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APPLICATION NUMBER:
21-902.

BOTANICAL REVIEW

BOTANICAL DRUG REVIEW

BY

BOTANICAL REVIEW TEAM

Application Type: NDA
Submission Number: 21-902
Submission Code: N000
Letter Date: 000
Stamp Date: 09-30-2005
Established Name: TBD
PDUFA Goal Date: 07-31-2006 [Extended to 10-31-2006]
Applicant: MediGene AG
Other (orphan, OTC, etc.) none
DMF #: ~
Amendment dated 09-28-2006 and 10-12-2006

Trade Name: Polyphenon[®] E Ointment 15%
Established Name: To be determined
Priority Designation: S
Route of Administration: Topical
Botanical Raw Material: Green Tea, the dried leaves of *Camellia sinensis* (L.) O. Kuntze [Family: Theaceae]
Botanical Drug Substance: Polyphenon[®] E, a partially purified green tea extract with 85-95% catechins
Indication(s) requested: Polyphenon[®] E, 15 % is indicated for the topical treatment of external genital and peri-anal warts (*Condylomata acumata*) in adult patients.

Botanical Review Team Reviewer: Jinhui Dou, Ph.D.
Review Amendment Number: 01
Purpose of Review Amendment: New botanical raw material information provided in DMF Amendments dated 09-28-2006 and 10-12-2006
Review Amendment Completion Date: 10-19-2006
Botanical Review Team Leader: Shaw T. Chen, M.D., Ph.D.

Review Division: Division of Dermatology and Dental Drug Products

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

CDER/OND/ODE-I/Botanical Review Team

Date: 09/15/2006
From: Shaw T. Chen, M.D., Ph.D., Botanical Review Team Leader, ODE-I
Through: Director, ODE-I
To: Director, Office of Medical Policy, CDER
Director, ODE-III, OND
Director, Div. of Dermatological & Dental Drug Products, ODE-III
Subject: Botanical Review of NDA 21-902, Veregen (kunecatechins) for genital and perianal warts

INTRODUCTION

This is a Botanical Review Team (BRT) Leader's memo to amend the review of NDA 21-902, Veregen 15% ointment for the treatment of genital/perianal warts. This NDA is the first ever submitted for a botanical drug product, at least¹ since the Agency started the drafting of CDER's *Guidance for Industry: Botanical Drug Products* over 10 years ago (the document is referred to as "Botanical Guidance" or "Guidance" in this memo, the final version of the document was released in June of 2004).

The BRT pharmacognosist, Dr. Jin-Hui Dou has completed a primary review of this application, which was submitted to the NDA file in DFS on April 28, 2006. Veregen is a relatively simple botanical derived from a single part of a single plant (green tea leaves), containing a class of well-studied chemical entities as the major active ingredients (catechins). From the BRT's perspective, there is no issue that should preclude the approval of this NDA. Additional measures to further strengthen the quality control and to ensure therapeutic consistency of the marketing batches are recommended by the BRT and CMC groups.

As the new drug divisions in OND are getting familiar with the Botanical Guidance and feel more comfortable handling initial IND submissions of botanical products in the past few years², late phase development of botanical new drugs remains a rarity and review experience with botanical NDA is still lacking. Many of the issues unique to botanical NDAs have just emerged with this submission (EOP2 meeting in 2001) and our approaches to these specific regulatory concerns were evolving during the past few years. Since we are now setting precedents with the first botanical NDA that

¹ There are a few OTC monographs that contain botanical ingredient(s), but no NDA has been submitted for a new botanical prescription drug.

² with an accumulated total of over ~~one~~ botanical INDs in OND divisions as of June 1, 2006

may affect future applications, it is important to delineate our reasoning for resolving these issues and to document how we arrived at the position for the current application.

BOTANICAL GUIDANCE & RELATED POLICY ISSUES

The Botanical Guidance of June 2004 provides that both purification and identification of the active ingredients in botanicals are optional and not required. While this provision has facilitated clinical studies of botanicals that have been used extensively in alternative medical practice, it does pose difficult regulatory issues for quality control of botanical products as most of our regulations were designed for pure chemical drugs. Nevertheless, as this NDA illustrated, these technical problems can be overcome and a reasonable sense of confidence in the product quality and its therapeutic consistency can be attained.

Because the botanical drug products are allowed to remain as complex mixtures, quality consistency is a more complicated issue than that of non-botanicals. It became necessary to extend the control of botanical drug substance and product to that of botanical raw material, and in some cases, to the agricultural aspects of growing/harvesting medicinal plants (GAP, or Good Agricultural Practice). However, requiring detail characterization of cultivated varieties (cultivars) (as we did for this NDA) or GAP compliance can only help to a certain degree; the chemical specifications (e.g., by HPLC fingerprinting) for botanicals would rarely be as precise as that of non-botanical drugs. As shown in this NDA, the number and choice of chemical entities subjected to monitoring is also another point of contention, especially when potential active ingredients are numerous and not yet identified. The Guidance also suggested development of clinically relevant bioassay to support quality control and clinical pharmacology studies, which has not been done for this application. The Agency does not require bioassay for approval of this NDA.

The Guidance also stipulates that because many botanicals have been used as medicine in alternative medical systems for long time, the prior human experiences may substitute for animal toxicology studies in the preliminary safety evaluation of IND studies. How these human data, mostly not of modern scientific quality, can be useful to support an NDA application was not clearly described in the Guidance. Instead, conventional non-clinical studies were suggested for the later phase development of most botanical drugs. For this NDA, the sponsor has conducted the full battery of non-clinical toxicity studies and did not request exemption from such requirements because of long history of green tea consumption in human (see pharmacology review).

For clinical data to support marketing approval, there should be no difference between botanical and non-botanical drugs. Aside from the concern of therapeutic consistency for marketing batches (see below), there is no botanical specific issue in the clinical development of this product.

In most parts, the Botanical Guidance was written with the IND submission and review in mind. Relatively little attention was paid to the requirements for approval of botanical NDA at the time of drafting the document, probably because few were sure that following the Guidance would lead to successful NDA submission and it was hard to image what a botanical NDA package would look like. Thus some NDA-related issues emerged only after rare discussions of late phase studies with sponsors and with the submission of this application. Our regulatory approaches to these issues were also evolving with these developments and it was not surprising that some of the recommendations in the Guidance may be ill-advised and should be changed. For example, it was suggested in the Guidance that one large single batch of the botanical product be used in the clinical trials to ensure interpretable results. However, it now appears that testing multiple batches in phase 3 trials may be necessary to examine the consistency of therapeutic effects in various batches (see below).

The issue of combination drug products, whether botanicals should be subject to the requirement of demonstrating contribution from each active ingredient, was not discussed in the Guidance. Instead, it was decided to revise the policy on combination products separately, which is currently under discussion in the Agency. While many details of the revision remain to be finalized, it is clear that natural mixtures in single parts of single plants will be considered as a monotherapy and not subject to the combination requirement. Combination drug product is thus not an issue for this NDA (tea leaves).

THE SCOPE OF BOTANICAL REVIEW

To implement the Botanical Guidance, we established a new review discipline in the OND, assembled a dedicated review team, and outlined the scope of botanical review. As described in the Manual of Policy and Procedure (CDER MaPP 6007.1) for processing botanical applications, the BRT review covers the following area:

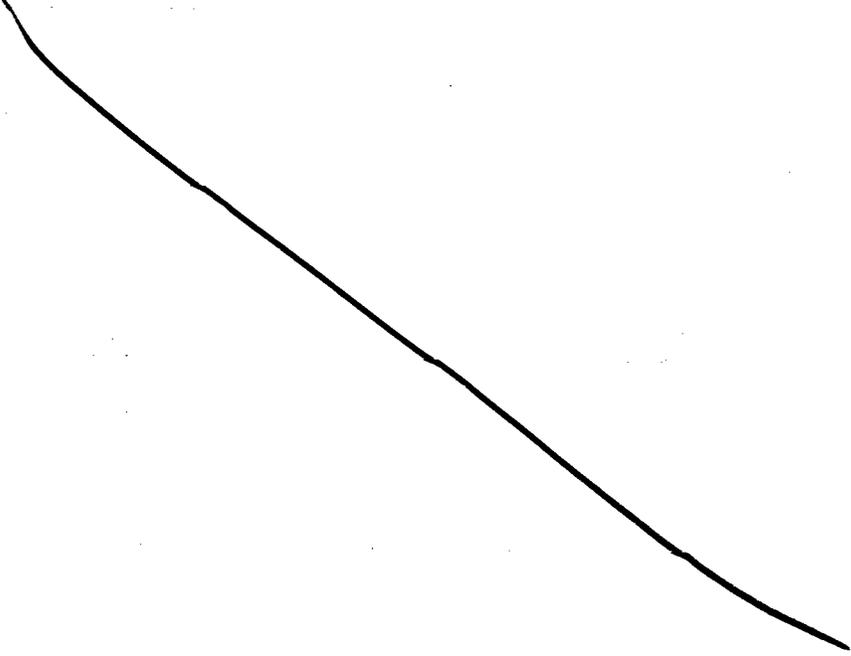
- i) **Biology of the medicinal plants** – identification, potential misuse of related species
- ii) **Pharmacology of the botanical product** – activity/toxicity in old documents and new testings
- iii) **Prior human experiences with the botanical product** – past clinical use and relevance to current setting

The purpose was to provide historical background of the botanical, to help the review division understand better the product and to search for information that may be relevant to the new use. Similar to the Guidance, the botanical MaPP was also designed mainly for the initial IND review. As the development of some botanical INDs progressed, other concerns more pertinent to NDA approval emerged. The scope of NDA review for botanical drugs was thus expanded to include:

- iv) **Selection of an established name** (USAN designation or generic name)
- v) **Assurance of therapeutic consistency of marketing batches**

To coin the new name for a botanical drug is an intellectually challenging and interesting exercise. For proper identity, the generic name of a botanical should not only identify the species and variety, but also catch the essence of unique agriculture and manufacturing processes. In this sense, the USAN-approved designation of “kunecatechins”³ (from combining “Kuntz”, author in the species name, and “catechins”) didn’t fully cover the uniqueness of the product for this NDA. We have accepted the USAN designation despite the shortfall. But the sponsor objects to this generic name, arguing that it is too non-specific, and may appeal for change.

