添付書類 E：データ総括表のサンプル

データ総括表のサンプル	
物理的／化学的特性	
水溶性[1]	
解離定数	
オクタノール／水分配係数の log 値(Log K_{OW})[1]	
蒸気圧またはヘンリーの法則係数	
収着／脱着(K_{OC})[1]	
低減メカニズム	
加水分解	
好気性微生物分解	
土壌微生物分解	
光分解	
代　謝	
環境影響[2]	
微生物阻害	
急性毒性	
慢性毒性	

[1] 解離定数によっては、水溶性及びオクタノール／水分配係数を pH 7 に加えて、pH 5 及び pH 9 で測定しなければならないことがある。あるいは K_{oc} 中性土壌に加えて、酸性及び／またはアルカリ性土壌で測定しなければならないことがある。指針については、IV.B.1.a.ii 項を参照。

[2] 生物の識別を示し、結果、例えば、ppm で示した有効成分の NOEC、MIC、EC_{50}、LC_{50} を報告する。

添付書類 F：機密／非機密

EA 書式項目	下位の項	非機密	機　密
1.　日　付	***	X	
2.　申請者／請願者の名称	***	X	
3.　住　所	***	X	
4.　申請措置の説明	a.　承認の要請	X	
	b.　措置の必要性	X	
	c.　使用場所	X	
	d.　廃棄場所	X	
5.　申請措置の対象である物質の識別	a.　名　称	X	
	b.　CAS 番号	X	
	c.　分子式	X	
	d.　分子量	X	
	e.　構造式	X	

EA 書式項目	下位の項	非機密	機　密
6. 環境問題 （IV.B 項に示された特定の環境問題）	a. 環境生物に対する毒性評価	例えば： * 環境に入るか、存在すると予想される物質 * 親（活性）化合物と比較した主な SRS の毒性／活性に関する総括考察 * 物理／化学特性に関する試験結果 * 環境濃度推定値計算法 * 空間的／時間的低減要素に関する支持情報 * 環境影響試験の結果	例えば： * SRS に対する特別毒性／薬理活性データ * 試験報告書 * 環境濃度推定値
	b. 動物植物の使用	例えば： * 用いた種に関する生物学的識別及び他の情報（例えば、植物成長速度） * 入手源の地理的地域 * 政府による監督 * 採取方法	例えば： * 有効成分 1 kg を製造するのに必要なバイオマスのバルク重量 * 採取量 * 予想患者集団及び 1 年当たりに使用すると予想される有効成分の kg 数
7. 緩和対策	***	X	
8. 申請措置に対する代替	***	X	
9. 作成者リスト	***	X	

EA 書式項目	下位の項	非機密	機　密
10. 参考文献	***	X	
11. 付属書	***	例えば： * 一般に入手可能でないか、または EA 中の特定の主張を支持するために使用した参照文献 * データ総括表	例えば： * 年間に使用予定の有効成分の推定 kg 数 * 試験報告書 * DMF の認可書

添付書類 G：用語解説

有効成分：分子またはイオンで、その医薬品を分子のエステル、塩（水素結合または共有結合を有する塩を含む）または他の非共有誘導体（錯体、キレートまたは包接化合物）とする分子の添付部分を除いた、原薬の生理学的または薬理学的作用をおこす部分（21 CFR 314.108(a)）。有効成分は、全分子またはイオンであって、「活性部位」ではない。

生物蓄積性：産業廃棄物、化学物質及び他の物質が生物組織中の徐々に蓄積するプロセス

生物濃縮性：産業廃棄物、化学物質及び他の物質が水中から直接的に水域生物に蓄積するプロセス

生物製剤：ヒトの疾患または健康状態の予防、治療または治癒に適用できるウイルス、治療用血清、毒素、抗毒素、ワクチン、血液、血液成分、誘導体、アレルゲン性製品または類似製品（Public Health Service Act（公衆衛生法）の section 351）

