaged directly as the finished product without the addition of excipients and further processing, this item and items listed in the immediately preceding two bullets will not apply.)

- A list of the quality control tests performed on each batch of the drug product, and the analytical procedures used and the available test results. These tests should include, but need not be limited to, the following attributes:

  – Appearance

  – Chemical identification by spectroscopic and/or chromatographic fingerprints

  – Assay for active constituents or characteristic markers, if available. If several botanical raw materials are combined to produce a multi-herb substance and a quantitative determination of each individual active constituent or marker is infeasible, a joint determination can be carried out for several active constituents or markers. When multiple active constituents or markers are known, they should be chemically characterized and their relative amounts should be defined.

  – Biological assay (when the active chemical constituent(s) are not known or quantifiable), if available. If the botanical drug substance is considered potent (i.e., highly active), toxic, addictive, or has abuse potential (e.g., ephedra or marijuana), an assay for biological activity and/or a chemical assay for the active constituent(s) should be performed.

  – Strength by dry weight (of drug substance)

  – Microbial limits

  – Other attributes specific to the dosage form of interest (e.g., dissolution for solid oral dosage forms, sterility and nonpyrogenicity for parenterals, animal safety test for parenterals, when appropriate).

- A description of the container/closure in which the drug product is to be packaged

- Available stability data on the drug product. The sponsor should develop stability-indicating analytical methods (using markers when feasible) and conduct stability studies as the IND progresses.

4. Placebo (see section VII.B.5)

5. Labeling (see section VII.B.6)

Additionally, a quantitative description of the drug substance per dosage unit (as described in section VIII.B.2.h and 3.b) should be provided. An example of a quantitative description for a multi-herb botanical drug product is shown below:

BRAND X. 100 tablets. Each 1-gram tablet contains:
300 mg of *Lonicera japonica* Thunb.4:1 solid extract and
300 mg of *Forsythia suspensa* Vahl. 6:1 solid extract

6. Environmental Assessment or Claim of Categorical Exclusion

A claim for categorical exclusion from the requirement for preparation of an EA ordinarily can be made for an IND (§ 25.31(e)). However, 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 (21 CFR 25.21; 40 CFR 1508.4). CDER will evaluate INDs on a case-by-case basis when the drug or biological product is derived from wild plants or animals to determine whether the extraordinary circumstance provision in § 25.21 is applicable. FDA encourages early consultation with the Agency on environment-related aspects of a requested action, especially one that involves harvesting a wild species, to ensure that planning and decisions reflect environmental values, avoid delays later in the process, and avoid potential conflicts (§ 25.10(b) and (c)). For additional information, see 21 CFR part 25, 40 CFR parts 1500-08, and the CDER/CBER guidance for industry on *Environmental Assessment of Human Drug and Biologics Applications* (July 1998). An environmental assessment or a claim for categorical exclusion must be provided as required under § 25.15(a).

C. Nonclinical Safety Assessment

1. Traditional Preparations

Nonclinical pharmacology and toxicology studies are particularly important in establishing the safety of a new botanical drug for which there is no current marketing experience. The information is used for assessing the botanical drug's risk-to-benefit ratio, guiding early clinical studies, and predicting potential toxicity.

Because of their extensive use in humans, there may be sufficient information on

traditional herbal medicines to support initial clinical studies without standard nonclinical testing. Therefore, such products may require fewer nonclinical safety studies under § 312.23(a)(8) than would be expected for synthetic or highly purified drugs with which there is little experience.

A traditional herbal preparation, which may have evolved over time, generally has the following characteristics:

- It meets official compendia or other published standards in terms of the botanical identity and plant part used for each botanical raw material.
- In the case of a multi-herb substance, it is composed of the same formulation as a historical formula, with the amount of each botanical ingredient falling within the range of traditional usage.
- It is prepared by the same processing methodology as traditionally used.
- It is used in the traditional manner in terms of therapeutic indication, route and schedule of administration, and quantities or doses.

For initial clinical studies on a botanical drug product that is not currently lawfully marketed in the United States or elsewhere but is prepared, processed, and used by humans according to an established methodology, sufficient information might be available to support the studies without standard nonclinical testing. In general, the considerations listed under section VII.C are applicable. When the initial clinical study for such a drug shows promising results and further clinical development of the drug is intended, pharmacology and toxicology studies carried out prior to the later phases of the clinical trials may be needed to support a risk-benefit assessment and to identify potential toxicities not readily detected in clinical studies (see section IX.C below).

2. Others

For a botanical product that is not prepared according to a traditional methodology, the extent of variation from the traditional formulation, preparation, or processing should be described in full detail. The nature of nonclinical pharmacology/toxicology information needed before conducting an initial clinical study (in addition to that described under section VII.C) will be determined on a case-by-case basis, depending on the indications, extent of safe human experience, and safety concerns about the new formulation, preparation, or processing methodology used.

3. Products with Known Safety Issues

For those botanical drugs for which there are known safety issues, the nature of the nonclinical pharmacology/toxicology information needed will be determined on a case-by-case basis to address those issues (see section VI.A).

D. Bioavailability

Pharmacokinetic and pharmacodynamic information is helpful in the design and

interpretation of clinical studies. As stated in section VII.D, a botanical product's active constituents may be unknown, and standard pharmacokinetic measurements to demonstrate systemic exposure to a product in animals and/or humans may be infeasible due to the complexity of the botanical drug. However, when feasible, a sponsor is encouraged to monitor the blood levels of known active constituents, representative markers, or other major chemical constituents in a botanical drug product. Because there is less human use experience with botanical products that have never been lawfully marketed than with those that have been, a sponsor of a drug that has not been lawfully marketed should consult FDA's guidances *Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro* (April 1997) and *In Vivo Drug Metabolism/Drug Interaction Studies—Design, Data Analysis, and Recommendations for Dosing and Labeling* (November 1999) to assess potential drug-drug interaction when a clinical study includes co-administration with another drug (see section IX.D).

For a botanical product that is prepared according to traditional methodology, the nature of clinical pharmacology information needed should be determined on a case-by-case basis, depending on the indications, extent of human experience, target patient population, and projected length of clinical use.

E. Clinical Considerations

In general, initial clinical investigations of nonmarketed botanical preparations should be similar to those of marketed products (see section VII.E). Because of the lack of current marketing experience, however, greater concerns could exist about toxicity. Therefore, FDA will seek greater assurance of the safety of the product for initial clinical trials in the United States. Such assurance may be provided in the form of additional chemical analysis and/or additional toxicology data. It may also be helpful to provide documentation of the product′s previous safe human use by referencing literature and/or pharmacopoeias.

IX. INDS FOR PHASE 3 CLINICAL STUDIES OF ALL BOTANICAL PRODUCTS

When conducting expanded (i.e., phase 3) clinical studies on a botanical drug product, an IND sponsor is expected to provide more detailed information on CMC and nonclinical safety than when conducting a phase 1 or phase 2 study (§ 312.22(b), 312.23(a)(7)(i) and (8)). The better definition of the product will ensure an ability to apply data from trials to a well-controlled, reproducible substance. The additional toxicology data are needed to support wider use. This additional information should be provided regardless of whether the product is currently lawfully marketed in the United States or elsewhere as a dietary supplement.

For phase 3 clinical studies of a botanical product, the following information should be provided in meeting the requirements of § 312.23:

A. Description of Product and Documentation of Human Experience

See sections VII.A and VIII.A for guidance on how to describe the botanical product and human experience with it.