As products of natural complex mixtures, the botanical new drugs can rarely have CMC specifications as precise as that of pure chemical drugs. Without the same degree of CMC control as for pure drugs, one critical question for approval of botanical drugs is whether the future marketing batches will have the same therapeutic effects as that observed in clinical trials. It is especially difficult for botanical drugs with unknown number and identities of the active ingredients. This problem is not just a conventional CMC issue, as therapeutic consistency of botanical drugs may rely on additional support from non-CMC data. On the other hand, because of our experience with pure drugs, therapeutic consistency of marketing batches is rarely a traditional concern for clinical or other reviewers. This is, thus, a unique botanical review issue not under the care of other disciplines and may require new regulatory thinking.



BOTANICAL ISSUES IN THIS NDA

Plant Biology of Tea

The biology of tea as a medicinal plant has been reviewed by the BRT's Dr. Dou. His recommendations that all the ~~the~~ cultivars⁵ used in clinical studies of this product should be identified and raw materials for future batches should be limited to these cultivars are necessary and reasonable. We also recommend that the only the farms in ~~the~~ , which provided the clinical trial material, supply the same cultivars for future manufacturing. GAP compliance will also help, but not absolutely required. Any changes, either in cultivars or tea farms, should be approved by the FDA first. These control measures will help reduce the variability at the plant and raw material level. We don't believe they will impose excessive regulatory burden.

CMC & GMP inspection

While establishing the chemical requirements is the CMC reviewer's prerogative, for botanicals, it could have more direct clinical impact than non-botanical drugs. Of

⁵ The sponsor has changed the number of cultivars used in clinical studies and for manufacturing ~~the~~ in a post submission meeting (see amendment to NDA).

course the quality specifications should be as stringent as technology permits, but they can rarely be as precise as that of pure drugs. Without the data to correlate variation in chemical quality with clinical response, setting the range of specifications can only follow that of clinical trial material (and not to include non-clinical lots as for non-botanical drugs). Even so, whether it is necessary to control each individual major and minor catechins (vs controlling the total catechins) and how close we should monitor the HPLC peaks with unknown identities remain to be negotiated between the CMC staff and the sponsor. But we do not consider this an approvability issue.

For this NDA, it was decided at the EOP-2 meeting that the GMP compliance and inspection will start from the drug substance, not raw material. Because this is a relatively simple botanical (single part of a single plant) with a class of well-studied active compounds (catechins) and robust CMC control, this is a reasonable compromise from that required in the Botanical Guidance. However, we should not invoke ICH 7A as the reason not to require more extensive GMP compliance. Although it is correct that inspection of botanical raw material is not required in ICH 7A, the ICH mandates are intended for pure chemical drugs as the end products. The ICH has never discussed botanicals as the drug product (not just as starting material) and it was never intended to cover botanicals as final new drug products. Although the conclusion (GMP started with substance) is correct for this particular product, a wrong reason will set a bad precedent to exempt all future botanical drugs from necessary GMP compliance of raw material.

Prior Experiences with Green Tea

Existing knowledge about the pharmacology of green tea and prior experience of human consumption have been described in the primary BRT review. There is extensive research on green tea, but the clinical benefits are mostly unsubstantiated and little is relevant to this application. Green tea related products are also the subjects of a ~~_____~~ so INDs submitted to several new drug divisions in OND. All are oral formulations and many for oncological indications.

Judged by the vast human exposure to tea as beverage drinks, dose up to that of heavy tea drinking (10 gm tea leave, or 1gm catechins) can be assumed to be safe. But drinks of concentrated tea is known to cause GI symptoms and serious adverse events have been associated with green tea extracts sold as dietary supplements for weight loss on the market. One dog study conducted by NCI in one of their INDs raised safety concerns of high dose green tea extract administered in a fasting state (see Pharmacology review). These reports, however, have little bearing on the safety of this NDA product because Veregen is a low concentration formulation (daily dose of catechins 0.1gm) with low systemic absorption rate (approximately 30 times lower than oral dose, see Clinical Pharmacology review for details). The clinical setting and treatment duration are also different from that of dietary supplement use. It should be noted that the sponsor has conducted a full battery of non-clinical toxicity studies and no safety problems were observed.

Overall, we conclude that, other than the safety of tea drinking, the prior experiences with green tea are irrelevant to the safe and effective use of this product.

Ensuring Therapeutic Consistency of Marketing Batches

For this NDA, we depend on the following to address this concern:

- 1) this is a relatively simple botanical (single part of a single plant) with a class of well-studies active compounds (catechins);
- 2) we will restrict the use of cultivars and farms to minimize variation at the plant level;
- 3) a robust CMC control measure as required by ONDQA (see CMC review);

We believe these are necessary and reasonable control measures, and together with

- 4) no significant difference between the two doses (10% and 15%) in clinical studies thus making the other uncontrollable variations and uncertainties less critical to clinical response.

we should have adequate assurance on therapeutic consistency of future marketing batches. Additional evidence as outlined above under "Scope of Botanical Review" may be considered when the sponsor request for changes in cultivars and/or farm facilities, but they are not required for approval of this initial NDA submission.

The sponsor has requested permission to extend the lower ends of specification because the 10% preparation cannot be differentiated clinically from the 15% formulation. We do not agree. "Flat dose response" will provide some assurance that the general variations and uncertainties (other than the HPLC peaks we can control) may not be critical to clinical response. But it cannot be used to justify changes in CMC specifications of the product, which provide the (stronger) confidence in consistency and further changes will require clinical studies for validation.

CONCLUSIONS & RECOMMENDATIONS

In conclusion, we found this first botanical NDA approvable from the BRT perspectives. Our recommendations and comments are summarized as follows:

Plant Biology of tea – It is a relatively simple botanical, with a well-studied class of active entities (catechins). Need to specify cultivars and use the same farms; approval required for future changes.

Pharmacology/Prior experiences of tea - Past information has no significant impact on the proposed new use.

Therapeutic consistency of marketing batches - Ensured by extended control on raw material and robust chemical characterization, plus flat dose response

These conclusions and the approvability of the application were concurred by the regulatory briefing of this NDA on September 15, 2006.

cc:

ORIG: NDA- 21-902

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/s/

Shaw Chen
10/24/2006 11:18:01 AM
BOTANICAL REVIEW TEAM REVIEWER

BOTANICAL DRUG REVIEW

BY

BOTANICAL REVIEW TEAM

Application Type: NDA
Submission Number: 21-902
Submission Code: N000
Letter Date: 000
Stamp Date: 09-30-2005
Established Name: TBD
PDUFA Goal Date: 07-31-2006
Applicant: MediGene AG
Other (orphan, OTC, etc.): none
DMF #: _____

Trade Name: Polyphenon[®] E Ointment 15%
Established Name: To be determined
Priority Designation: S
Route of Administration: Topical
Botanical Raw Material: Green Tea, the dried leaves of *Camellia sinensis* (L.) O. Kuntze [Family: Theaceae]
Botanical Drug Substance: Polyphenon[®] E, a partially purified green tea extract with 85-95% catechins
Indication(s) requested: Polyphenon[®] E, 15 % is indicated for the topical treatment of external genital and peri-anal warts (*Condylomata acumata*) in adult patients.

Botanical Review Team Reviewer: Jinhui Dou, Ph.D.
Review Completion Date: 04-28-2006
Botanical Review Team Leader: Shaw T. Chen, M.D., Ph.D.

Review Division: Division of Dermatology and Dental Drug Products

TABLE OF CONTENTS

1.	EXECUTIVE SUMMARY	3
1.1	Recommendations	
1.1.1	Recommendations on Approvability	
1.1.2	Recommendations on Botanical Issues	
1.1.3	Recommendations on Labeling	
1.2	Summary of Botanical Review	
2.	INTRODUCTION OF BOTANICAL REVIEW	8
3.	MEDICIANAL PLANT BIOLOGY	9
3.1	Identity of the Tea Plant	
3.2	Good Agriculture Practice (GAP) Issues	
3.3	Major Groups of Compounds in Tea	
3.4	Initial Processing of Botanical Raw Material	
3.5	Summary	
4.	NDA OVERVIEW OF BOTANICAL RAW MATERIAL, DRUG SUBSTANCE, AND DRUG PRODUCT	16
4.1	Botanical Raw Material	
4.2		
4.3	Polyphenon [®] E Drug Substance	
4.4	Polyphenon [®] E Ointment, 15% Drug Product	
4.5	Summary	
5.	PREVIOUS HUMAN USE AND PHARMACOLOGY OF GREEN TEA AND ITS POLYPHENOLS	23
5.1	Pharmacological Activities from Previous Human Use	
5.2	Known Toxicities from Previous Human Use	
5.3	Published Pharmacology Data and Bioassays	
5.4	Selected NDA Pharmacology Data and Bioassays	
5.5	Summary	
6.	BOTANICAL RELATED CLINICAL ISSUES	30
6.1	Past Clinical Use and Treatment Effects of Green Tea Polyphenols and Polyphenon [®] E	
6.2	Ensuring Therapeutic Consistency in Marketing Batches	
6.3	Summary	
7.	SUMARY OF REGULATORY ISSUES	32
8.	OVERALL CONCLUSIONS AND RECOMMENDATIONS	33
	REFERENCES	35

1. EXECUTIVE SUMMARY

1.1 Recommendations

1.1.1 Recommendations on Approvability

- There are no Botanical Review Team issues identified that may affect the approvability of the botanical drug, Polyphenon[®] E Ointment, 15%, for the treatment of genital warts.
- The extensive previous human oral use and limited topical use of green tea and green tea polyphenols do not raise any safety concerns, and further more, do not provide significant additional information on the safety and effectiveness of this topical product.