バイオマス：医薬品または生物製剤に加工するために収集される植物、植物の一部（例えば、樹皮、葉、花、種子）、動物または動物の一部（例えば、皮膚、肝臓、胃）

医薬品：最終剤形、例えば、錠剤、カプセルまたは溶液で、一般的に原薬を含むが、必ずしも1つまたは複数の成分と関連している必要はない．（21 CFR 314.3(b)）

原　薬：疾患の診断、治癒、緩和、治療または予防において薬理活性または他の直接的な作用を与えるか、または人体の構造や機能に影響を与えることを目的とする活性成分、ただし，当該成分の合成に使用する中間体を含まないもの（21 CFR 314.3(b)）

予測環境濃度（Expected environmental concentration; EEC）：空間または時間濃度や、希釈、分解、収着、生物蓄積性などの低減要素を考慮した後に、環境中（水面等）で生物が曝露される対象有効成分または他の構造的に関連のある物質の予測濃度。Predicted environmental concentration; PEC と言うこともある。

廃棄に対する予測導入濃度（Expected introduction concentration; EIC）：廃棄により環境中に入る可能性のある有効成分の予測導入濃度。本文に示すように、環境中に入る前に生じる低減メカニズムを計算で考慮できる。

使用に対する予測導入濃度（EIC）：5ヵ年販売推定量に基づく、使用により環境中に入る可能性のある有効成分の予測導入濃度。環境中に入る前に生じる低減メカニズムと人体による代謝を、本文に示すように計算で考慮できる。

半減期（$t_{1/2}$）：物質が半分減少するのに要する時間

最小影響濃度（LOEC）：毒性試験において対照と比較して試験生物の曝露集団に対し統計学的に有意な有害影響を及ぼす最低濃度

マスターファイル：申請書の審査時に参照してもらう意図のある人による FDA に対する情報の提出。ドラッグ・マスターファイルに関する特定情報については、21 CFR 314.420 を参照。

最高予測環境濃度（MEEC）：予測導入濃度（EIC）または予測環境濃度（EEC）のうち、値が高い方。

50%影響濃度（EC_{50}）：生物が曝露される濃度で、試験生物の 50%になんらかの亜致死性反応を起こすのに有効と推定される濃度。通常、EC_{50} は時間依存変数として表現される（例えば、24 時間 EC_{50}）

50%致死濃度（LC_{50}）：生物が曝露される物質の濃度で、試験生物の 50%に致死的と推定される濃度。通常、LC_{50} は時間依存変数として表現される（例えば、24 時間 LC_{50}）。

最小阻止濃度（MIC）：試験生物の目にみえる増殖を阻害する化学物質の最低濃度

新成分：米国において、単一成分として、または配合製品の一部あるいは立体異性体の混合物の一部として医薬品で使用するために、医薬品用の有効成分として以前に承認または市販されたことのない有効成分（未修飾の塩基（親）化合物あるいはエステルまたは塩、包接体、他の塩基（親）化合物の非共有誘導体として存在する）

無影響濃度（NOEC）：毒性試験において対照と比較して試験生物の曝露集団に対し統計学的に有意な有害影響を及ぼさない最高濃度

オクタノール／水分配係数（K_{OW}）：平衡状態にある n-オクタノールと水中での化学物質の溶解性の比で、P とも表現される。医薬品または生物製剤の親油性の測定値で、細胞膜を通過する能力の指標。P または K_{OW} の対数は、化学物質が生体内蓄積するか、または土壌や堆積物に吸着する傾向の推定値として使用される。

Parts per billion（ppb）：溶媒（例えば水）または生物（例えば、組織）の 10 億（10^9 単位あたり、化学物質 1 単位（通常、質量で示される）。水に対しては 1 μg/L＝1 ppb、組織に対しては、1 μg/kg＝1 ng/g＝1 ppb

Parts per million（ppm）：溶媒（例えば水）または生物（例えば、組織）の 100 万（10^6 単位あたり、化学物質 1 単位（通常、質量で示される）。水に対しては 1 mg/L＝1 ppm、組織に対しては、1 mg/kg＝1 μg/g＝1 ppm