B. Chemistry, Manufacturing, and Controls

To support phase 3 clinical trials of a botanical product, regardless of its marketing experience in the United States or other countries, the following CMC information should be provided in accordance with § 312.23(a)(7) unless already submitted in the IND for phase 1/phase 2 studies on the product:

1. Expanded Clinical Studies

a. Botanical raw material

- A description of the botanical raw material as outlined in sections VII.A.1 and VIII.A.1. If the botanical has no documented history of use, this should be indicated. Proper identification by trained personnel of the plant, plant parts, alga, or macroscopic fungus used, including organoleptic, macroscopic, and microscopic examination, should be provided. The identification should be done against a voucher specimen (reference specimen). If more than one variety or source of a given species is used, they should be blended in a fixed proportion in a consistent manner. A sample of the plant, plant parts, or other botanical materials should be retained for every batch by the raw material supplier and drug substance manufacturer, and stored under appropriate conditions for future verification of identity. In addition, a certificate of authenticity and information on the grower and/or supplier, growing conditions (including pesticides used), harvest location, harvest time (including stage of plant growth at harvest), handling, and shipping should be provided.
- A spectroscopic and/or chromatographic fingerprint of each botanical raw material and the chemical identity of the active constituents or characteristic markers in the botanical raw material
- The name and address of the botanical raw material manufacturer (processor)
- A description of the preparation of the botanical raw material, including collection, washing, drying, preservation, and/or detoxification and preservation procedures. Equipment and quantity used, temperature employed, processing time, in-process controls, and yield should be specified.
- The quality control tests and analytical procedures applied by the botanical raw material supplier, and the proposed acceptance criteria. These tests should include, but need not be limited to, the following attributes:

  – Botanical identification

  – Chemical identification by spectroscopic and/or chromatographic fingerprint

  – Chemical identification for active constituents or characteristic markers if

active constituents are not known

– Assay for active constituents or characteristic markers if active constituents are not known

– Biological assay (when the active chemical constituents are not known or quantifiable), if available

– Heavy metals

– Microbial limits

– Residual pesticides, including parent pesticides and their major toxic metabolites

– Adventitious toxins (e.g., aflatoxins)

– Foreign materials and adulterants

In some cases (e.g., when the botanical raw material undergoes further processing to prepare the botanical drug substance), reduced testing may be appropriate for certain assays (e.g., heavy metals), if these assays are routinely performed on the botanical drug substance. If some of these tests cannot be performed by the raw material supplier, the botanical drug substance manufacturer should perform the tests upon receipt of the botanical raw material.

- A photocopy of the voucher specimen (reference specimen) of the botanical raw material used in identification, fingerprinting, and other comparative and noncomparative tests
- A certificate of analysis for representative batch(es) of the botanical raw material
- A description of the storage conditions, including the container/closure system and temperature

b. Botanical drug substance (§ 312.23(a)(7)(iv)(*a*))

- A qualitative and quantitative description of the drug substance and the name and address of the manufacturer (see section VIII.B.2).
- A chemical identification for the active constituents or characteristic markers in the drug substance, if possible. If the chemical identity is unknown, a representative spectroscopic and/or chromatographic fingerprint may suffice.
- Appropriate acceptance specifications (tests, test procedures, and acceptance criteria) for the botanical raw material, similar to the list of quality control specifications in section IX.B.1.a, established by the botanical drug substance manufacturer. Upon receipt of each batch of the raw material and its certificate of analysis, the manufacturer should, at a minimum, conduct an identification test and assay.
- A description of the manufacturing process for the botanical drug substance. The description should include the quantity of botanical raw material,

equipment, solvents, temperature/time for mixing, grinding, extraction and/or drying, yield, and in-process controls. The yield of the process, expressed as the amount of the original botanical raw material relative to the amount of the extract, also should be indicated. If more than one botanical raw material is introduced to produce a multi-herb substance, the quantity of each raw material and the sequence of addition, mixing, grinding, and/or extraction should be provided. If a multi-herb substance is prepared by combining two or more individually processed botanical drug substances, the process leading to each botanical drug substance should be described separately.

- The quality control tests performed on each batch of drug substance, the analytical procedures used, and the proposed acceptance criteria. These tests should include, but need not be limited to, the following attributes:

  – Appearance

  – Chemical identification by spectroscopic and/or chromatographic fingerprints

  – Chemical identification for the active constituents or, if unknown, the characteristic markers

  – Chemical assay for the active constituents, or the characteristic markers if the active constituents cannot be determined. If several botanical raw materials are combined to produce a multi-herb substance and a quantitative determination of each individual active constituent or marker is infeasible, a joint determination can be made for several active constituents or markers. When multiple active constituents or markers are known, they should be chemically characterized and their relative amounts should be defined.

  – Biological assay (when the active chemical constituents are not known or quantifiable), if available. If the botanical drug substance is considered potent (i.e., highly active), toxic, or addictive, or has abuse potential (e.g., ephedra or marijuana), an assay for biological activity and/or a chemical assay for the active constituent(s) should be performed.

  – Strength by dry weight

  – Residue on ignition

  – Water content

  – Residual solvents

  – Heavy metals

  – Microbial limits

  – Animal safety test, if applicable

  – Residual pesticides

  – Radioisotope contaminants, if applicable

– Adventitious toxins (e.g., aflatoxins)

– Endogenous toxins (e.g., pyrrolizidine alkaloids)

– Other attributes specific to the botanical raw materials from which the drug substance is derived

- Validation reports of all analytical procedures, where appropriate
- A description of the batch of botanical drug substance designated as the *reference standard* for use in fingerprinting and other comparative tests
- Batch analysis (i.e., test results for representative batches)
- A description of the container and closure used to package the botanical drug substance
- Sufficient stability data on the drug substance to support its safe use during clinical studies; stability-indicating analytical methods
- Information on the container label as described in section VIII.B.2

c. Botanical drug product (§ 312.23(a)(7)(iv)(*b*))

- A qualitative description and the composition of the dosage form and the name and address of the manufacturer (see section VIII.B.3)
- Appropriate acceptance specifications established by the botanical drug product manufacturer for the botanical drug substance, similar to the quality control tests in section IX.B.1.b. Upon receipt of each batch of the drug substance and its certificate of analysis, the manufacturer should, at a minimum, conduct an identification test and assay.
- A description of the manufacturing process, without the actual batch record. The description should include weighing, mixing, blending, sieving, in-process controls, and other processes, as appropriate.
- The quality control tests performed on each batch of drug product, the analytical procedures used, and the proposed acceptance criteria. These tests should include, but need not be limited to, the following attributes:

  – Appearance

  – Chemical identification by spectroscopic and/or chromatographic fingerprints

  – Chemical identification for the active constituents or, if unknown, the characteristic markers

  – Chemical assay for active constituents or, if unknown, the characteristic markers. If several botanical raw materials are combined to produce a multi-herb substance and a quantitative determination of each individual active constituent or marker is infeasible, a joint determination can be

made for several active constituents or markers. When multiple active constituents or markers are known, they should be chemically characterized and their relative amounts should be defined.

– Biological assay (when the active chemical constituent(s) are not known or quantifiable), if available. If the botanical drug substance is considered potent (i.e., highly active), toxic, addictive, or has abuse potential (e.g., ephedra or marijuana), an assay for biological activity and/or a chemical assay for the active constituent(s) should be performed.

– Strength by dry weight (of drug substance)

– Residual solvents

– Microbial limits

– Adventitious toxins (e.g., aflatoxins)

– Other attributes specific to the dosage form of interest (e.g., dissolution for solid oral dosage forms, sterility for parenterals, animal safety test for parenterals, when appropriate).

- Validation reports of all analytical procedures, where appropriate
- Batch analysis (i.e., test results for representative batches)
- A description of the container and closure used to package the finished product
- Sufficient stability data on the drug substance to support its safe use during clinical studies. Stability-indicating analytical methods should be established.

d. Placebo (see section VII.B.5)

e. Labeling (see sections VII.B.6 for investigational labels and VIII.B.5 for quantitative description)

f. An EA or a claim of categorical exclusion (see section VIII.B.7)

2. End-of-Phase 3 Clinical Studies and Pre-NDA Considerations

Sponsors must continue to characterize the drug substance and the drug product throughout the entire clinical development program (§ 312.23(a)(7)). By the end of the phase 3 clinical trial, as the sponsor prepares to submit an NDA, the following objectives should be reached:

- Adequate controls for botanical raw materials should be established.
- The manufacturing processes of the drug substance and the drug product should be finalized and validated, and in-process controls should be established. An executed

batch record should be available.

- Batch-to-batch consistency should be demonstrated for the botanical drug substance and drug product based on results from all chemical, physical, and biological tests on all relevant batches. To achieve this goal, multiple fingerprints, using a combination of analytical methods with different separation principles and test methods, can be useful. All chemical constituents detected by spectroscopic and/or chromatographic fingerprinting should be qualitatively and quantitatively comparable from batch to batch.

- Appropriate specifications (i.e., tests, analytical procedures, and acceptance criteria), including identification and assay for active constituents, identification and assay for characteristic markers, and/or biological assay (when the active chemical constituent(s) are not known or quantifiable), should be established to control the quality of the drug substance and product. Both the active constituents and the biological assay should be clinically relevant. If the identity of the active constituents is not known or a suitable assay cannot be developed, the characteristic markers should be demonstrated to be clinically relevant by direct or indirect correlation to the clinical outcome.

- Analytical procedures should be properly validated. Analytical procedures used for fingerprinting should be verified for specificity and should be capable of detecting as many chemical classes (e.g., proteins, carbohydrates, fatty acids, small organic compounds) present and as many individual chemical constituents as possible. Additionally, when multiple fingerprints are used, the analytical procedures in combination should be able to demonstrate the mass balance in the test sample, on the basis of the different classes of chemicals and, if appropriate, among the individual constituents detected within a chemical class.