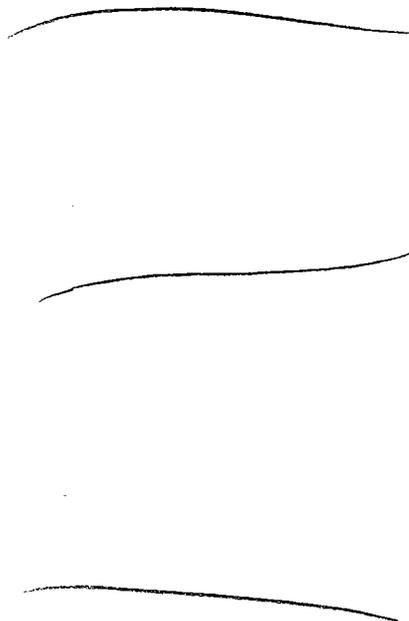
1.1.2 Recommendations on Botanical Issues

- The applicant should properly identify the tea variety/cultivars and provide common synonyms of *Camellia sinensis* (L.) O. Kuntze. There are two commonly accepted varieties of *Camellia sinensis* (L.) O. Kuntze, i.e., variety *C. sinensis* var. *sinensis* – (tea, or China tea) and variety *C. sinensis* var. *assamica* (J. Masters) Kitam. (Assam tea). The extreme varieties in China tea and Assam tea could have differences as large as those between different species. The Assam tea variety was classified as a separate species, *Camellia assamica* (Masters) Wight.
- Significant variations of catechins and other chemical components have been identified from the tea leaves of different varieties/cultivars. Using the established cultivars that have already been tested in the drug development process is important for maintaining the consistency of the botanical raw material and the botanical drug substance. The introduction of new varieties/cultivars that have not been previously tested should be pre-approved by the Agency before mass production of marketing batches.
- If other tea farms are going to be added as new providers of green tea, select only tea farms with the same cultivars that have been identified and previously used as the botanical raw material. In addition, natural/environmental conditions related to the geographical locations (climate, soil, etc.) should also be taken into consideration. The Agency review and approval is requested for changing the suppliers of the botanical raw material.
- Follow International or National GAP (e.g., WHO Guidances on Good Agricultural and Collection Practices (GACP) for Medicinal Plants; GAP for Traditional Chinese Medicine, People's Republic of China) procedures for

medicinal plants in addition to the tea growing guidelines issued by the Chinese government for tea production for food/beverage uses, as appropriate. Through compliance with proper raw material control and manufacturing specifications, drug product and clinical effect consistency can be expected with no major practical difficulties.

- Bioassays have been used for comparing the similarity of different batches in the NDA. These bioassays should be further developed and validated. More importantly, chemically, pharmacologically and even clinically relevant bioassays should be developed to assist, as necessary, in the CMC of future marketing batches, or as a mean to evaluate new sources of botanical raw material. When adding new cultivars, changing providers of previously used cultivars, or implementing other manufacturing changes, it is recommended to demonstrate the similarity/equivalency between the batches of Polyphenon® E drug substance prepared under the new conditions with a “standard batch” from the existing conditions. A more comprehensive approach, such as combining bioactivity equivalence and CMC specifications will be much preferable than only the CMC specifications.

1.1.3 Recommendations on Labeling



1.2 Summary of Botanical Review

The botanical drug product under review is Polyphenon[®] E Ointment, 15%, which is proposed for the treatment of genital warts. The drug substance, Polyphenon[®] E, consists of 8 catechins (85-95% by weight) and approximately [redacted] of unidentified compounds derived from the botanical raw material (green tea), the dried leaves of *Camellia sinensis* (L.) O. Kuntze [Family: Theaceae].

The major botanical review issues include the correct identification of the original plant, raw material control and its contribution to the consistency of drug substance and drug product; the evaluation of previous human experience and known pharmacological activities, especially those related to topical applications; and providing input on the relationships between the consistency of the chemical composition and that of the clinical effects of the botanical drug product (Polyphenon[®] E Ointment, 15%).

Because the botanical drug substance, Polyphenon[®] E, is a botanical mixture with unidentified compounds, its quality and consistency is affected by that of the botanical raw material and extensive control of processing and manufacturing of both raw material and substance is needed. Controlling the extraction and purification process for the manufacturing Polyphenon[®] E of drug substance is a chemistry review issue. This Botanical Review Team (BRT) review focuses on identification and control of the botanical raw material (green tea). NDA 21-902 provided limited information related to the botanical raw material (Green tea) [redacted] which is the green tea extract used as starting material for Polyphenon[®] E drug substance. The applicant referred the Agency to reference DMF [redacted] for additional information. For DMF related issues, please see Chemistry's DMF review. Both data submitted in the NDA 21-902 and published literatures are used in this review to address botanical related issues.

For quality of the botanical raw material, precise identification of the original plant is extremely important. The scientific name of the tea plant is correctly identified at the species level, i.e., *Camellia sinensis* (L.) O. Kuntze, but the applicant did not provide specific variety and cultivar information in the NDA. The botanical raw material was provided from [redacted] tea farms in [redacted] China, and is supposed to be the dried leaves of China tea, *Camellia sinensis* var. *sinensis*. The applicant should clarify and identify the variety (varieties/cultivars) of the tea plant that has been used to produce botanical raw materials. The variety that was not tested during the drug development process should not be used in manufacturing of marketing batches without Agency approval.

How to arrange the three taxa of the “true tea plants”, i.e., China tea, Assam tea, and Cambod tea, remain as confusing issues. Assam tea is treated as either a variety, i.e., *C. sinensis* var. *assamia* (J. Masters) Kitam or a separate species, *Camellia assamica* (Masters) Wight, by different taxonomists. A third taxon, Cambod tea, *C. sinensis* var. *assamia* ssp. *lasiocalyx* (syn. *Camellia assamica* ssp. *lasiocalyx* (Planchon ex Watt) Wight) is also recognized by some taxonomists as the intermediate between China tea (variety) and Assam tea (variety). Others don't recognize Cambod tea as an additional taxon to China tea (variety) and Assam tea (variety). Nevertheless, the commercial tea production is still separated into China tea, Assam tea, and Combod tea. Besides Assam and China tea varieties, two uncommon varieties of *Camellia sinensis*, were discovered in 1980-90s as Dehong tea, var. *dehungensis* (HT Chang et Chen) Ming and Baimao (white hair) tea, var. *publilimba* H.T. Chang. These two varieties are natives of _____, _____, and other provinces further south and have no natural distributions in _____, where the _____ tea farms providing the botanical raw material located. Through morphological, chemical, and molecular genetic methodologies, identification and classification of China tea, Assam tea, and Cambod tea have been demonstrated in published literature. Assam and China tea have different ratios of dihydroxylated to trihydroxylated catechins which are considered as a practical parameter to segregate the Assam and China-tea varieties (with ratios of 1:4 and 1:5, respectively).

Many cultivars exist for producing green tea. In addition to identifying the tea plant at species and variety levels, it is also important to further specify the cultivars. New tea taxa selected through cross hybridizations, especially interspecific hybridizations, will have significant variations in biochemical and pharmacological properties similar to those of different species. The content of catechins in commercial tea samples varies significantly, from 81.9 mg/g to 262.7 mg/g in the major tea producing regions of China. Established tea cultivars are commonly propagated from cutting or grafting, and thus will have relatively small intra-cultivar variation on catechins and other compounds. Considering China has many tea producing provinces, only limited numbers of tea cultivars would be planted in _____ farms. This may not sufficiently represent all the cultivars. Even with pre-extraction blending of green tea, total catechin content, ratios of each catechin, and the associated compounds may still be substantially different due to the large number of cultivars. Identifying and tracing the botanical sources to its cultivars could, therefore, provide better control of the botanical raw material and maintain consistency of the drug substance.

Using varieties/cultivars not previously used will add potential inconsistency of the botanical raw material, because of variations in catechin contents of different green tea varieties/cultivars, especially those grown at different geological locations with different soil, climate and other environmental conditions. Cultivation and collection of tea in China are guided by a set of guidances similar to some of the principles/requirements of good agricultural practices (GAP). Although acceptable, GAP guidances (e.g., WHO guidances on good agriculture practice and collection (GACP) for medicinal plants; GAP for traditional Chinese medicine, People's Republic of China) can also be referenced to further improve the standardization of the conditions related to the production of the botanical raw material, such as propagation, cultivation, harvest, storage and initial

drying process, as appropriate. Identification of commercial cultivars is requested in the WHO guidance of GACP for medicinal plants.

The Polyphenon[®] E drug substance is consisted of two parts, the known catechins and the mostly unidentified and un-quantified associated compounds. Catechins have also been extensively studied for their pharmacological activities, and are considered as the major active ingredients of the drug substance. The "associated compounds" (approximately _____ of drug substance) from green tea may also contribute to the activities of the drug substance. The chemical makeup of the associated compounds is not well defined and could be variable between batches. Control of the botanical raw material will reduce the variations in the total catechins, the yield of Polyphenon[®] E, the ratio of the known catechins, and composition of the associated compounds.

Comparing with previous human use, the daily dosing of Polyphenon[®] E Ointment is not considered a high exposure. The proposed daily dose of 750 mg Polyphenon[®] E Ointment, 15% contains 112.5 mg of Polyphenon[®] E drug substance with 95.6-106.9 mg total catechins _____ of "associated compounds". The yield of Polyphenon[®] E drug substance is approximately 1.9% from green tea, and thus the 112.5 mg of Polyphenon[®] E drug substance is approximately equivalent to a maximum of 5.9 g green tea. Comparing with the oral applications (including tea drinking), the amount of catechins (and other compounds) that can reach systemic circulation is much lower from the topical application of Polyphenon E[®] Ointment, 15%. Topical green tea products have been used as herbal medicine with similar tolerability as oral preparations. The extensive previous human oral use and limited topical applications of green tea and green tea polyphenols did not raise any serious safety concerns nor provide additional instruction on effective use of the product.