Parts per trillion（pptr）：溶媒（例えば水）または生物（例えば、組織）の 1 兆（10^{12} 単位あたり、化学物質 1 単位（通常、質量で示される）。水に対しては 1 ng/L＝1 pptr、組織に対しては、1 ng/kg＝1 pptr

土壌または堆積物／水分配係数（K_{OC}）：平衡状態にある溶液中の化学物質の濃度に対する土壌または堆積物中の有機炭素の単位重量あたりに吸着される化学物質の比

毒　性：生物に有害な影響を起こす物質固有の可能性または能力

Figure 1
Tiered Approach to Fate and Effects Testing

可能性のある影響の環境を決定する
大気，水生あるいは陸生動物

分解機構の調査　　微生物抑制試験　　Stop

分解機構が早くなく，不完全

微生物抑制試験

Log $K_{ow} \geq 3.5$ であれば慢性毒性試験の開始を考える　　Tier 3
Log $K_{ow} < 3.5$ or Log $K_{ow} \geq 3.5$ で判断

TIER 1
急性毒性
1 動物種　　LC_{50} or $EC_{50} \geq 1000$
MEEC　　MEEC で無影響　　Stop
MEEC で影響　　Tier 3

LC_{50} or $EC_{50} < 1000$
MEEC

TIER 2
急性毒性
水生 and/or
陸生生物　　LC_{50} or $EC_{50} \geq 100$
MEEC　　MEEC で無影響　　Stop
MEEC で影響　　Tier 3

LC_{50} or $EC_{50} < 100$
MEEC

TIER 3
慢性毒性試験
水生 and/or
陸生生物　　LC_{50} or $EC_{50} \geq 10$ であり，MEEC で無影響　　Stop
MEEC

LC_{50} or $EC_{50} < 10$ あるいは MEEC で無影響
MEEC

CDER/CBER と相談

Note: MEEC = EEC と EIC の高い方

EIC-Aquatic (ppb) = A x B x C x D

A：直接使用のための年間製造量（活性成分として）　kg
B：１日の公共下水処理　(POTWs)量　L
　(EPA では 1.214×10^{11} L/day，定期更新)
C：365 日
D：10^9ug/kg (変換計数)

K_{ow}：オクタノール／水　分配係数

ＥＥＣ：予想環境中濃度
ＥＩＣ：予想廃棄濃度（環境中に廃棄された地点での濃度）
ＭＥＥＣ：最小予想環境中濃度

＜Tier 1 試験＞
・水生動物の試験が一般的

＜Tier 2 試験＞
・水生動物および／あるいは陸生動物の最低基本試験一組

水生動物を用いる試験
１．魚の急性毒性
２．無脊椎動物の急性毒性
３．藻類のバイオアッセイ
陸生動物を用いる試験
１．植物の初期成育試験
２．ミミズの毒性試験
３．土壌微生物毒性試験

＜Tier 3 試験＞
・水生動物および／あるいは陸生動物の慢性毒性試験
・当局と協議し試験系を選択

試験法：
FDA: Environmental Assessment Technical Handbook
EPA: 40 CFR 797
OECD ガイドライン

	米国
ガイドライン等	Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications (July 1998)
対象	新医薬品 * ただし下記 Categorical Exclusion に該当する場合は対象外 (1) NDA, ANDA, 生物学的製剤の承認申請，およびこれら申請の supplements で，承認されても活性本体の使用量が増加しない場合 (2) NDA, ANDA, およびこれら申請の supplements で，承認により活性本体の使用量は増加するが，水生環境中の予測濃度(EIU)が 1 part per billion (ppb) = 1 μg/l 未満である場合 (3) 自然界にある物質の NDA, ANDA, 生物学的製剤の承認申請，およびこれら申請の supplements で，承認により，その物質の環境中の濃度，分布，代謝，分解が大きく変化しない場合 (4) IND (5) 輸血用血液あるいは血漿成分の承認申請
試験項目	微生物による分解性試験 ↓ 急性毒性試験(1 動物種) ↓ 急性毒性試験(水生，陸生生物) ↓ 慢性毒性試験(水生，陸生生物)
添付資料としての位置付け	