- A suitable voucher specimen (reference specimen) for each of the botanical raw materials should be established, along with a reference standard for the drug substance and drug product.

- Stability-indicating analytical methods should be developed to monitor the stability of the drug substance and drug product. The stability of a botanical drug substance or product generally should not be based entirely on the assay of the active constituents, assay of the characteristic markers, or biological assay, because degradants formed during storage from other chemical constituents in the botanical drug substance or product should also be controlled. An analytical method capable of detecting these degradants (such as a spectroscopic and/or chromatographic fingerprint) should be established through exploratory studies by subjecting the drug substance and drug product to stress conditions.

- A biological assay, when used for characterization and quality control of a drug substance and drug product, should be properly validated. The ICH Guideline *Q6B Specifications: Test Procedures and Acceptance Criteria for*

Biotechnological/Biological Products (August 1999) and the USP XXV *Biological Tests <111>: Design and Analysis of Biological Assays* provide useful information on biological assays. Performing a biological assay calls for the use of a suitable reference standard and, frequently, positive and negative controls. Because biological assays are usually more variable than chemical assays, a relatively higher coefficient of variation is generally justifiable.

- A comparison of the similarities and/or differences in CMC among the nonclinical, clinical, and intended commercial products should be made regarding raw materials, drug substance, and drug product.

- The manufacturing, processing, and controls (receipt, identification, storage, handling, sampling, testing, and approval or rejection of components, drug products, and container closures) for botanical drug products must be in conformance with CGMP as set forth in 21 CFR parts 210 and 211. In addition, the manufacturing, processing, and controls for the botanical drug substance (starting from the botanical raw material) should be in conformance with CGMP because these elements can affect the quality, safety, and efficacy of the drug product. A satisfactory inspection is necessary for NDA approval.

- A sponsor should be preparing the submission in the NDA of either an EA or a claim for categorical exclusion from the requirement for preparation of an EA (§ 25.15(a)). Classes of NDAs that are categorically excluded and, therefore, ordinarily do not require preparation of an EA are listed in § 25.31. However, 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 (§ 25.21; 40 CFR 1508.4). The Agency regards the submission of an NDA for a drug derived from plants taken from the wild as an extraordinary circumstance requiring the submission of an EA. See section VIII.B.6 for additional information.

Applicants are encouraged to discuss with the review division any CMC issues regarding a botanical drug prior to the preparation and submission of an NDA.

C. Nonclinical Safety Assessment

To support safety for expanded clinical studies or to support marketing approval of a botanical drug product, toxicity data from standard toxicology studies in animals may be needed in accordance with § 312.23(a)(8). A botanical product submitted for marketing approval as a drug will be treated like any other new drug under development. Safety data from previous clinical trials conducted in foreign countries will be considered in determining the need for nonclinical studies. However, previous human experience may be insufficient to demonstrate the safety of a botanical drug product, especially when it is indicated for chronic therapy. Systematic toxicological evaluations could be needed to supplement available knowledge on the general toxicity, teratogenicity, mutagenicity, and carcinogenicity of the final botanical drug product. Depending on the indication

(e.g., target patient population, disease to be treated), route of administration, and duration of recommended drug exposure, the timing of these animal studies in relation to concurrent clinical trials and other requirements for nonclinical animal studies can vary.

In general, animal studies should, as much as possible, be conducted using the same drug substance prepared and processed in the same manner as the drug substance used in clinical trials.

The following are points to consider in preparing a nonclinical pharmacology/toxicology development plan for a botanical drug product that is intended to be used in large-scale human trials or to support an NDA. If questions arise during any stage of the clinical development of a botanical drug, sponsors are encouraged to consult the appropriate review division in CDER.

1. Repeat-Dose General Toxicity Studies

The primary objective of long-term, repeat-dose toxicity studies in animals is to identify the organs and/or systems that are the targets of the drug's toxicity and the threshold doses for producing toxic effects. The studies provide information valuable for designing long-term clinical studies at safe doses, with appropriate monitoring for predicted adverse reactions. Existing literature on the animal toxicity of a botanical drug is often limited to single-dose (acute) studies. These studies would be inadequate to support long-term use.

To support expanded clinical trials, repeat-dose toxicity of a botanical drug should usually be evaluated in two mammalian species (one of which is a nonrodent) by employing sufficiently high doses to produce a toxic effect or by using a maximum feasible dose. If possible, the drug should be tested using the same route of administration as proposed for clinical use. Animal studies should be of a duration at least equal to that of the clinical trial (usually a minimum of 2 weeks). Routinely, general animal toxicity studies need not exceed 6 months of testing in a rodent species and 9 months of testing in a nonrodent species. For additional information on the timing of animal toxicity studies in relation to clinical trials, see the ICH guidance *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals* (November 1997).

2. Nonclinical Pharmacokinetic/Toxicokinetic Studies

In the development of a new drug that is a single molecular entity, it is often useful to compare pharmacokinetics in animals and humans and to relate exposure levels to toxicities in both animals and humans. Because botanical drugs usually consist of more than one chemical constituent, standard pharmacokinetic measurements to substantiate the systemic exposure of a botanical drug product in animals may be technically infeasible. However, monitoring representative chemical constituents in a botanical drug can provide valuable information regarding systemic exposure. Depending on the complexity of the botanical drug product to be studied, pharmacokinetics could be helpful in the design and interpretation of toxicity studies. For additional information on

toxicokinetic evaluations, see the ICH guidances *S3A Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies* (March 1995) and *S3B Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies* (March 1995).

3. Reproductive Toxicology

Reproductive toxicology studies, such as those on fertility/reproductive performance, teratology, and prenatal/perinatal development in animals, provide information on the potential of a botanical drug for producing toxicity during the different stages of reproductive and developmental processes. In the absence of documented data on reproductive toxicity in humans or animals, these tests should be conducted prior to expanded clinical trials. For detailed information regarding reproductive toxicology, sponsors should refer to the ICH guidances *S5A Detection of Toxicity to Reproduction for Medicinal Products* (September 1994) and *S5B Detection of Toxicity to Reproduction for Medicinal Products: Addendum on Toxicity to Male Fertility* (April 1996).

4. Genotoxicity Studies

We recommend that information on the potential of a botanical drug to produce genetic toxicity be obtained as early as possible, preferably before the initiation of human clinical trials (see ICH *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals* (November 1997)). A complete assessment of genetic toxicity may be needed before expanded clinical trials. A standard battery of tests is defined in the ICH guidances *S2A Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals* (April 1996) and *S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals* (November 1997).

If the standard battery of tests chosen indicate that a drug is devoid of genetic toxicity, additional genotoxicity studies may not be needed to comply with § 312.23(a)(8)(ii)(*a*). If one or more test results are positive, the sponsor may need to carry out additional genotoxicity tests to comply with this provision, in consultation with the appropriate CDER review division.

5. Carcinogenicity Studies

Carcinogenicity studies may be needed to comply with § 312.23(a)(8)(ii)(*a*) to support marketing approval of a botanical drug, depending on the duration of therapy or any specific cause for concern. The toxicity profile of the botanical drug and the indication and duration of the intended use may influence the need under this regulation for carcinogenicity studies and their timing relative to clinical development (see ICH *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals* (March 1996)). Draft protocols for carcinogenicity studies should be submitted to the appropriate review division and the CDER Carcinogenicity Assessment Committee for review and concurrence prior to the initiation of such studies to ensure the acceptability of dose selection and study design. Study types should be in accordance with the ICH guidance *S1B Testing for Carcinogenicity of Pharmaceuticals* (February 1998). Doses

used should be chosen according to the principles outlined in the ICH guidances *S1C Dose Selection for Carcinogenicity Studies of Pharmaceuticals* (March 1995) and *S1C(R) Dose Selection for Carcinogenicity Studies of Pharmaceuticals: Addendum on a Limit Dose and Related Notes* (December 1997).

6. Special Pharmacology/Toxicology Studies

A general evaluation of the pharmacological effects of a drug on physiological functions (e.g., central nervous system, cardiovascular system) is often performed during new drug development. This evaluation can be accomplished using established in vitro and in vivo assays of broad specificity that screen for the modes and sites of action of the botanical drug. When significant and unique toxicities to certain organs and/or systems are evident, the sponsor should provide further explanation of the mechanism of toxic actions, if appropriate, by performing additional in vitro or in vivo studies.

7. Regulatory Considerations

Nonclinical toxicity studies conducted as part of botanical drug development and intended to support safety must be in accordance with regulations governing good laboratory practices under 21 CFR part 58. Both the drug substance and the drug product should be made with batch-to-batch consistency. If changes occur in the drug substance or product during clinical development, bridging toxicity studies might be needed to comply with § 312.23(a)(8)(ii)(*a*).