On the proposed label and Physician package insert of the NDA, it stated that

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2. INTRODUCTION OF BOTANICAL REVIEW

The botanical drug product under review is Polyphenon[®] E Ointment, 15% which is proposed for the treatment of genital warts. The drug substance, Polyphenon[®] E, consists of 8 catechins (85-95% by weight) and approximately [REDACTED] of unidentified compounds derived from the botanical raw material (green tea), the dried leaves of *Camellia sinensis* (L.) O. Kuntze [Family: Theaceae].

The major botanical review issues include correct identification of the original plant, raw material control and its contribution to the consistency of drug substance and drug product; evaluation of previous human experience and known pharmacological activities, especially those related to topical applications; and providing input on the relationships between the consistency of the chemical composition and that of the clinical effects of the botanical drug product Polyphenon[®] E Ointment, 15%.

The contents of this botanical NDA review include the following major sections:

- Medicinal plant biology;
- NDA overview of botanical raw material, drug substance, and drug product;
- Previous human use and known pharmacology of green tea and its polyphenols;
- Botanical related clinical issues; and
- Summary of regulatory issues.

NDA 21-902 provided limited information on the botanical raw material (green tea) and [REDACTED] the green tea extract used as starting material for Polyphenon[®] E drug substance. The applicant referred the Agency to Drug Master File (DMF) [REDACTED] for raw material and drug substance Chemistry, Manufacturing and Control (CMC) information. For DMF related issues, please see separated reviews by Chemistry. Since there is no designated botanical section in the NDA, information summarized from published literature by the reviewer is used to explain the botanical issues when deemed appropriate. Summary data in the NDA submission that related to the quality and specifications of drug substance/product, non-clinical and clinical were also referenced and discussed to address the botanical issues.

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3. MEDICIANAL PLANT BIOLOGY

The botanical source of green tea, the botanical raw material for the NDA, is the leaves of tea plant, *Camellia sinensis* (L.) O. Kuntze [Fam. Theaceae]. The naming convention of tea plant, *Camellia sinensis* (L.) O. Kuntze was explained in an Information Amendment Response to Filing Communication (December 8, 2005). The following discussion is based primarily on review of a limited number of available published literatures by the reviewer to provide general information about the tea plant that is relevant to the botanical raw material control.

3.1 Identity of the Tea Plant

The tea plant, *Camellia sinensis* (L.) O. Kuntze [Fam. Theaceae], is a small evergreen tree or shrub originated from China and nearby Asian countries. The word “Camellia”, represents the genus with the first letter capitalized in the Latin binomial naming convention. Camellia was derived from Kamel (1661-1706), a Moravian Jesuit, who studied the plants in Asia. The epithet “*sinensis*” (with first letter in lower case) representing the species, was initially assigned by Carl von Linné (abbreviated as Linn. or L.). After rearrangement later by another botanist Otto Kuntze in 1881, the name of the tea plant bears the names of two botanists written in an abbreviated form as (L.) O. Kuntze or (L.) O. Ktze. The synonyms of *Camellia sinensis* (L.) O. Kuntze include *Camellia sinensis* var. *sinensis* L., *Camellia sinensis* var. *sinensis* f. *parvifolia* (Miq) Sealy, and *Thea sinensis* L.

From a synthesis of foliar, floral morphology and growth features, the bulk of the commercially grown tea today, the China, Assam, and Cambod tea, can be classified to three taxa, *Camellia sinensis*, *Camellia assamica* (Masters) Wight, and *Camellia assamica* ssp. *lasiocalyx* (Planchon ex Watt) Wight, respectively, according to the classification proposed by Wight (1962). China tea is a shrub and generally erect (or erectophile with leaf angle < 50°) small-leaved; Assam tea is a tree and horizontal (oligophile with leaf angle > 70°) broad-leaved. The morphology of Cambod tea is in between that of the China tea and Assam tea. Assam, Combod, and China tea are indigenous to different geographic regions of Southeast Asia, i.e., Assam in India, Indochina, and China, respectively. Detailed habitat, foliar and reproductive characteristics of the three principal taxa of cultivated tea is summarized in the book edited by Wilson and Clifford.¹

Another earlier classification by Sealy in 1958 named Assam, Combod, and China tea as three varieties of *Camellia sinensis* L., i.e., var. *assamica*, var. *assamica* ssp. *lasiocalyx*, and var. *sinensis*, respectively.^{1,2} The current Germplasm Resources Information Network – GRIN, an online Database of USDA, ARS, National Genetic Resources Program using the classification of the tea plants similar to the proposal by Sealy, i.e., treat Assam tea as a variety of *Camellia sinensis* (L.) O. Kuntze rather than a separated species, i.e., *Camellia sinensis* var. *assamica* (J. Masters) Kitam, instead of *Camellia assamica* (Masters) Wight. Thus, *Camellia sinensis* (L.) O. Kuntze has two major

varieties, var. *sinensis* and var. *assamica*.³ The classification of *Camellia sinensis* and its position in the Plant Kingdom is illustrated at the USDA website as the following.

Class Magnoliopsida -- dicots, dicotylédones, dicotyledons

Subclass Dilleniidae

Order Theales

Family Theaceae -- tea

Genus *Camellia* L. -- camellia

Species *Camellia sinensis* (L.) O. Kuntze -- tea

Direct Children:

Variety *Camellia sinensis* var. *assamica* (J. Masters)

Kitam. -- Assam tea

Variety *Camellia sinensis* var. *sinensis* (L.) Kuntze – tea

Besides Assam tea and China tea, two less common varieties of *Camellia sinensis*, Dehong tea, var. *dehungensis* (HT Chang et Chen) Ming and Baimao (white hair) tea, var. *publilimba* H.T. Chang were identified in the 1980-90s and included in the “Monograph of the Genus *Camellia*”.⁴ The authors consider that the classification of Assam tea as a variety of *Camellia sinensis* is appropriate. Further, the authors do not recognize the existence of Cambod tea as a subspecies of Assam tea.⁴

As discussed above, *Camellia sinensis* (L.) O. Kuntze is generally considered as having two common varieties: the small-leaved China variety, i.e., *Camellia sinensis* var. *sinensis* and the broader-leaved Assam tea variety, *Camellia sinensis* var. *assamica* (J. Masters) Kitam. Because the green tea botanical raw material of this NDA was collected in

China, *Camellia sinensis* (L.) O. Kuntze is interpreted as including only *Camellia sinensis* var. *sinensis* in this review. The names of tea plant, *Camellia sinensis* (L.) O. Kuntze, *Camellia sinensis* var. *sinensis*, *Camellia sinensis* and *C. sinensis* are used to identify “China tea” and “China tea variety”. *Camellia assamica* (Masters) Wight, *Camellia sinensis* var. *assamica* (Masters) Kitam, are used to identify “Assam tea” or “Assam tea variety”. The third important taxon of tea is *Camellia sinensis* var. *assamica* ssp. *lasiocalyx*, syn. *Camellia assamica* ssp. *lasiocalyx* (Planchon ex Watt) Wight, commonly known as “Cambod tea” or “Cambod tea variety”. Some experts do not separate Cambod tea as a subspecies of Assam tea. Nevertheless, commercial tea products are often separated as China tea, Assam tea, and Combod tea. In addition, *Camellia sinensis* has two other varieties, Dehong tea (*Camellia sinensis* var. *dehungensis*) and Baimao (white hair) tea (*Camellia sinensis* var. *publilimba*), which are not widely distributed nor commonly cultivated. Because of lack of importance and relevance, these two varieties will not be further discussed in this review.

Collectively, the three main taxa for growing tea today are grouped as “the true tea species” while other *Camellia* taxa are considered as “the non-tea tea species”. Tea taxonomists have been interested in several “non-tea” tea species, especially *C. irrawadiensis* and *C. taliensis*, because of their suspected involvement in the genetic pool of the “true tea species”.¹ Breeding programs also use interspecific hybridization of *C.*

sinensis with other *Camellia* species, e.g., *C. sinensis* x *C. japonica*, for green tea with traits of high or low caffeine or polyphenols.⁵ Continued hybridization would further complicate the genetic pool of the tea plant as well as the chemical compositions of green tea.

Cross-hybridization among the true tea taxa, especially the China tea (*C. sinensis*) and Assam tea (*C. assamica*) can be easily carried out and has been a common practice for generating new tea varieties/cultivars. Also, interspecific hybridization of *C. sinensis* with other *Camellia* species, e.g., *C. sinensis* x *C. japonica*, has also been used for breeding of tea plants. Some hybrids and introgressants are expected to have a mixed genotypes from two or more species or varieties.⁶ The hybrids and introgressants can be arranged in a cline based on morphological characteristics that extend from small-leaved China type through intermediates (usually Combod type) to those of Assam origin. Based on Nei's gene diversity index, China tea (*C. sinensis*) was revealed to be more variable than Assam tea (*C. assamica*) and that a higher proportion of over-all diversity resided within varieties as compared to between varieties. This characteristic of higher diversity within groups as compared to between-groups diversity indicated that tea plants are out-crossing species. Some experts believe that because of many years of cross-hybridization that the pure tea archetypes may no longer exist.⁶

Molecular genetic methodologies have been used for identification and classification of the true tea plants, which include randomly amplified polymorphic DNA (RAPD), restriction fragment length polymorphism (RFLP) and amplified fragment length polymorphism (AFLP).^{2,6-8} RAPD analyses of 38 clones of tea based on band sharing were able to separate the Assam, China, and Cambod tea populations into groups consistent with both the taxonomy of tea and with the known pedigrees of some clones. RAPD analysis also discriminated all of the 38 commercial clones, even those which cannot be distinguished on the basis of morphological and phenotypic traits.² In another study, even though no specific DNA profile was found for Assam and China tea following any single PCR-RFLP analysis, a factorial correspondence analysis of all genotypes and markers allow separation of the tea samples into two distinct groups (i.e., Assam and China tea). The study also indicated that large difference exists between the polyphenolic profiles of Assam and China tea.⁶

The catechin ratios of dihydroxylated to trihydroxylated catechins [e.g., (EGCG+EGC)/(EC+ECG)] is considered a practical parameter to separate the Assam and China tea groups, with ratios of 1:4 and 1:5, respectively. In addition, the study found that China tea had low total catechins when compared to Assam tea. The catechin ratio was considered useful to complement the molecular biology techniques like RFLP, AFLP and RAPD in determination of genetic diversity.⁸ Through studies of genetic makeup, polyphenol composition and their relationship to the morphology traits of different cultivars would be sufficient in the differentiation/identification of the China tea and Assam tea.