FDA 試験法リスト

初期

要求データ／試験	Environmental Assessment Technical Handbook	
オクタノール／水	3,02	OECD107, 117
水中有酸素生分解	3.11	OECD302(A,B,C)
土壌中有酸素生分解	3.12	OECD304A
微生物抑制試験	4.02	OECD209

Tire 1

要求データ／試験	Environmental Assessment Technical Handbook	
ミジンコ急性毒性	4.08	OECD202（急性遊泳阻害試験のみ）

（通常水生動物１種）

Tier 2

要求データ／試験	Environmental Assessment Technical Handbook	
魚の急性毒性	4.11	OECD203
無脊椎動物の急性毒性	4.10	OECD202（急性遊泳阻害試験のみ）
藻類のバイオアッセイ	4.01	OECD201
植物の初期成育試験	4.07	OECD208
ミミズの毒性試験	4.12	OECD207
土壌微生物毒性試験	不明	OECD216 および 217 が該当すると考えられる.

（基本試験一組以上）

Tier 3

要求データ／試験	Environmental Assessment Technical Handbook	
ミジンコ慢性毒性試験	4.09	OECD211 のオオミジンコ繁殖試験が検討されると考えられる.

（当局と協議し試験系を選択）

Guidance for Industry

Environmental Assessment of Human Drug and Biologics Applications

Copies of this guidance are available from the Office of Training and Communications, Division of Communications Management, Drug Information Branch, HFD-210, 5600 Fishers Lane, Rockville, MD 20857 (Phone 301-827-4573) or from the Internet at http://www.fda.gov/cder/guidance/index.htm.

Copies also are available from the Office of Communication, Training and Manufacturers Assistance, HFM-40, CBER, FDA, 1401 Rockville Pike, Rockville, MD 20852-1448, or from the Internet at http://www.fda.gov/cber/guidelines.htm. Copies also may be obtained by fax from 1-888-CBERFAX or 301-827-3844 or from Voice Information at 800-835-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
July 1998
CMC 6
Revision 1

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GUIDANCE FOR INDUSTRY[1]

Environmental Assessment of Human Drug and Biologics Applications

I. INTRODUCTION

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impacts of their actions and to ensure that the interested and affected public is informed of environmental analyses. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impacts of approving drug and biologics applications as an integral part of its regulatory process. FDA's regulations in 21 CFR part 25 specify that environmental assessments (EAs) must be submitted as part of certain new drug applications (NDAs), abbreviated applications, applications for marketing approval of a biologic product, supplements to such applications, investigational new drug applications (INDs) and for various other actions (see 21 CFR 25.20), unless the action qualifies for categorical exclusion.

Under the President's reinventing government (REGO) initiatives, announced in April 1995, FDA reevaluated and revised its environmental regulations to reduce the number of EAs required to be submitted by industry and, consequently, the number of findings of no significant impact (FONSIs) prepared by the Agency under NEPA. FDA issued for public comment a notice of proposed rulemaking on April 3, 1996 (61 FR 14922) (republished May 1, 1996 (61 FR 19476)), that proposed additional categorical exclusions for those actions that have been identified as normally not having a significant effect, individually or cumulatively, on the quality of the human environment. The final rule was published on July 29, 1997 (62 FR 40569), and became effective August 28, 1997. All applications or petitions requesting Agency action (e.g., NDAs, abbreviated new drug applications (ANDAs), INDs, biologics license applications (BLAs), supplements to such applications) must be accompanied by either an EA or a claim of categorical exclusion. Failure to provide (1) a claim of categorical exclusion or (2) an adequate EA, is sufficient grounds for ***refusing to file or approve*** the application (21 CFR 314.101(d)(4), 601.2(a) and (c), and 25.15(a)). An EA that is adequate for filing is one that addresses the relevant environmental issues. An EA adequate for approval is one that contains sufficient information to enable the Agency to determine whether the proposed action may affect significantly the quality of the human environment. This guidance provides information on when an EA should be submitted; it also makes recommendations on how to prepare EAs for submission of drug or biologics applications to the Center for Drug Evaluation and Research (CDER) and the Center for

[1] This guidance has been prepared under the direction of the Chemistry Manufacturing Controls Coordinating Committee, Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on environmental assessments. 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 statute, regulations, or both.