D. Bioavailability and Clinical Pharmacology

The general requirements for in vivo bioavailability data in an NDA, described in § 320.21, are applicable to botanical drug products. The type of bioavailability study that is appropriate for a specific botanical drug product is based on the following: (1) information on the active constituent, if known; (2) the complexity of the drug substance; and (3) the availability of analytical methods. Because there could be more than one active constituent in a botanical drug or the active constituent may not be identified, it could be difficult or impossible to perform standard in vivo bioavailability and pharmacokinetic studies (e.g., by measuring, as a function of time, the concentration of the active moiety, active ingredients, or active metabolites in whole blood, plasma, serum, or other appropriate biological fluid, or by measuring the excretion of the active moiety or active metabolites in urine). In some cases, it may be possible to measure an acute pharmacological effect as a function of time using an appropriate biological assay method. If this is not possible, the bioavailability of a botanical drug could be based on clinical effects observed in well-controlled clinical trials.

The general criteria for waiver of in vivo bioavailability data in an NDA, described in § 320.22, are applicable to botanical drug products. FDA may, for good cause, waive or defer the in vivo bioavailability study requirement if a waiver or deferral is compatible with the protection of the public health (§ 320.22(e)).

Interactions between botanicals and other commonly used drugs and/or dietary supplements should be investigated. This may include characterization of the metabolic enzymes and/or pathway affected by the drug (see section VIII.D).

Where possible, the effects of impaired clearance (renal or hepatic) on the drug's pharmacokinetics should be examined. This is easiest when the active substance(s) are known, but even if they are not, knowledge of the major constituents should make it possible to determine the effects of impaired clearance. Dose-response information may indicate the proper level of concern about impaired excretion.

As with synthetic and/or highly purified drugs, pharmaceutical and biopharmaceutics studies for botanical drug products are important for product quality control, batch comparison, and linkage between different strengths. These studies may involve, for example, in vitro dissolution testing, in situ drug absorption testing, in vitro-in vivo correlation studies, or in vitro percutaneous absorption/penetration testing, depending on the indication and formulation of the botanical product.

E. Clinical Considerations

Expanded studies of botanicals have the same purpose as expanded studies of synthetic drugs, including further evaluation of dose-response for favorable and unfavorable effects and evaluation of long-term safety and effectiveness, different populations, different stages/severity of disease, and drug-drug interactions. Many general and therapy-specific guidances are available on CDER's Web page (see title page for URL).

GLOSSARY

The following definitions are intended for use in this guidance only and may not be appropriate in other contexts.

Active Constituent: The chemical constituent in a botanical raw material, drug substance, or drug product that is responsible for the intended pharmacological activity or therapeutic effect

Botanical; Botanical Product: A finished, labeled product that contains vegetable matter, which may include plant materials (see below), algae, macroscopic fungi, or combinations of these. Depending in part on its intended use, a botanical product may be a food, drug, medical device, or cosmetic.

Botanical Drug Product; Botanical Drug: A botanical product that is intended for use as a drug; a drug product that is prepared from a botanical drug substance. Botanical drug products are available in a variety of dosage forms, such as solutions (e.g., teas), powders, tablets, capsules, elixirs, and topicals.

Botanical Drug Substance: A drug substance derived from one or more plants, algae, or macroscopic fungi. It is prepared from botanical raw materials by one or more of the following processes: pulverization, decoction, expression, aqueous extraction, ethanolic extraction, or other similar process. It may be available in a variety of physical forms, such as powder, paste, concentrated liquid, juice, gum, syrup, or oil. A botanical drug substance can be made from one or more botanical raw materials (see Single-Herb and Multi-Herb Botanical Drug Substance or Product). A botanical drug substance does not include a highly purified or chemically modified substance derived from natural sources.

Botanical Ingredient: A component of a botanical drug substance or product that originates from a botanical raw material

Botanical Raw Material: Fresh or processed (e.g., cleaned, frozen, dried, or sliced) part of a single species of plant or a fresh or processed alga or macroscopic fungus

Cosmetic: An article intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, or an article intended for use as a component of any such article, except that such term does not include soap (21 U.S.C. 321(i))

Dietary Supplement: The following definition is taken directly from 21 U.S.C. 321(ff).

The term *dietary supplement* —

"(1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent,

extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E);

(2) means a product that (A)(i) is intended for ingestion in a form described in section 411(c)(1)(B)(i) [of the Act]; or (ii) complies with section 411(c)(1)(B)(ii); (B) is not represented for use as a conventional food or as a sole item of a meal or the diet; and (C) is labeled as a dietary supplement; and

(3) does (A) include an article that is approved as a new drug under section 505 [of the Act] or licensed as a biologic under section 351 of the Public Health Service Act (42 U.S.C. 262) and was, prior to such approval, certification, or license, marketed as a dietary supplement or as a food unless [FDA] has issued a regulation, after notice and comment, finding that the article, when used as or in a dietary supplement under the conditions of use and dosages set forth in the labeling for such dietary supplement, is unlawful under section 402(f) [of the Act]; and (B) not include (i) an article that is approved as a new drug under section 505 [of the Act], certified as an antibiotic under section 507 [of the Act], or licensed as a biologic under section 351 of the Public Health Service Act (42 U.S.C. 262), or (ii) an article authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, which was not before such approval, certification, licensing, or authorization marketed as a dietary supplement or as a food unless [FDA], in [its] discretion, has issued a regulation, after notice and comment, finding that the article would be lawful under this Act. Except for purposes of section 201(g), a dietary supplement shall be deemed to be a food within the meaning of this Act."

Dosage Form: A pharmaceutical product type, for example, tablet, capsule, solution, or cream, that contains a drug ingredient (substance) generally, but not necessarily, in association with excipients

Drug: The following definition is taken directly from 21 U.S.C. 321(g)(1).
The term drug means "(A) articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C). A food or dietary supplement for which a claim, subject to sections 403(r)(1)(B) and 403(r)(3) [of the Act] or sections 403(r)(1)(B) and (r)(5)(D), is made in accordance with the requirements of section 403(r) is not a drug solely because the label or the labeling contains such a claim. A food, dietary ingredient, or dietary supplement for which a truthful and not misleading statement is made in accordance with section 403(r)(6) is not a drug under clause (C) solely because the label or the labeling contains such a statement."

Drug Product: A finished dosage form, for example, tablet, capsule, solution, etc. (21 CFR 210.3 (b)(4))

Drug Substance: An active ingredient that is intended for use to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body (21 CFR 314.3(b))

Food: The term *food* means (1) articles used for food or drink, (2) chewing gum, and (3) articles used for components of such articles (21 U.S.C. 321(f)).

Formulation: A formula that lists the components (or ingredients) and composition of the dosage form. The components and composition of a multi-herb botanical drug substance should be part of the total formulation.

Marker: A chemical constituent of a botanical raw material, drug substance, or drug product that is used for identification and/or quality control purposes, especially when the active constituents are not known or identified.

Multi-Herb (Botanical Drug) Substance or Product: A botanical drug substance or drug product that is derived from more than one botanical raw material, each of which is considered a botanical ingredient. A multi-herb botanical drug substance may be prepared by processing together two or more botanical raw materials, or by combining two or more single-herb botanical drug substances that have been individually processed from their corresponding raw materials. In the latter case, the individual single-herb botanical drug substances may be introduced simultaneously or at different stages during the manufacturing process of the dosage form.

Plant Material: A plant or plant part (e.g., bark, wood, leaves, stems, roots, flowers, fruits, seeds, or parts thereof) as well as exudates thereof.

Single-Herb (Botanical Drug) Substance or Product: A botanical drug substance or drug product that is derived from one botanical raw material. Therefore, a single-herb substance or product generally contains only one botanical ingredient.

Spectroscopic and/or Chromatographic Fingerprint: A spectroscopic and/or chromatographic profile of a botanical raw material, drug substance, or drug product that is matched qualitatively and quantitatively against that of a reference sample or standard to ensure the identity and quality of a batch and consistency from batch to batch.

QUESTIONS AND ANSWERS

Q1: Are INDs required for clinical studies of botanical products that are lawfully marketed as dietary supplements in the United States?

A1: It depends on what the botanical product is being studied for. If a lawfully marketed botanical dietary supplement is studied for a dietary supplement use, i.e., effect on the structure and/or a function of the body, an IND is not required (see final rule on "Structure and Function Claims for Dietary Supplements," 65 FR 1000, January 6, 2000). Although an IND is not legally required for such a study, CDER encourages sponsors to submit one. If you have questions on how to design such a study, FDA would be willing to review and provide advice on protocols. You may contact CDER's Botanical Review Team at 301-827-2250 or BOTANICALTEAM@cder.fda.gov. If a botanical preparation is being studied for its effects on a disease in the proposed investigation (i.e., to cure, treat, mitigate, prevent, or diagnose disease, including its associated symptoms), it is considered a new drug and will need to be studied under an IND (see § 312.2).