The relatively high genetic diversity within the *C. sinensis* types, indicates that there could be significant variations of polyphenol/catechin and other associated compounds

among China tea cultivars. Indeed, a study showed that the tea polyphenols content increases gradually from northern and eastern provinces to southern provinces in that country.⁵ Another study also reported a general trend of catechin contents is lower in China tea than in Assam tea.⁸ Interestingly, unlike the tea samples with the highest polyphenols in Yunnan of southern China, the tea samples from Hunan province (in the middle of the major tea producing provinces in China) had the highest catechin content.⁵ This diversity among the China tea cultivars suggested that the cultivars should be specified in all green tea drug products. Many cultivated varieties of *C. sinensis* have been developed. Also, different cultivars often have different tolerance to the weather (e.g., frost tolerance) and are corresponding to different geographical locations of the tea growing regions in China. Tea samples from different growing provinces in China can be highly variable in their total polyphenol and catechin contents.⁵ The polyphenol content could be affected by many factors, and may correlate with the higher genetic diversity in *C. sinensis*.

Tea plants are commonly propagated from cutting or grafting. A tea farm may have a few closely related cultivars and thus would be able produce batches of botanical raw materials with more comparable contents of catechins and other compounds. Using a group of known cultivars of the tea plant increases traceability of the botanical raw material, and enhances the ability of quality control of the botanical drug substance. On the other hand, different tea cultivars may have significant differences such as cultivars through interspecific cross-hybridization may have differences similar to those of two species. The Assam tea and China tea are considered as different tea varieties or cultivars, but others believe the extreme Assam tea and China tea varieties have sufficient differences to be considered as separated species. Introducing of new or not-previously tested tea cultivars will add inconsistency to the botanical raw material and should be subject to regulatory review and approval before implementation.

3.2 Good Agriculture Practice (GAP) Issues

As one of the most important beverage crops, the tea plant is cultivated with local and national guidances in the raw material product area, _____, China. International GAP guidances related to medicinal plants, food, and other plant crops could also be referenced by the botanical raw material providers (tea farms).

Cultivated tea is maintained as a low bush in a continuous vegetative phase of growth and characteristics of this phase are essential in the differentiation of the tea taxa. Many tea cultivars have been developed through centuries of effort of selecting high grade tea which included conventional breeding programs starting with plants from existing natural populations. Such selected plants are multiplied vegetatively by single node cuttings and released as clones or used in hybridization programs. Different cultivars developed for tea leaf quality and weather tolerability (e.g., frost) through hybridization and selection of natural populations could have significant variation on the contents of catechins, caffeine and other tea associated compounds. Once established, further propagation by vegetative means (cutting) of the cultivar is expected to retain the specific characters. Thus, the catechins content and other compounds will have smaller intra-cultivar variations and

much larger inter-cultivar variations. Introducing new or not previously used cultivars is likely to significantly affect the composition of the catechins and the associated compounds of the botanical raw material.

There are many environmental factors that may also influence the quality of the botanical raw material. For examples, changes of the geographical locations (e.g., soil composition, altitude) and weather conditions (e.g., precipitation, temperature, and sunshine) may affect the catechin composition and the associated compounds in the tea leaves. These factors should be considered in choosing new farms. Since the tea cultivars are often selected suitable for growing under certain natural conditions (e.g., altitude, soil, temperature), monitoring and controlling the cultivars also help to minimize the quality variations of green tea due to uncontrollable natural conditions. It is also of importance to monitor environmental pollutions caused by human activities. Fertilization, irrigation, and using other chemicals, such as insecticides, herbicides should follow national, and/or international guidances for tea and medicinal plant. Cultivation and collection of tea in China are guided by a set of guidances with similarity to the requirements of good agricultural practices (GAP). Although implementation of these guidances for growing of the botanical drug raw material for this NDA is acceptable, GAP guidances (e.g., WHO guidances on good agriculture practice and collection (GACP) for medicinal plants; GAP for traditional Chinese medicine, People's Republic of China) can also be referenced to further improve and standardize the conditions for producing of the botanical raw material.

3.3 Major Groups of Compounds in Tea

The major components in green are polyphenolic compounds including catechins. Other compounds found in green tea include protein (up to 15%), amino acids (about 4%), lignin (about 6.5%), and small amount of essential oil.^{5,9-11} The main tea components (polyphenols, catechins, caffeine, and amino) and water extraction ratio of 596 tea samples from China were analyzed and published (see the table below).⁵

Table 1. The comparison of main quality components of tea genetic resources in different provinces

Province	Tea polyphenols (%) ^a	Catechins (g/kg)	Amino acids (%)	Caffeine (%)	Water extract (%)
Yunnan (YN)	31.9 ± 4.6a	133.9 ± 27.4bcd	3.2 ± 0.8b	4.5 ± 0.5a	46.1 ± 2.1a
Guangxi (GX)	30.2 ± 4.0ab	148.4 ± 35.6bc	3.1 ± 0.7bc	4.0 ± 0.5cd	42.5 ± 1.5cd
Guizhou (GZ)	29.2 ± 5.3bc	—	3.2 ± 0.6b	4.4 ± 0.3ab	46.2 ± 6.8b
Guangdong (GD)	27.6 ± 5.8cd	127.9 ± 16.3cd	3.8 ± 0.7a	4.1 ± 0.3c	43.9 ± 2.9b
Fujian (FJ)	27.5 ± 4.1d	152.5 ± 23.0b	3.0 ± 0.8bc	4.3 ± 0.4b	42.0 ± 2.5de
Sichuan (SC)	27.3 ± 2.8cd	—	3.8 ± 0.7a	3.8 ± 0.4ef	42.1 ± 2.2de
Hubei (HB)	27.2 ± 3.7de	—	3.8 ± 0.6a	4.1 ± 0.3c	43.4 ± 2.7bc
Hunan (HN)	26.2 ± 7.6def	177.3 ± 48.4a	2.9 ± 0.9c	3.9 ± 0.7de	40.2 ± 4.6f
Jiangxi (JX)	25.8 ± 4.8ef	133.4 ± 7.0bcd	3.7 ± 0.6a	4.0 ± 0.3cd	41.8 ± 3.6de
Shanxi (SX)	25.1 ± 4.7f	—	3.8 ± 0.8a	4.0 ± 0.3cd	41.1 ± 1.5ef
Zhejiang (ZJ)	22.0 ± 3.6g	125.3 ± 23.8d	3.7 ± 0.6a	3.7 ± 0.5f	40.2 ± 4.6f
LSD _{0.05}	1.7	22.0	0.3	0.2	1.1
LSD _{0.01}	2.2	29.1	0.4	0.3	1.5

Note. All the quality component contents were on a dry weight base. The same was as below.

^aMean ± SD between different provinces within a column with the same letter were not significantly different ($p > 0.05$).

The polyphenol content on dry weight bases varied from 13.6 to 47.8%, average 28.4%. The tea polyphenol content increases gradually from northern and eastern provinces to southern provinces of China, with the tea samples from Yunnan, a southwestern province, the highest. The content of catechins ranged from 82 mg/g to 263 mg/g, averaging 145 mg/g. The tea samples from Hunan province had the highest catechin content of 177 mg/g), followed by the tea from Fujian and Guangxi provinces.⁵

Large variations of total monomeric polyphenols among commercial green tea samples were observed in another study, ranging from 23.95 mg/g to 145.6 mg/g.¹¹ Many other factors may influence the levels of polyphenols in tea, and a study has reported that a general trend of total polyphenols in tea was in the order of green tea (older leaves) > green tea (younger leaves) and oolong tea > black tea. Another compound of interest in tea is caffeine. The levels of caffeine in green, oolong, and black tea are usually similar and have relatively smaller variances among different tea samples (11.2-43.8 mg/g).¹¹

3.4 Initial Processing of the Botanical Raw Material

Different drying and preparation techniques are applied to fresh tea leaves to make black tea, green tea, and oolong tea. Green tea is usually dried by heating shortly after picking to prevent the enzymatic oxidation, commonly referred as a “fermentation” process catalyzed by polyphenol oxidase.

The initial drying is an important process to preserve the catechins and has impact on the quality of the botanical raw material. The polyphenol monomers (catechins), such as epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), catechin epicatechin (EC), and galocatechin gallate (GCG), are largely preserved in green tea. On the other hand, extensive fermentation or polymerization of polyphenols to form dimmers and oligomers are allowed to take place in the making of dried black tea leaves. During the processing of black tea, about 90-95% of the polyphenols undergo enzymatic oxidation to theaflavins and thearubigins.⁵ The processing of oolong tea is basically allowing “partial fermentation” to oxidize some of the catechins. Tea leaves after processed to green tea, oolong tea, or black tea, will have significantly different of the contents in catechin and other associated compounds. The process of making oolong tea, especially black tea, will significantly reduce the catechin content. In this NDA, fresh tea leaves are processed according the method of making green tea and only green tea is used as the botanical raw material.