Biologics Evaluation and Research (CBER). Topics covered include (1) when categorical exclusions apply, (2) when to submit an EA, (3) the content and format of EAs, (4) specific guidance for the environmental issues that are most likely to be associated with human drugs and biologics, (5) test methods, (6) an applicant's treatment of confidential information submitted in support of an EA, and (7) master files for drugs and biologics.

This guidance, which is based on the July 1997 final rule, will remain in effect until superseded by new regulations or new guidance. The guidance is intended to supersede CDER's *Guidance for Industry For the Submission of an Environmental Assessment in Human Drug Applications and Supplements,* which was published in November 1995. Information in this guidance, along with information in the Code of Federal Regulations (CFR) at 21 CFR part 25 and 40 CFR parts 1500-1508 and the FDA *Environmental Assessment Technical Handbook* (NTIS Publication Number PB 87 175345/AS), which provides information on acceptable test methods, represents the core information available from CDER and CBER to assist industry in preparing an EA.

II. WHAT TYPES OF ACTIONS ARE SUBJECT TO CATEGORICAL EXCLUSION?

Certain classes of actions are subject to categorical exclusion and, therefore, ordinarily do not require the preparation of an EA because, as a class, these actions, individually or cumulatively, do not significantly affect the quality of the human environment (21 CFR 25.5(c)). However, as required under 21 CFR 25.21 and 40 CFR 1508.4, FDA will require "at least an EA" for any specific action that ordinarily would be excluded if extraordinary circumstances indicate that the specific proposed action may significantly affect the quality of the human environment.[2] See section III.C for additional information regarding extraordinary circumstances.

Submissions to CDER or CBER that ordinarily are excluded categorically under the regulations include actions on (1) NDAs, abbreviated applications, applications for marketing approval of a biologic product, and supplements to such applications if FDA's approval of the application does not increase the use of the active moiety; (2) NDAs, abbreviated applications, and supplements to such applications if FDA's approval of the application increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb); (3) NDAs, abbreviated applications, applications for marketing approval of a biologic product, and supplements to such applications for substances that occur naturally in the environment when the approval of the application does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment; (4) INDs; and (5) applications for marketing approval of a biologic product for transfusable human blood or blood components and plasma. An applicant is eligible

[2] Regulations would require an EIS (environmental impact statement) when "evaluation of data or information in an EA or otherwise available to the agency leads to a finding by the responsible agency official that a proposed action may significantly affect the quality of the human environment (21 CFR 25.22(b)).

to file a claim of categorical exclusion from the requirement to submit an EA if the action meets the criteria of at least one categorical exclusion.

A person submitting an application or petition of a type subject to categorical exclusion under 21 CFR 25.31 is not required to submit an EA if the person states that the action requested qualifies for categorical exclusion, citing the particular categorical exclusion that is claimed, and states that to the applicant's knowledge, no extraordinary circumstances exist (21 CFR 25.15(d)). An applicant ordinarily need not provide data to demonstrate that the action qualifies for categorical exclusion. CDER and CBER can rely on other information submitted in an application to evaluate the appropriateness of a claim for categorical exclusion. In the limited instances when it may be necessary, CDER or CBER will request additional information as needed to establish to their satisfaction that the criteria for categorical exclusion have been met.

III. WHEN IS AN EA REQUIRED?

Preparation of an environmental assessment ordinarily is required unless the proposed action qualifies for an exclusion under 21 CFR 25.30 or 25.31. An EA would also be required if extraordinary circumstances indicate that the specific proposed action may significantly affect the quality of the human environment (21 CFR 25.21).

Detailed information is provided below for the most common situations when actions would not qualify for categorical exclusion.