Q2: Are INDs required for clinical studies on marketed dietary supplements for research purposes only?

A2: Again, it depends on the use. If the intent is to study the effect of the product on the structure and/or a function of the body, no IND is needed. If the study is to assess the effects on disease, an IND is needed.

Q3: Is there any other setting in which an IND is not required for the botanical study?

A3: When a nonmarketed botanical preparation is studied in the United States for a dietary supplement use, an IND is not required. In addition, clinical studies conducted in foreign countries require no IND. However, FDA will accept an IND for either kind of study. In the absence of an IND, an investigational new drug intended for export for the purpose of clinical investigation must comply with the requirements set forth in § 312.110(b)(2) unless the new drug has been approved or authorized for export under section 802 of the Act (21 U.S.C. 382).

Q4: May a sponsor submit an IND for a phase 3 study of a botanical product not previously studied under an IND?

A4: Yes. Clinical data collected from phase 1 and phase 2 studies conducted without an IND can be used to support a phase 3 study involving the same drug substance if they are adequately designed and conducted. The formulation/dosage form of the botanical product used in the proposed phase 3 study ideally would be the same as that of the product used in phase 1 and 2 studies as well as in the preclinical (nonclinical) studies. If the product is different, additional studies may be appropriate.

Q5: For NDA approvals of botanical drug products, must all studies be carried out under

INDs?

A5: No. FDA does not require that all studies submitted in an NDA be conducted under an IND. Clinical studies need not necessarily be conducted under an IND (i.e., if they are carried out abroad). The clinical data generated from these studies conducted without an IND can be used to support an NDA if the studies were adequately designed and conducted under good clinical practices.

Although an IND is not required by law in all cases, the sponsor is encouraged to go through the IND process. Compliance with the IND requirements will help to ensure that an adequate pharmaceutical product development program is in place so that the material will meet the quality standards not only for various phases of clinical trials but also for eventual marketing. It will also help to ensure that the clinical trials will be well designed so that data generated can be persuasive.

Q6: It appears that the changes in regulatory approaches described in the guidance on Botanical Drug Products concern only IND applications. How will these changes be applied to the NDA requirements for botanical drugs?

A6: To facilitate the clinical development of botanical drugs, FDA decided to focus initially on a guidance for INDs, especially the early phases of clinical study. The standards for the safety and efficacy required for marketing approval of a botanical drug are the same as those required for a conventional chemical drug for the same indication. However, the product quality standards for a botanical drug can be different from those for a purified chemical drug. The Botanical Drug Products guidance contains recommendations for establishing appropriate quality standards for botanical drugs.

Q7: Some botanical preparations are not administered orally, e.g., intravenous, topical, and inhalation products. How are these nonoral formulations considered in the guidance?

A7: The guidance applies to all dosage forms of botanical products. All parenteral, topical, inhalation, or other nonorally administered botanical products are considered to be drugs, not dietary supplements, and must be studied under an IND for any use (see section 201(ff) of the Act). Just as for purified chemical drugs, the type of quality testing varies from dosage form to dosage form. For example, all injectables are required to be sterile and pyrogen-free (211.165(b) and 211.167 and 314.50(d)(1)(ii)(b); oral tablets are not. In addition, dietary supplements are orally ingested and the human experience of an orally administered botanical dietary supplement may not be applicable to the same botanical product given through other routes.

Q8: In terms of IND requirements and regulatory review by the Agency, is there any difference between a commercial development program and an academic research project?

A8: No. The Agency applies the same standards to both commercial and academic sponsors when evaluating the safety and quality of human studies proposed in INDs.

Q9: Intellectual property rights are a difficult issue for developing new drugs from well-known botanical preparations. How does FDA protect the confidentiality of a sponsor's submission? What kind of IND/NDA data may FDA release without prior permission from the sponsor?

A9: IND information generally is not publicly available (see §§ 312.130, 314.430). Once an NDA is approved, FDA may release certain safety and efficacy information (§ 314.430(e)). Manufacturing information (including information related to growers and suppliers) provided in an NDA or a Drug Master File (DMF) is considered proprietary and may not be released (21 U.S.C. 331(j); 21 CFR 20.61).

Q10: How does FDA ensure that the new* Botanical Drug Products *guidance will be implemented consistently across the different new drug review divisions?

A10: FDA will provide reviewers in all divisions with training on how to implement the guidance.

Q11: One of the major premises of the new guidance is that because many botanical products have been used by a large population for a long period of time, they are presumed to be safe enough to be studied in clinical trials without first undergoing conventional nonclinical studies. What kind of documentation should a sponsor submit to demonstrate prior human experience with the sponsor's product?

A:11 The Agency recognizes that prior human experience with a botanical product can be documented in many different forms and sources, some of which may not meet the quality standards of modern scientific testing. The sponsor is encouraged to provide as much data as possible, and the review team for the botanical drug IND generally will accept all available information for regulatory consideration. FDA will assess the quality of the submitted data on a case-by-case basis. It should be emphasized that, in reviewing botanical drugs, the Agency does not lower or raise the safety and efficacy standards for marketing approval that apply to purified chemical drugs. The guidance simply recommends the use of different types of data for preliminary safety consideration of human trials (for example, large quantities of mostly anecdotal human data instead of animal studies).

Q12: In many cases, botanical therapies are highly individualized with variations in relative contents of multiple plant ingredients tailored for each patient. Must a sponsor submit a separate IND for every change in composition, if similar patients are being treated for the same indication?

A12: Studies can be designed to take into account individualized treatments. Multiple formulations can be included in one IND if they are being studied under a single clinical trial. It is important that the IND provide the rationale for using multiple formulations and the criteria used to assign patients to different treatment regimens.

Q13: Many medicinal plants with therapeutical potential are quite toxic. Does the new

guidance address the study of such botanicals?

A13: The guidance discusses this issue in the sections addressing botanical drug products with known safety issues (e.g., section VI.A). Well-known examples of safety issues concerning botanicals include the nephrotoxicity associated with herbal preparations containing aristolochic acid and the hepatotoxicity associated with comfrey products containing pyrrolizidine alkaloid. Other examples include the cardiovascular and central nervous system effects associated with yohimbe and the hepatotoxicity associated with germander and chapparal. In such cases, FDA will evaluate the known risk and the potential benefit of an investigational drug for its intended use. When the potential benefit of an investigational drug outweighs its risk in the intended patient population, clinical trials may be allowed to proceed under an IND (see § 312.42). For example, FDA will accept a relatively higher level of toxicity of an investigational drug when studied to treat terminally ill cancer patients. However, additional nonclinical studies may be appropriate to adequately characterize the toxicity (e.g., can a dose be identified that would not be expected to produce toxicity?) and/or additional monitoring may be appropriate during the clinical trial. Also, FDA may recommend against human studies (e.g., bioavailability, clinical pharmacology) in healthy volunteers.

Q14: There is a concern that if a botanical is being studied under an IND or is approved as a new drug in an NDA, its subsequent status as a dietary supplement may be jeopardized. Is this true?

A14: No, it is generally not true for products already on the market before approval of an NDA. It is also generally not true for products marketed before authorization of an IND for which substantial clinical investigations have been instituted and the existence of such investigations has been made public (see section 201(ff)(3) of the Act).

Q15: What is FDA's advice on the initial approach for sponsors not familiar with new drug development and regulatory processes?

A15: A sponsor should first consult the guidance. If there are questions concerning the guidance document or other questions about the submission of INDs for botanical drugs, consult the appropriate CDER review division for the therapeutic class of the sponsor's product. CDER also grants pre-IND meetings with sponsors.

Q16: The guidance states that the submission of an NDA for a drug derived from plants taken from the wild is an extraordinary circumstance requiring the submission of an environmental assessment (EA) under § 25.21. Are plants maintained in their native setting on private land considered wild?

A16: Yes. Plants that are obtained from their native setting on either public or private land are considered to be taken from the wild. Cultivated plants are considered those that are grown collectively in controlled settings such as plantations, farms, or greenhouses, i.e., purposely segregated from wildlife to the extent practicable.

Q17: Is a drug made with a commercially available crude extract viewed the same as a drug derived from plants taken from the wild for purposes of determining the need for an EA?