3.5 Summary

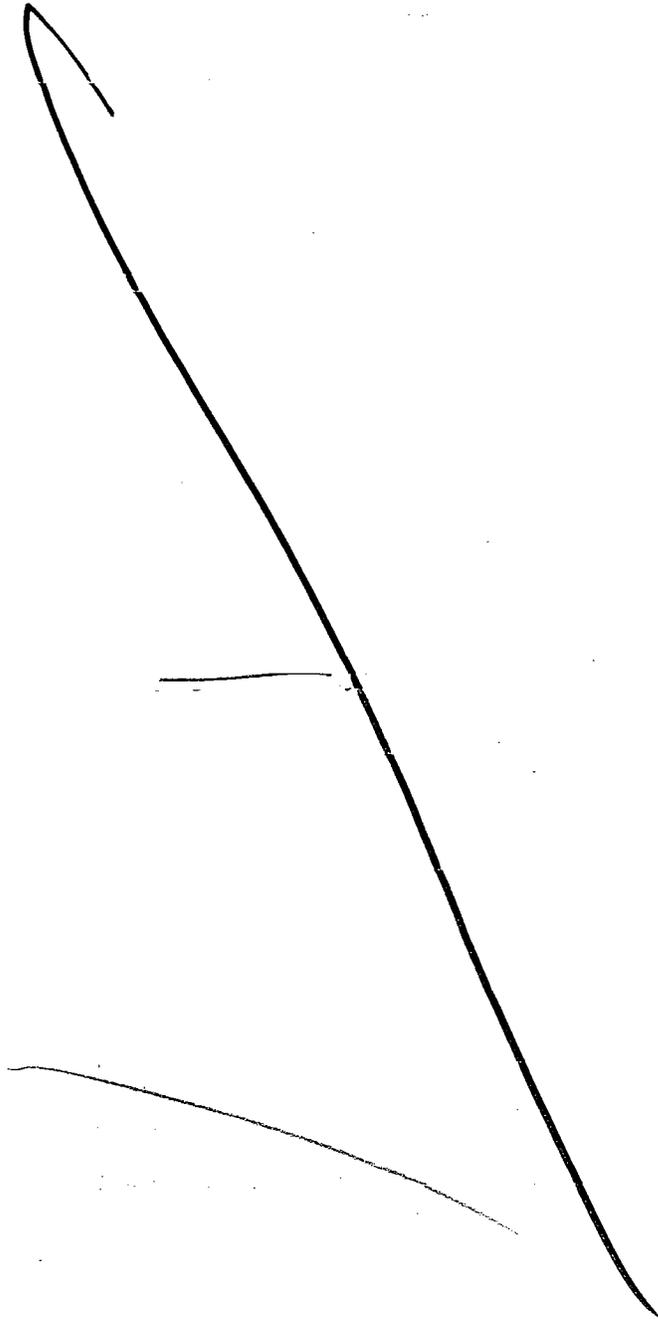
Three main taxa of “true tea plants”, *Camellia sinensis*, *Camellia assamica* (Masters) Wight, and *Camellia assamica* ssp. *lasiocalyx* (Planchon ex Watt) Wight are commonly identified to represent commercial China, Assam, and Cambod teas, respectively. Another taxonomy classification put China tea and Assam tea as two cultivars under *Camellia sinensis*, i.e., var. *sinensis* and var. *assamica*. Tea leaves of *Camellia sinensis* from — farms — are dried according to the green tea drying process and used as the raw materials for the botanical new drug of this NDA. The applicant did not

provide information to further identify *Camellia sinensis* to its varieties/cultivars. Morphological, reproductive and growth features, as well the catechin ratios of dihydroxylated to trihydroxylated catechins and molecular biology techniques (e.g., RFLP, AFLP and RAPD) are complementary methods in the identification of the tea taxa.

The main tea components are polyphenols, catechins, caffeine, and amino acids. The content of catechins from published literature ranged from 82 mg/g to 263 mg/g, averaging 145 mg/g. The genetic tea samples from Hunan province had the highest catechin content (177 mg/kg), followed by Fujian and Guangxi provinces. The catechins content and other tea related compounds are expected to have smaller intra-cultivar variations and much larger inter-cultivar variations. Tracing and controlling the tea cultivar is useful to maintain the consistency of the botanical raw material and may also help to minimize the quality variations of green tea caused by uncontrollable natural conditions. The initial process of green tea preparation using the polyphenol oxidase is an important procedure to protect the catechin components from oxidative degradations.

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**4. NDA OVERVIEW OF BOTANICAL RAW MATERIAL, DRUG
SUBSTANCE, AND DRUG PRODUCT
(NDA21-902 Module 2 Vol 1.1 and Module 3 Vol 1.1)**



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6 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(4) Draft Labeling

§ 552(b)(5) Deliberative Process

Withheld Track Number: Botanical 6

5. PREVIOUS HUMAN USE AND PHARMACOLOGY OF GREEN TEA AND ITS POLYPHENOLS

Summary of literature data on the “non-drug” previous human experience in the United States and elsewhere (e.g., traditional Chinese medicine or TCM) and known pharmacological activities, especially those related to topical applications of green tea and its polyphenols, are provided in this section to address whether additional safety or efficacy issues could be identified that will affect the approvability of the NDA, and/or appropriate use of the product.

5.1 Pharmacological Activities from Previous Human Use

Today, tea is the second most popular beverage only behind water and tea drinking is part of the daily routine for many around the world. Fresh tea leaves from the true-tea plants are commonly processed to three major commercial commodities: black tea (about 70-80%), green tea (about 20%), and oolong tea (about 1-2%). Black tea is most popular in Western countries while green tea is most popular in Asia and a few African countries. Green tea brew with primarily catechins has a much lighter color. The color of the black tea brew is from conjugated catechin dimmers and polymers, theaflavins and thearubigin with molecular weight of 700-40,000.¹² Small volatile monoterpenes give refreshing “grassy” aroma of the tea, especially green tea. Caffeine is the compound primarily responsible for the stimulant effect of tea, green, oolong, or black. The amount of tea typically consumed by regular tea drinkers in Asian countries is 3-4 grams of tea leaves per day (3-4 cups, with 240-320 mg of polyphenols and approximately 100 mg of caffeine). About 10-15% of the tea drinkers may consume up to 10 grams of tea leaves per day. Some heavy tea drinkers consume 1-2 g of catechins a day from tea leaves used in ~20 cup of tea (references use 50-100 mg catechins per gram of green tea leaves and 1 cup tea has 1 g of tea leaves).

Green tea has been extensively studied in *vitro* and *in vivo* animal models as well.^{9,12-17} In certain cultures, tea drinking and other forms of tea products have also been ingested for its presumed health benefits.¹⁸⁻²¹ However, there is still no conclusive evidence to support the health benefits of green tea and green tea polyphenols.

In TCM, green tea is considered useful in “detoxifying of the body, clearing up the brain, and improving the digestive power” and is used to treat different diseases/symptoms, such as diarrhea, jaundice, headache, and gastroenteritis. The typical daily doses of green tea used in TCM are 8-12 g, but higher doses (e.g., 20 g/day) are also used.¹⁰ In China, tea drinking is also reputed to reduce the potential harms caused by smoking, heavy alcohol drinking, and animal fat in the diet. New generation of TCM products of green tea polyphenols in capsule/tablet forms at doses of 200 mg (total polyphenols) are used three times per day for different purposes defined in TCM, e.g., sharpening and clearing the mind, lowering blood lipids and treating dizziness, shortness of breath and chest tightness, fatigue and lack of strength. These claims, however, are largely unsubstantiated from western medicine perspectives.

In the United States, green tea or its extract (polyphenols with or without caffeine) is among the top selling dietary supplements. Over 600 dietary supplement products containing green tea as one of their ingredients are available.²¹ One such product uses Polyphenon 70 green tea extract (100 mg/capsule), which is similar to [REDACTED]. These products are marketed mostly for weight loss and increasing mental sharpness. Green tea extract products for weight loss are associated with over a dozen hepatotoxicity cases.

In TCM, the recorded topical uses of green tea include treatment of dermatitis and athlete's foot or similar foot skin eruptions/diseases.¹⁰ In western countries, including the United States, green tea bags are used topically as a wash to soothe sunburn and to stop the bleeding of tooth sockets. Green tea in chewable candy is marketed for gingivitis. Green tea is also used topically to prevent skin damage and cancer due to ultraviolet (UV) radiation (e.g., sunburn) and other environmental causes. Two topical cream formulations (one for acne and another not-specified skin use) with Polyphenon 70 green tea extract [REDACTED] are also available in the United States.²¹ There is no conclusive evidence whether the above mentioned topical use of green tea products are helpful. To this date, topically applied green tea extract has not been linked to known serious adverse events.

5.2 Known Toxicities from Previous Human Use

Based on the popularity of tea drinking, it is generally believed that drinking green tea at moderate amounts (a few cups with approximately 0.5-1 g of green tea per cup) is safe. Although tea was considered a panacea for some, as a *Materia Medica* in TCM, tea is known to have side effects. In ancient TCM herbology books, the stimulant effect of green tea was observed and used for correcting "sleepiness", but over dose could cause sleeplessness or insomnia.¹⁰ In "Compendium of Chinese Material Medica", published in 1590, tea was considered unhelpful or even harmful for people with "deficiency syndromes" characterized by feeling cold or with cold extremities on touch, thin and weak with pale complexion. In addition, drinking tea with an empty stomach may bring "cold" pathogens inwards and cause internal harm.²² Other TCM works also reported that drinking concentrated tea can cause nausea and vomiting.