A. NDAs, Abbreviated Applications, and Supplements

Note: Section 1, below, should be used to assess increased use of a biological product as referenced in 21 CFR 25.31(a). Section 2 does not apply to biologics license applications (BLAs) because BLAs are not included in the categorical exclusion on which this section is based (21 CFR 25.31(b)). BLAs should be evaluated for whether they are eligible for categorical exclusion using 21 CFR 25.31(a) or (c) or other appropriate categorical exclusions found in 21 CFR 25.30 and 25.31.

NDAs, abbreviated applications, and supplements to such applications would not qualify for categorical exclusion if FDA's approval of the application increases the use of the active moiety ***and*** the estimated concentration of the substance at the point of entry into the aquatic environment will be 1 ppb or greater.

1. Increased Use

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

Attachment A contains examples of actions that would not be considered to increase the use of a drug and Attachment B contains examples of actions that would be considered to increase the use of a drug or biologic. These lists are not inclusive. An applicant is encouraged to contact the appropriate Center if any questions arise as to whether a particular action is considered to increase the use of a drug or biologic.

2. Estimating the Concentration of a Substance at the Point of Entry into the Aquatic Environment

The expected introduction concentration (EIC) of an active moiety into the aquatic environment should be calculated as follows:

EIC-Aquatic (ppb) = A x B x C x D where

A = kg/year produced for direct use (as active moiety)
B = l/liters per day entering POTWs*
C = year/365 days
D = 10^9 µg/kg (conversion factor)

* 1.214 x 10^{11} liters per day entering publicly owned treatment works (POTWs), Source: *1996 Needs Survey, Report to Congress.* Information regarding the *Needs Survey* is available on the Internet at http://www.epa.gov/owm. It is updated periodically.

This calculation assumes:

- All drug products produced in a year are used and enter the publicly owned treatment works (POTW) system.
- Drug product usage occurs throughout the United States in proportion to the population and amount of waste water generated.
- There is no metabolism.

The estimate of the kilogram/year active moiety should be based on or include (1) the highest quantity of the active moiety expected to be produced for direct use in any of the next five years. *Produced for direct use* means the quantity intended for use in humans during a given year (i.e., excludes any quantity produced for inventory buildup), (2) the quantity used in all dosage forms and strengths included in the application, and (3) the quantity used in an applicant's related applications. Related applications include those for other dosage forms using the same active moiety and for products using different forms of the active moiety (e.g., level of hydration, salt, free acid/base). All concentrations should be reported as the

concentration of active moiety, rather than the salt or complex.

The calculation of the expected introduction concentration (EIC) of an active moiety entering into the aquatic environment from patient use can consider the extent of metabolism of the active moiety to less pharmacologically active or inactive compounds, if that information is available. The pharmacological activity of metabolites relative to the active moiety should be considered when calculating the EIC. The weighted contribution of the metabolite to the EIC should be calculated (e.g., kg/year active moiety x 10% x 0.5 for a metabolite found at a level of 10% and that has half the pharmacological activity of the active moiety). If the pharmacological activity of the metabolite is unknown, it can be assumed to be the same as the active moiety.

An alternative calculation should be used if the drug product is intended for use in a specific geographic location (e.g., use an alternative value for the amount of liters per day entering POTWs — term B in the EIC calculation above). Moreover, if an alternative calculation is used to estimate localized use, or for any other reason, the calculation and the source and basis for the alternative calculation should be provided when filing an EA or a claim of categorical exclusion and would be subject to review.

B. Applications for Substances that Occur Naturally in the Environment

NDAs, abbreviated applications, applications for marketing approval of a biologic product and supplements to such applications for substances that occur naturally in the environment would not qualify for categorical exclusion under 21 CFR 25.31(c) when FDA's approval of the application alters significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. This might be the case when the use and disposal occur in a geographic area where the substance does not naturally occur. However, the application may be eligible for a categorical exclusion under other provisions in 21 CFR 25.31.

In addition to drug and biologic products derived from natural sources or from biological systems, substances can be considered naturally occurring even if they are chemically synthesized. The Agency will consider the form in which the FDA-regulated article will exist in the environment when determining whether the drug or biologic is a naturally occurring substance. For example, a modified active moiety (e.g., salt) that does not occur naturally could be considered a naturally occurring substance if it is established that, in vivo and in the environment, the active moiety exists in a form that is found naturally.