A17: Yes. If an NDA is submitted for a drug made from a crude extract or intermediate from a plant taken from the wild, an EA is required under § 25.21. This is true whether or not the extract or intermediate is commercially available. As for an IND for a drug made from a crude extract or intermediate from a plant taken from the wild, FDA will decide on a case-by-case whether an EA is required.

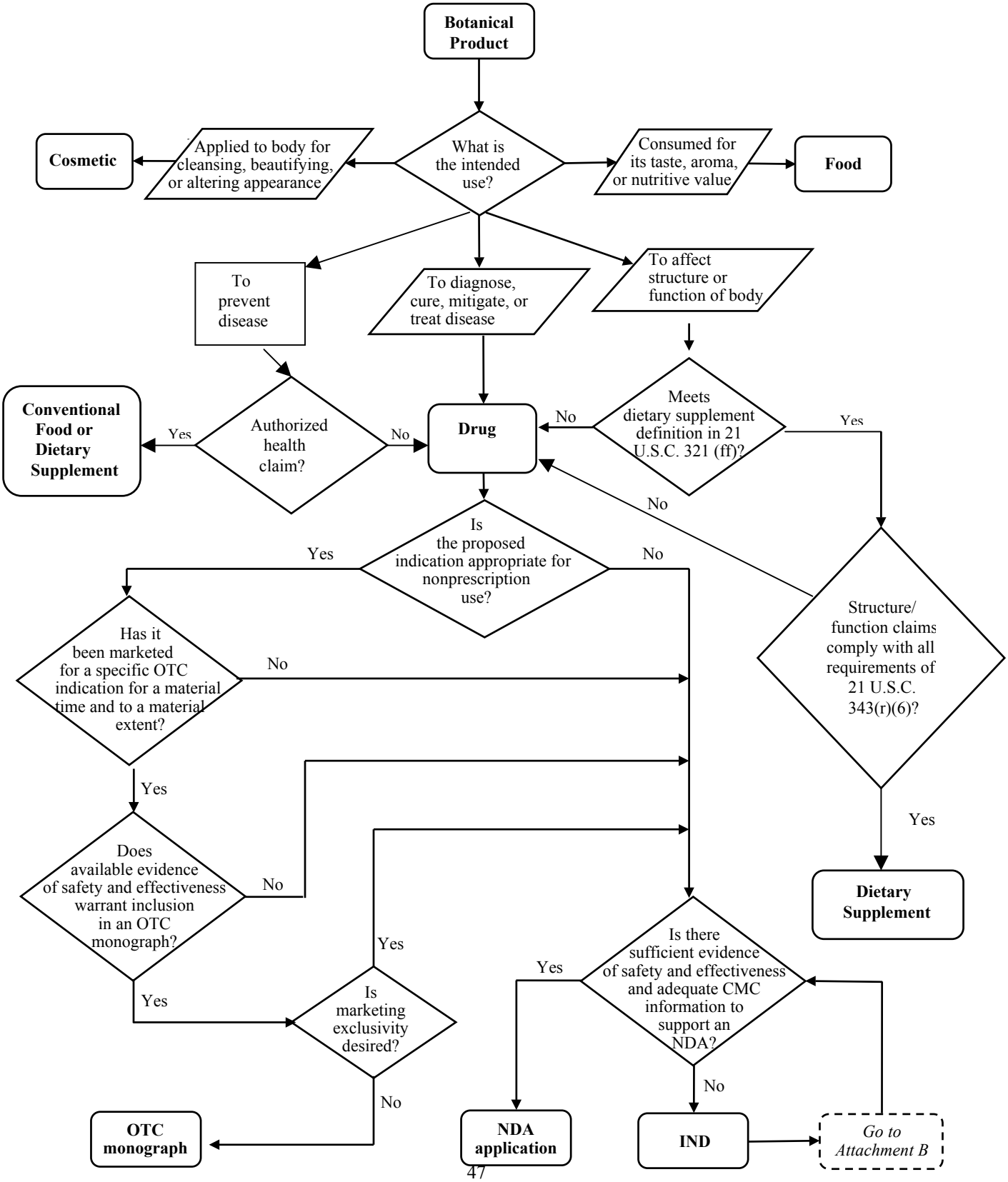
Q18: What is the GMP status of botanical raw materials (starting materials) in terms of compliance and inspection?

A18: Starting materials of botanical origin that are used to produce a botanical drug substance should be evaluated for quality. The use of appropriate starting materials and the drug substance manufacturer's ability to control the source depend on appropriate specifications (tests, analytical procedures, and acceptance criteria). In addition to establishing specifications, manufacturers can achieve adequate quality control of starting materials by applying the principles outlined in FDA's botanical guidance and by following good agricultural and good collection practice for starting materials of herbal origin (e.g., European Medicines Evaluation Agency *HMPWP/31/99*). Upon receipt of the starting materials at a processing facility, it is the responsibility of the drug substance manufacturer to determine the suitability of these raw materials before use. This can be accomplished by examining and/or testing to ensure that the acceptance criteria are met and by documenting the quality control for the processing of the starting materials. FDA will review the inspection and examination of starting materials upon receipt when conducting a current good manufacturing practice (CGMP) inspection of a drug substance manufacturer.

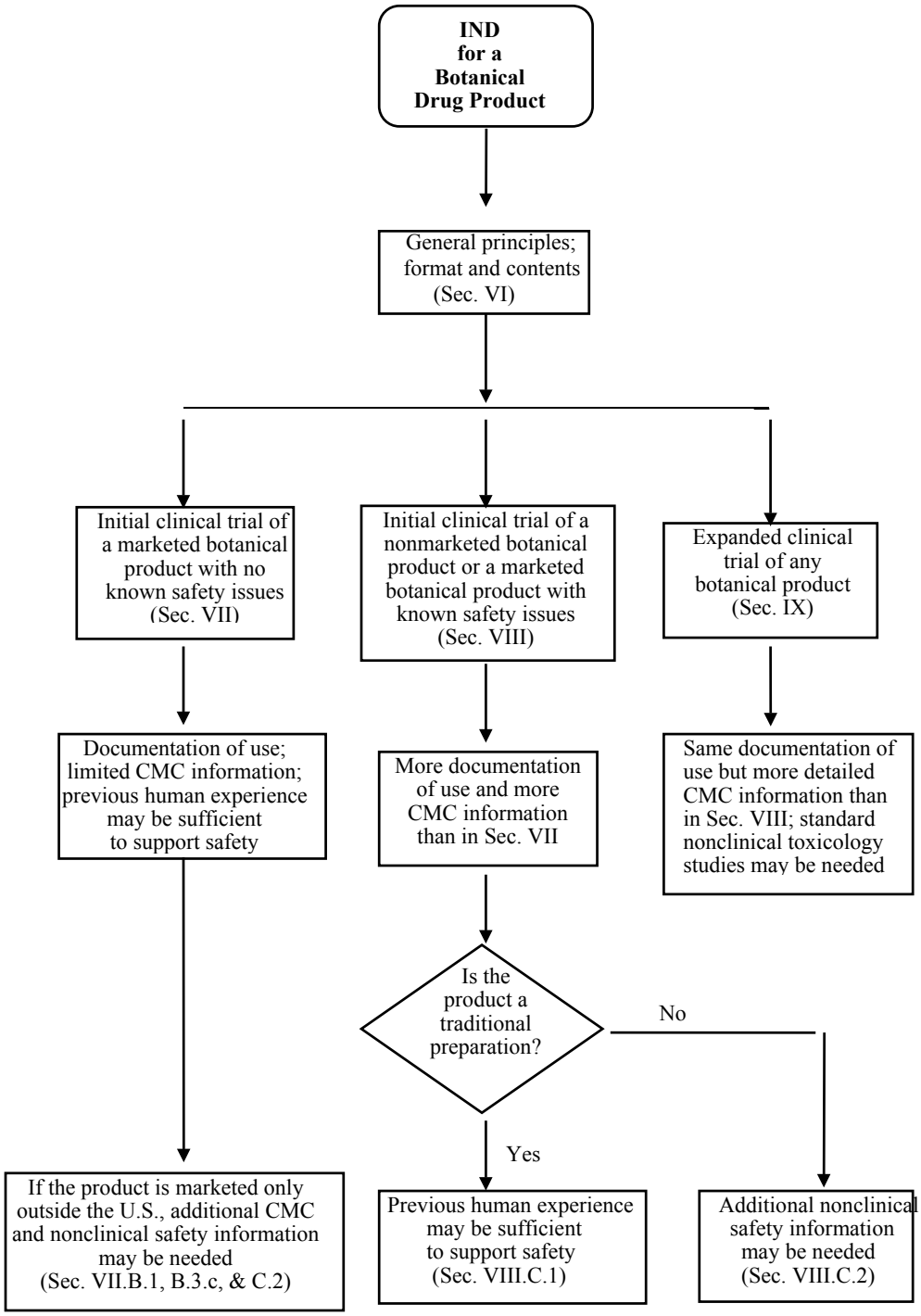
Q19: Will FDA assign the same level of priority to botanical drug products as to other drugs with respect to meeting with IND sponsors and NDA applicants?