In recent years, dietary supplement use and/or clinical studies of oral green tea extracts have been associated with several common but usually mild side effects, including nausea, vomiting, abdominal bloating and pain, dyspepsia, flatulence, and diarrhea.²¹ Other adverse effects that related to central nervous system stimulation such as dizziness, insomnia, fatigue, agitation, tremors, restlessness and confusion have also been observed, probably resulted from the relatively high caffeine intake. However, the possibility of other tea components contributing to the CNS side effects could not be completely ruled out.

Despite the seemingly safe and extensive human experience of oral green tea consumption, at least 15 cases of hepatotoxicity associated with different weight-loss dietary supplement products containing green tea polyphenols have been reported.²³⁻²⁵

Two of these cases required liver transplants. Some of these cases are summarized below.

In 2003, a particular commercial green tea product, Exolise[®], was suspended by French and Spanish Advisory Boards and was later taken off the market completely by the manufacturer after 13 women developed hepatotoxicity associated with its use. In the majority of cases, the injury was reversible upon discontinuation. However, one patient did not recover and required liver transplantation.²³ Exolise[®] (containing 53% total polyphenols) was made from 80% ethanolic extract of green tea by Arkopharma Laboratories (Carros, France).

In October 2005, there was another case of liver toxicity in a Canadian woman who had take a regular dose of Green Lite (a dietary supplement product with water extract of green tea) three times per day (total dose of 600 mg catechins/day) for about 6 months. Her situation worsened later and resulted in liver transplant.²⁴

A most recent reported case is a 37-year old Hispanic woman who had been using a weight-loss supplement “The Right Approach Complex” (Pharmanex, Provo, Utah) for 4 months and developed hepatotoxicity. The Right Approach Complex is a complex mixture of green tea polyphenols (the major ingredient by weight, 384 mg per 3 capsules), minerals and other herbs. The report also summarized several other cases of hepatotoxicity associated with products containing green tea extracts. Most patients were younger than 40 and 7 of 9 were women. All patients improved after stopping the products and had normal liver test results within 4 months after withdrawal.²⁵

All the above mentioned hepatotoxicity cases involved individuals trying to lose weight. They seem more likely to take the green tea products with none or little food, suggesting fasting/less food intake may increase the potential risk of developing hepatotoxicity. Although no liver toxicity was reported, a published single dose oral bioavailability study in healthy individuals showed that taking Polyphenon[®] E under fasting condition can lead to >3.5 times in maximum plasma concentration of EGCG compared to taking the same amount of Polyphenon[®] E with food.²⁶

Topical application of Polyphenon[®] E Ointment, 15% at 750 mg/day provides 112.5 mg of the drug substance with up to 107 mg catechins. Only 2% of the topically applied catechins is expected to be absorbed and about 0.2% penetrated through the skin and became available systemically. Thus it is very unlikely that Polyphenon[®] E drug substance provided topically as 750 mg Polyphenon[®] E Ointment, 15%, will cause liver toxicity or other side effects associated with the oral applications of green tea polyphenols. No serious adverse effects have been reported in the experience with topical preparations of green tea and its extracts for gingivitis, sunburn, and acne.

5.3 Published Pharmacology Data and Bioassays

Hundreds of scientific studies and dozens of reviews/books on green tea have been published, many in the last two decades.^{9,12-21} Since tea is commonly ingested in

drinking, most of the *in vivo* studies on systemic effects of green tea polyphenol were of oral administrations. Of the small numbers of studies on the effects of green tea polyphenols by topical or oral administrations on healthy or abnormal skin (e.g., cervical lesions), one reported the use of Polyphenon® E Ointment to treat genital warts.¹² Exemplary pharmacological effects of green tea polyphenols are summarized as follows.

The bulk of the reported activities of green tea and green tea polyphenols include, for example, antioxidant and free radical scavenging, cancer prevention in animals, plasma lipid and glucose lowering, antibacterial, antiviral, and hypotensive activities.^{9,12-21} *In vitro*, EGCG and green tea extract have demonstrated strong antioxidative activity against microsomal lipid peroxidation system and are highly effective as scavengers of superoxide radicals.¹³ Green tea or its polyphenols have also shown cancer prevention activity in several laboratory animal models of lung, liver, skin, esophagus, prostate and stomach cancers.^{14-15,17,28,29}

Two green tea extracts with different polyphenols and catechins (80-85% polyphenols, 64-68% EGCG vs 47.5-52.5% polyphenols, 38-42% EGCG) and EGCG (98%) were tested for their cell-specific cytotoxic responses of rodent macrophage-like RAW 264.7 and human promyelocytic leukemic HL60 cell lines. Green tea extracts with lower percentages of EGCG have comparable cytotoxicity as the same concentrations of the pure compound indicated that other components in green tea extracts also contributed to the cytotoxic effects.²⁹

While the results from most *in vitro* and *in vivo* studies suggested favorable antioxidant activities and the popular human use of green tea and its polyphenols, other studies indicated that green tea or Polyphenon E may act as oxidants instead of antioxidants and cause DNA-damage *in vitro*.²⁹⁻³¹ A study indicated that EGCG might have a dual function of anti-oxidant and pro-oxidant potentials. It may be a dose related issue, because at higher concentrations, green tea polyphenols/EGCG causing oxidative DNA damage, while suppressing oxidative DNA breakage at lower concentrations.³⁰ There is no *in vivo* data to confirm the *in vitro* oxidant effect or whether it correlates to systemic effects or may cause skin damage on contact. Two *in vivo* assays, indicated green tea polyphenols only poses very low levels of genotoxicity in mice.³¹

Studies of green tea polyphenol induced effects and cellular/molecular responses in the epidermal systems may help in understanding the mechanism of action.³² The activities include UV protection (inhibition of tumorigenesis, inhibition UV-induced mitogen-activated protein kinase activation, inhibition UV-induced activator protein-1 activation; etc.), antioxidant (elimination of reactive oxygen species; inhibition of NO synthase, lipoxigenase, COX, xanthine oxidase, lipid peroxidase; etc.), anti-inflammation (inhibition of ornithine decarboxylase, COX, lipoxigenase; inhibition of IL-1, IL-8, IL-10, and IL-12 release), acceleration of keratinocyte differentiation and wound healing (induction of P57, filaggrin, keratins, involucrin, and transglutaminase activity; induction of caspase 14), anticarcinogen (inhibition of tumorigenesis, inhibition of carcinogen-DNA binding), protection of psoralen and UVA-induced carcinogenesis (inhibition of erythema and DNA damage), and protection of hair follicles from

radiation (inhibition of radiation-induced apoptosis). Some of these studies use oral formulation, not topical application, of green tea polyphenols.

5.4 Selected NDA Pharmacology Data and Bioassays

Additional pharmacological studies were performed by the applicant in order to describe the relationship between dose and pharmacodynamic activity of Polyphenon® E drug substance. The literature reported antioxidant activity, the inhibition of several enzymes (e.g., oxygenases, kinases, and proteases) and the inhibition of tumor cell growth were demonstrated. The mode of action of Polyphenon® E drug substance involved in the clearance of genital and perianal warts is not well understood. Detailed description for these data is referred to the pharmacology and toxicology review.

Skin penetration studies performed *in vitro* with human skin demonstrated that of the topically applied and Polyphenon® E Ointment 15%, only about 2% catechins penetrated into the skin, 0.3% penetrated into the epidermis, and about 0.2% penetrated through the skin and became systemically available. Application of up to 2 g Polyphenon E® Ointment 15% to minipigs, 3 times per day, for 28 days, resulted in maximum plasma concentration of free EGCg of about 30 ng/ml on Day 28. (Data from NDA Table 2.6.5.4 C). The resulted mean exposure was 285 ng*h/ml (i.e., 17.1 µg*min/ml). In a reported bioavailability study in healthy human volunteers, oral application of 800 mg EGCg as Polyphenon E® (i.e., ~ 1200 mg Polyphenon E® per day), for 4 weeks, resulted in maximum plasma concentration of free EGCg of about 287 ng/ml and a mean exposure of 158 µg*min/ml on Day 28.³³ The human oral application resulted about 9 times higher systemic exposure rate than the topical application of Polyphenon E® Ointment, 15%. Most importantly, dermal application of Polyphenon E® Ointment, 15% in patients resulted even lower systemic rate than the dermal application of the same product in minipigs. It can be concluded that low systemic availability of catechins contained in Polyphenon® E drug substance in patients following dermal applications. It is unlikely that dermal application of Polyphenon® E Ointment, 15% will cause serious systemic toxicity in patients at regularly applied doses.

Several applicant conducted *in vitro* assays indicated dose-dependant activities of the Polyphenon® E drug substance. A molecular weight of 400 g/mol is used for the calculations of Polyphenon® E drug substance concentration. Three *in vitro* bioassays, DPPH antioxidant assay, inhibition of 15-lipoxygenase assay, and inhibition of epidermal growth factor receptor (EGF-R) assay, were applied by the applicant to compare the bioactivities of 4 batches of Polyphenon® E drug substance and green tea extracts (details in 4.2.1.1.3 Report, PE_PX_0407). The 4 batches of Polyphenon® E drug substance or green tea extracts have variable catechin () and EGCG contents (). The anti-oxidant assay showed comparable IC₅₀ values between 4.49 µM (SD ± 0.43 µM) and 5.39 µM (SD ± 0.30 µM). This indicates that green tea extract with similar total catechin contents, but with some variation in the individual catechin content, had comparable antioxidant activities *in vitro*. These 4 lots of Polyphenon® E drug substance and extracts inhibited 15-lipoxygenase with comparable activity and the IC₅₀ values were between 0.384 µM (SD ± 0.03 µM) and

0.55 μM (SD \pm 0.003 μM). From the EGF-R assay, the IC₅₀ values were between 0.024 μM (SD \pm 0.004 μM) and 0.031 μM (SD \pm 0.004 μM). Although not catechin specific, the three assays seem to be reasonably sensitive and reproducible, especially the 15-lipoxygenase inhibition assay and the EGF-R assay. The applicant did not state intention to implement these bioassays as part of the quality control of Polyphenon[®] E drug substance.