Biological and biotechnological products will be similarly evaluated. For example, a protein or DNA comprising naturally occurring amino acids or nucleosides, but having a sequence different from that of a naturally occurring substance, will normally qualify as a

naturally occurring substance after consideration of metabolism. The same principle would apply to synthetic peptides and oligonucleotides and living and dead cells and organisms. CDER and CBER may rely on other information submitted in an application (e.g., information about metabolism, excretion, and stability; viability (if applicable); and physical and/or chemical characteristics of the product) in determining whether the FDA-regulated article would be considered a naturally occurring substance.

CDER and CBER will evaluate on a case-by-case basis the appropriateness of categorical exclusions claiming that the quantity of the naturally occurring substance that is expected to enter the environment as a result of an action will not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

C. Extraordinary Circumstances

As stated in 21 CFR 25.21 and 40 CFR 1508.4, FDA will require at least an EA for any specific action that ordinarily would be categorically excluded if extraordinary circumstances indicate that the specific proposed action could significantly affect the quality of the human environment. Extraordinary circumstance can be shown by data available either to the Agency or the applicant and can be based on the production, use, or disposal from use of the FDA-regulated article. Data available to the Agency can include public information, information submitted in the application, and data available to the Agency on the same or similar products.

1. Actions for which available data establish that there is a potential for serious harm to the environment at the expected level of exposure.

FDA considers harm to the environment to include not only toxicity to environmental organisms but also environmental effects other than toxicity, such as lasting effects on ecological community dynamics.

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

Actions that adversely affect a species or the critical habitat of a species determined under the Endangered Species Act to be endangered or threatened, wild fauna or flora listed in the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES), or wild fauna or flora that are entitled to special protection under some other Federal law or international treaty to which the United States is a party would be considered an extraordinary circumstance, and an EA should be submitted unless there are specific exemptions relating to the

pharmaceutical substances or FDA action. An example of an exception would be when a species is afforded special protection under Federal law or international treaty, but the pharmaceutical is derived only from nonwild specimens. If nonwild specimens are exempted from Federal law or treaty, the action would be eligible for categorical exclusion as indicated in section III.C.3.a. Both direct effects (e.g., pharmaceuticals derived from fauna or flora, see section III.C.3) and indirect effects (e.g., adverse effects from manufacturing site emissions) should be considered.

Under the U.S. Endangered Species Act (ESA), Congress declared, "[T]he United States has pledged itself as a sovereign state in the international community to conserve to the extent practicable the various species of fish or wildlife and plants facing extinction, pursuant to the Convention on International Trade in Endangered Species of Wild Fauna and Flora" (16 U.S.C. 1531(a)(4)(F)). Identification as an endangered or threatened species does not preclude the use of such fauna or flora. However, under the ESA, if a species has been determined to be endangered or threatened, a Federal agency is required to consult with the Secretary of Interior or the Secretary of Commerce to ensure that the agency's actions are not likely to jeopardize the continued existence of endangered or threatened species or their critical habitats (16 U.S.C. 1536).

3. Use of Fauna or Flora

FDA intends to examine closely the proposed actions for FDA-regulated articles obtained from fauna and flora and will use the extraordinary circumstances provision to require an EA in any instance in which it appears from an examination of the proposed action that the action may jeopardize the continued existence of a species. The following sections discuss CDER's and CBER's current position on when the use of fauna or flora normally would constitute an extraordinary circumstance for which an EA should be submitted to support the application.[3]

a. Cultivated Specimens

Actions involving drug or biologic products derived from cultivated plants (e.g., plantation, nursery stock) or bred or domestic animals (e.g., laboratory breed, cows, pigs) are not normally considered an extraordinary circumstance that would require an EA for an action that is normally categorically excluded (see section III.C.2 for a possible exception).

b. Wild Specimens

[3] FDA may clarify the environmental information that must be submitted to the Agency in marketing applications for specific drug or biologic products derived from plants or animals (e.g., paclitaxel, 61 FR 58694).