A19: Yes, FDA treats botanical and purified chemical drugs the same.

ATTACHMENT A: REGULATORY APPROACHES FOR MARKETING BOTANICAL DRUG PRODUCTS



ATTACHMENT B: INFORMATION TO BE PROVIDED IN AN IND FOR A BOTANICAL DRUG



DIRECTIVE 2004/24/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 31 March 2004

amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission [1],

Having regard to the opinion of the European Economic and Social Committee [2],

Acting in accordance with the procedure laid down in Article 251 of the Treaty [3],

Whereas:

(1) Directive 2001/83/EC [4] requires that applications for authorisation to place a medicinal product on the market have to be accompanied by a dossier containing particulars and documents relating in particular to the results of physico-chemical, biological or microbiological tests as well as pharmacological and toxicological tests and clinical trials carried out on the product and thus proving its quality, safety and efficacy.

(2) Where the applicant can demonstrate by detailed references to published scientific literature that the constituent or the constituents of the medicinal product has or have a well-established medicinal use with recognised efficacy and an acceptable level of safety within the meaning of Directive 2001/83/EC, he/she should not be required to provide the results of pre-clinical tests or the results of clinical trials.

(3) A significant number of medicinal products, despite their long tradition, do not fulfil the requirements of a well-established medicinal use with recognised efficacy and an acceptable level of safety and are not eligible for a marketing authorisation. To maintain these products on the market, the Member States have enacted differing procedures and provisions. The differences that currently exist between the provisions laid down in the Member States may hinder trade in traditional medicinal products within the Community and lead to discrimination and distortion of competition between manufacturers of these products. They may also have an impact on the protection of public health since the necessary guarantees of quality, safety and efficacy are not always provided at present.

(4) Having regard to the particular characteristics of these medicinal products, especially their long tradition, it is desirable to provide a special, simplified registration procedure for certain traditional medicinal products. However, this simplified procedure should be used only where no marketing authorisation can be obtained pursuant to Directive 2001/83/EC, in particular because of a lack of sufficient scientific literature demonstrating a well-established medicinal use with recognised efficacy and an acceptable level of safety. It should likewise not apply to homeopathic medicinal products eligible for marketing authorisation or for registration under Directive 2001/83/EC.

(5) The long tradition of the medicinal product makes it possible to reduce the need for clinical trials, in so far as the efficacy of the medicinal product is plausible on the basis of long-standing use and experience. Pre-clinical tests do not seem necessary, where the medicinal product on the basis of the information on its traditional use proves not to be harmful in specified conditions of use. However, even a long tradition does not exclude the possibility that there may be concerns with regard to the product's safety, and therefore the competent authorities should be entitled to ask for all data necessary for assessing the safety. The quality aspect of the medicinal product is independent of its traditional use so that no derogation should be made with regard to the necessary physico-chemical, biological and microbiological tests. Products should comply with quality standards in relevant European Pharmacopoeia monographs or those in the pharmacopoeia of a Member State.

(6) The vast majority of medicinal products with a sufficiently long and coherent tradition are based on herbal substances. It therefore seems appropriate to limit the scope of the simplified registration in a first step to traditional herbal medicinal products.

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[1] OJ C 126 E, 28.5.2002, p. 263.

[2] OJ C 61, 14.3.2003, p. 9.

[3] Opinion of the European Parliament of 21 November 2002 (OJ C 25 E, 29.1.2004, p. 222), Council Common Position of 4 November 2003 (OJ C 305 E, 16.12.2003, p. 52), Position of the European Parliament of 17 December 2003 (not yet published in the Official Journal) and Council Decision of 11 March 2004.

[4] OJ L 311, 28.11.2001, p. 67; Directive as last amended by Commission Directive 2003/63/EC (OJ L 159, 27.6.2003, p. 46).

(7) The simplified registration should be acceptable only where the herbal medicinal product may rely on a sufficiently long medicinal use in the Community. Medicinal use outside the Community should be taken into account only if the medicinal product has been used within the Community for a certain time. Where there is limited evidence of use within the Community, it is necessary to assess carefully the validity and relevance of use outside the Community.

(8) With the objective of further facilitating the registration of certain traditional herbal medicinal products and of further enhancing harmonisation, there should be the possibility of establishing a Community list of herbal substances that fulfil certain criteria, such as having been in medicinal use for a sufficiently long time, and hence are considered not to be harmful under normal conditions of use.

(9) Having regard to the particularities of herbal medicinal products, a Committee for Herbal Medicinal Products should be established within the European Agency for the Evaluation of Medicinal Products (hereinafter 'the Agency') set up by Council Regulation (EEC) No 2309/93 [1]. The Committee should carry out tasks concerning the simplified registration and authorisation of medicinal products as provided for in this Directive. Its tasks should relate in particular to establishing Community herbal monographs relevant for the registration as well as the authorisation of herbal medicinal products. It should be composed of experts in the field of herbal medicinal products.

(10) It is important to ensure full consistency between the new Committee and the Committee for Human Medicinal Products already existing within the Agency.

(11) In order to promote harmonisation, Member States should recognise registrations of traditional herbal medicinal products granted by another Member State based on Community herbal monographs or consisting of substances, preparations or combinations thereof contained in a list to be established. For other products, Member States should take due account of such registrations.

(12) This Directive allows non-medicinal herbal products, fulfilling the criteria of food legislation, to be regulated under food legislation in the Community.

(13) The Commission should present a report on the application of the chapter on traditional herbal medicinal products to the European Parliament and to the Council including an assessment on the possible extension of traditional-use registration to other categories of medicinal products.

(14) It is therefore appropriate to amend Directive 2001/83/EC accordingly,

HAVE ADOPTED THIS DIRECTIVE:

Article 1

Directive 2001/83/EC is hereby amended as follows:

1. in Article 1 the following is added:

'29. *Traditional herbal medicinal product:*

a herbal medicinal product that fulfils the conditions laid down in Article 16a(1);

30. *Herbal medicinal product:*

any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations;

31. *Herbal substances:*

All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author);

32. *Herbal preparations:*

preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.'

[1] OJ L 214, 24.8.1993, p. 1; Regulation as last amended by Regulation (EC) No 1647/2003 (OJ L 245, 29.9.2003, p. 19).

2. The following chapter is inserted in Title III:

'*CHAPTER 2a*

Specific provisions applicable to traditional herbal medicinal products

Article 16a

1. A simplified registration procedure (hereinafter "traditional-use registration") is hereby established for herbal medicinal products which fulfil all of the following criteria:

(a) they have indications exclusively appropriate to traditional herbal medicinal products which, by virtue of their composition and purpose, are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment;

(b) they are exclusively for administration in accordance with a specified strength and posology;

(c) they are an oral, external and/or inhalation preparation;

(d) the period of traditional use as laid down in Article 16c(1)(c) has elapsed;

(e) the data on the traditional use of the medicinal product are sufficient; in particular the product proves not to be harmful in the specified conditions of use and the pharmacological effects or efficacy of the medicinal product are plausible on the basis of long-standing use and experience.

2. Notwithstanding Article 1(30), the presence in the herbal medicinal product of vitamins or minerals for the safety of which there is well-documented evidence shall not prevent the product from being eligible for registration in accordance with paragraph 1, provided that the action of the vitamins or minerals is ancillary to that of the herbal active ingredients regarding the specified claimed indication(s).

3. However, in cases where the competent authorities judge that a traditional herbal medicinal product fulfils the criteria for authorisation in accordance with Article 6 or registration pursuant to Article 14, the provisions of this chapter shall not apply.

Article 16b

1. The applicant and registration holder shall be established in the Community.

2. In order to obtain traditional-use registration, the applicant shall submit an application to the competent authority of the Member State concerned.

Article 16c

1. The application shall be accompanied by:

(a) the particulars and documents:

(i) referred to in Article 8(3)(a) to (h), (j) and (k);

(ii) the results of the pharmaceutical tests referred to in the second indent of Article 8(3)(i);

(iii) the summary of product characteristics, without the data specified in Article 11(4);

(iv) in case of combinations, as referred to in Article 1(30) or Article 16a(2), the information referred to in Article 16a(1)(e) relating to the combination as such; if the individual active ingredients are not sufficiently known, the data shall also relate to the individual active ingredients;

(b) any authorisation or registration obtained by the applicant in another Member State, or in a third country, to place the medicinal product on the market, and details of any decision to refuse to grant an authorisation or registration, whether in the Community or a third country, and the reasons for any such decision;

(c) bibliographical or expert evidence to the effect that the medicinal product in question, or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the Community. At the request of the Member State where the application for traditional-use registration has been submitted, the Committee for Herbal Medicinal Products shall draw up an opinion on the adequacy of the evidence of the long-standing use of the product, or of the corresponding product. The Member State shall submit relevant documentation supporting the referral;

(d) a bibliographic review of safety data together with an expert report, and where required by the competent authority, upon additional request, data necessary for assessing the safety of the medicinal product.

Annex I shall apply by analogy to the particulars and documents specified in point (a).

2. A corresponding product, as referred to in paragraph 1(c), is characterised by having the same active ingredients, irrespective of the excipients used, the same or similar intended purpose, equivalent strength and posology and the same or similar route of administration as the medicinal product applied for.

3. The requirement to show medicinal use throughout the period of 30 years, referred to in paragraph 1(c), is satisfied even where the marketing of the product has not been based on a specific authorisation. It is likewise satisfied if the number or quantity of ingredients of the medicinal product has been reduced during that period.

4. Where the product has been used in the Community for less than 15 years, but is otherwise eligible for simplified registration, the Member State where the application for traditional-use registration has been submitted shall refer the product to the Committee for Herbal Medicinal Products. The Member State shall submit relevant documentation supporting the referral.

The Committee shall consider whether the other criteria for a simplified registration as referred to in Article 16a are fully complied with. If the Committee considers it possible, it shall establish a Community herbal monograph as referred to in Article 16h(3) which shall be taken into account by the Member State when taking its final decision.

Article 16d

1. Without prejudice to Article 16h(1), Chapter 4 of Title III shall apply by analogy to registrations granted in accordance with Article 16a, provided that:

(a) a Community herbal monograph has been established in accordance with Article 16h(3), or

(b) the herbal medicinal product consists of herbal substances, preparations or combinations thereof contained in the list referred to in Article 16f.

2. For other herbal medicinal products as referred to in Article 16a, each Member State shall, when evaluating an application for traditional-use registration, take due account of registrations granted by another Member State in accordance with this chapter.

Article 16e

1. Traditional-use registration shall be refused if the application does not comply with Articles 16a, 16b or 16c or if at least one of the following conditions is fulfilled:

(a) the qualitative and/or quantitative composition is not as declared;

(b) the indications do not comply with the conditions laid down in Article 16a;

(c) the product could be harmful under normal conditions of use;

(d) the data on traditional use are insufficient, especially if pharmacological effects or efficacy are not plausible on the basis of long-standing use and experience;

(e) the pharmaceutical quality is not satisfactorily demonstrated.

2. The competent authorities of the Member States shall notify the applicant, the Commission and any competent authority that requests it, of any decision they take to refuse traditional-use registration and the reasons for the refusal.

Article 16f

1. A list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products shall be established in accordance with the procedure referred to in Article 121(2). The list shall contain, with regard to each herbal substance, the indication, the specified strength and the posology, the route of administration and any other information necessary for the safe use of the herbal substance as a traditional medicinal product.

2. If an application for traditional-use registration relates to a herbal substance, preparation or a combination thereof contained in the list referred to in paragraph 1, the data specified in Article 16c(1)(b)(c) and (d) do not need to be provided. Article 16e(1)(c) and (d) shall not apply.

3. If a herbal substance, preparation or a combination thereof ceases to be included in the list referred to in paragraph 1, registrations pursuant to paragraph 2 for herbal medicinal products containing this substance shall be revoked unless the particulars and documents referred to in Article 16c(1) are submitted within three months.

Article 16g

1. Articles 3(1) and (2), 4(4), 6(1), 12, 17(1), 19, 20, 23, 24, 25, 40 to 52, 70 to 85, 101 to 108, 111(1) and (3), 112, 116 to 118, 122, 123, 125, 126, second subparagraph, and 127 of this Directive as well as Commission Directive 91/356/EEC (*) shall apply, by analogy, to traditional-use registration granted under this chapter.

2. In addition to the requirements of Articles 54 to 65, any labelling and user package leaflet shall contain a statement to the effect that:

(a) the product is a traditional herbal medicinal product for use in specified indication(s) exclusively based upon long-standing use; and

(b) the user should consult a doctor or a qualified health care practitioner if the symptoms persist during the use of the medicinal product or if adverse effects not mentioned in the package leaflet occur.

A Member State may require that the labelling and the user package leaflet shall also state the nature of the tradition in question.

3. In addition to the requirements of Articles 86 to 99, any advertisement for a medicinal product registered under this chapter shall contain the following statement: Traditional herbal medicinal product for use in specified indication(s) exclusively based upon long-standing use.

Article 16h

1. A Committee for Herbal Medicinal Products is hereby established. That Committee shall be part of the Agency and shall have the following competence:

(a) as regards simplified registrations, to:

— perform the tasks arising from Article 16c(1) and (4),

— perform the tasks arising from Article 16d,

— prepare a draft list of herbal substances, preparations and combinations thereof, as referred to in Article 16f(1), and

— establish Community monographs for traditional herbal medicinal products, as referred to in paragraph 3 of this Article;

(b) as regards authorisations of herbal medicinal products, to establish Community herbal monographs for herbal medicinal products, as referred to in paragraph 3 of this Article;

(c) as regards referrals to the Agency under Chapter 4 of Title III, in relation to herbal medicinal products as referred to in Article 16a, to perform the tasks set out in Article 32;

(d) where other medicinal products containing herbal substances are referred to the Agency under Chapter 4 of Title III, to give an opinion on the herbal substance where appropriate.

Finally, the Committee for Herbal Medicinal Products shall perform any other task conferred upon it by Community law.

The appropriate coordination with the Committee for Human Medicinal Products shall be ensured by a procedure to be determined by the Executive Director of the Agency in accordance with Article 57(2) of Regulation (EEC) No 2309/93.

2. Each Member State shall appoint, for a three-year term which may be renewed, one member and one alternate to the Committee for Herbal Medicinal Products.

The alternates shall represent and vote for the members in their absence. Members and alternates shall be chosen for their role and experience in the evaluation of herbal medicinal products and shall represent the competent national authorities.

The said Committee may coopt a maximum of five additional members chosen on the basis of their specific scientific competence. These members shall be appointed for a term of three years, which may be renewed, and shall not have alternates.

With a view to the coopting of such members, the said Committee shall identify the specific complementary scientific competence of the additional member(s). Coopted members shall be chosen among experts nominated by Member States or the Agency.

The members of the said Committee may be accompanied by experts in specific scientific or technical fields.

3. The Committee for Herbal Medicinal Products shall establish Community herbal monographs for herbal medicinal products with regard to the application of Article 10(1)(a)(ii) as well as traditional herbal medicinal products. The said Committee shall fulfil further responsibilities conferred upon it by provisions of this chapter and other Community law.

When Community herbal monographs within the meaning of this paragraph have been established, they shall be taken into account by the Member States when examining an application. Where no such Community herbal monograph has yet been established, other appropriate monographs, publications or data may be referred to.

When new Community herbal monographs are established, the registration holder shall consider whether it is necessary to modify the registration dossier accordingly. The registration holder shall notify any such modification to the competent authority of the Member State concerned.

The herbal monographs shall be published.

4. The general provisions of Regulation (EEC) No 2309/93 relating to the Committee for Human Medicinal Products shall apply by analogy to the Committee for Herbal Medicinal Products.

Article 16i

Before 30 April 2007, the Commission shall submit a report to the European Parliament and to the Council concerning the application of the provisions of this chapter.

The report shall include an assessment on the possible extension of traditional-use registration to other categories of medicinal products.

(*) OJ L 193, 17.7.1991, p. 30.'

Article 2

1. The Member States shall take the necessary measures to comply with this Directive by 30 October 2005. They shall forthwith inform the Commission thereof.

When Member States adopt these measures, they shall contain a reference to this Directive or shall be accompanied by such a reference on the occasion of their official publication. The methods of making such reference shall be laid down by the Member States.

2. For the traditional herbal medicinal products as referred to in Article 1, which are already on the market on the entry into force of this Directive, the competent authorities shall apply the provisions of this Directive within seven years after its entry into force.

Article 3

This Directive shall enter into force on the day of its publication in the *Official Journal of the European Union*.

Article 4

This Directive is addressed to the Member States.

Done at Strasbourg, 31 March 2004.

For the European Parliament	*For the Council*
The President	*The President*
P. COX	D. ROCHE