5.5 Summary

Tea drinking as a major way of green tea consumption was generally regarded as safe at a few grams of tea leaves a day. Green tea has been used in traditional medicine (e.g., TCM), including both oral and topical applications. Orally administered green tea catechins or catechin-rich green tea extracts were reported to have several health benefits including anti-oxidative, chemo-preventive, anti-tumor, and other health protective activities. However, products containing green tea extracts for weight loss were associated with rare, but serious cases of hepatotoxicity. Animal studies and human clinical studies have indicated that under fasting conditions, green tea catechins have a much higher plasma concentrations and thus could cause more serious adverse effects. The NDA referenced 200 publications as secondary supporting data on the mechanisms of the pharmacological effects and safety of catechins.

Overall, the previous human oral use of green tea and green tea polyphenols did not raise any safety concerns for that the topical application of Polyphenon E at the proposed doses of Polyphenon[®] E Ointment, 15%. Comparing with the oral applications (including tea drinking), the amount of catechins (and other compounds) that can reach systemic circulation from the topical use of Polyphenon[®] E Ointment, 15% seem insignificant. Topical products of green tea have been used in alternative and complementary medicine (e.g., TCM) and western herbal medicine with similar tolerability as oral preparations.

Data from applicant performed studies, as well as published literatures, suggested that Polyphenon[®] E drug substance has two main pharmacodynamic activities in the clearance of genital and perianal warts. These two activities are regulation of cell growth and viability in keratinocytes and induction of immune mechanisms. The applicant also conducted standard non-clinical safety studies for Polyphenon[®] E Ointment, 15% as a topical drug product.

The applicant has used *in vitro* bioassays (e.g., inhibition of 15-lipoxygenase assay, and inhibition of EGF-R assay) to compare the bioactivities of 4 batches of Polyphenon[®] E drug substance and green tea extracts with different catechin contents. These or other bioassays can be used in combination with established CMC specifications to compare the similarity of botanical raw materials (e.g., currently used variety/cultivar and variety/cultivar for future use) and different batches of Polyphenon[®] E drug substance. When adding new cultivars, changing providers of previously used cultivars, or implementing other manufacturing changes, it is recommended to demonstrate the similarity/equivalency between the batches of Polyphenon[®] E drug substance prepared

under the new conditions with a “standard batch” from the existing conditions. A more comprehensive approach, such as combining bioactivity equivalence and CMC specifications will be much preferable than only the CMC specifications. The most desirable bioassays would include those that are able to correlate the bioactivity of the drug substance with the clinical effects.

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6. BOTANICAL RELATED CLINICAL ISSUES

6.1 Past Clinical Use and Treatment Effects of Green Tea Polyphenols and Polyphenon® E

The vast majority of past human experience of green tea in general and Polyphenon® E in particular is related to oral administrations. There is limited past human experience of green tea and Polyphenon® E for topical applications. Based on the extensive human oral use (dietary supplements and especially tea drinking), there is no reason to suspect that topical use of Polyphenon E® will have significant systemic toxicity.

The applications of topical green tea polyphenol products for several skin disorders have been reported, which include protection against UV or aging caused damage,^{34,35} cancer chemoprevention,^{36,37} treatment of periodontal disease,³⁸ and Human Papilloma Viruses (HPV) infected cervical lesions.³⁹ In a double-blinded, placebo-controlled trial, combined topical application of 10% green tea cream and oral administration of 300 mg, twice per day, for skin photoaging, no clinically significant changes were detected after 8-week of treatment. Only histologic grading of skin biopsies showed some improvement in elastic tissue content.³⁴ Application of green tea extracts resulted in a dose-dependent inhibition of the erythema response evoked by UV radiation. The (-)-epigallocatechin-3-gallate (EGCG) and (-)-epicatechin-3-gallate (ECG) polyphenolic fractions were most efficient at inhibiting erythema, whereas (-)-epigallocatechin (EGC) and (-)-epicatechin (EC) had little effect.³⁵ In another study, 51 patients with HPV infected cervical lesions were treated with Polyphenon® E ointment and/or Polyphenon® E capsules, the overall response rate after 8-12 weeks of treatment was 69% (35/51), comparing to the 10% (4/39) in the untreated group.³⁹

6.2 Ensuring Therapeutic Consistency in Marketing Batches

Multiple drug product batches were used in the phase 3 clinical studies. The batch size of the drug substance is limited to approximately  and each drug product batch uses multiple drug substance batches (Module 2, Vol 1.1 2.3.P, p 61). The drug product with different formulation composition (excipients) was provided on page 31 (Module 2, Vol 1.1 2.3.P) with batch numbers and sizes on page 60 (Module 2, Vol 1.1 2.3.P). No head-

to-head comparison of different batches was conducted in the clinical studies. Specifications of total and the individual amount of 8 catechins and 3 associate compounds were established by the applicant based on multiple batches of manufactured drug substance. For detailed review of the drug substance and drug product specifications, see Chemistry review. The proposed ranges of the specifications are typical of botanical products.

Of the two doses studied (15% Ointment and 10% ointment), the 15% ointment gave a slightly, but insignificantly, higher response rate. The flat dose-response relationship of the drug product suggests that the therapeutic effects may not be sensitive to the difference in batches with acceptable CMC specifications. The less precise dosing of topical application also argues that therapeutic effect will not be affected by cross batch variations. In addition, with appropriate controlling of the botanical raw material at the source (e.g., specific varieties/cultivars grown under GAP or GAP-comparable conditions) and CMC specifications for the drug substance/product, adequate quality and consistency of the drug substance/product can be achieved. These considerations provide adequate assurance that the clinical therapeutic effects will be consistent in the future marketed batches.

6.3 Summary

Overall, the previous human experience of topical applied green tea products is limited and not strong enough to provide significant additional support on the approval ability of the NDA.

In addition to the to-be-marketed formulation, Polyphenon[®] E Ointment, 15%, a 10% ointment was also studied. Although no significant changes were observed between the two dose groups in the Phase 3 studies (CT 1017 and CT 1018), the 15% ointment gave a slightly higher, but nonsignificant, response rate. Multiple batches of Polyphenon[®] E drug substance (each batch about 100 kg) is used for manufacturing the drug product, Polyphenon[®] E Ointment, 15% Ointment at batch sizes 100 kg and a proposed post-marketing batch size of 100 kg. The few batches of Polyphenon[®] E Ointment, 15% made from blended batches of qualified drug substance has adequate consistency. Since both the 15% and 10% ointments of Polyphenon[®] E are similarly effective, the variation of the drug product brought by the small variations of drug substance would not affect adversely the therapeutic consistency of the batches.

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7. SUMMARY OF REGULATORY ISSUES

This review addresses several major botanical issues, including correct identification of the original plant, raw material control and its contribution to the consistency of drug substance and drug product; evaluation of previous human experience and known pharmacological activities, especially those related to topical applications; and providing input on the relationships between the consistency of the chemical composition and that of the clinical effects of the botanical drug product Polyphenon[®] E Ointment, 15%.

Because the drug substance is a mixture containing unidentified components of the botanical raw material, green tea, controlling the botanical raw material is an important CMC mechanism to ensure the consistency of the botanical drug product. As a botanical derived drug substance, Polyphenon[®] E is reasonably well defined with _____ of green tea associated components not identified or not quantified. By controlling the botanical source (traceability and identification to cultivars, good agriculture practice and initial drying process etc.) and adequate blending, in combination with other down stream CMC controls on the _____ processes, adequate quality assurance and consistency of the drug substance/product consistency can be achieved. In addition, the apparent flat dose response and the imprecise nature of topical dosing provide further assurance that the therapeutic consistency can be maintained.

Green tea and different green tea extracts (including Polyphenon[®] E) have been marketed for dietary supplement use in the United States. Because of the different routes of administrations (topical *versus* oral), approving and marketing of Polyphenon[®] E Ointment, 15% will not have a direct impact on the status of the dietary supplement status of green tea, green tea extract, and even Polyphenon[®] E marketed for dietary supplement, food/beverage or other non-drug use. However, CFSAN would be notified of the outcome of this application and both its and CDER's compliance office may need to watch for companies making false claims or connections of the dietary supplement use with the topical application. In this NDA, there is no new safety issue or additional information identified that may affect the current use of green tea polyphenol products as dietary supplements or topical products.

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8. OVERALL CONCLUSIONS AND RECOMMENDATIONS

There are no Botanical Review Team issues identified that may affect the approvability of the botanical drug, Polyphenon® E Ointment, 15%, for the treatment of genital warts.

The extensive previous human oral use and limited topical applications of green tea and green tea polyphenols did not raise any safety concerns nor provide significant addition on the safety and effectiveness of this topical product.

The botanical raw material is dried tea leaves from *Camellia sinensis* (L.) O. Kuntze, which has two major varieties (according to one classification): the small-leaved China variety, *Camellia sinensis* var. *sinensis*, and the broader-leaved Assam tea, *Camellia sinensis* var. *assamica* (J. Masters) Kitam. The extreme China tea and Assam tea varieties could have species level differences, and some botanists classify them as different species, *Camellia sinensis* (L.) O. Kuntze and *Camellia assamica* (Masters) Wight, respectively. There are two less common varieties of *Camellia sinensis*, i.e., Dehong tea, var. *dehungensis* (HT Chang et Chen) Ming and Baimao (white hair) tea, var. *pubilimba* H.T. Chang.

The applicant should properly identify and provide the names of tea variety/cultivars and the common synonyms of *Camellia sinensis* (L.) O. Kuntze.

The introduction of new varieties/cultivars that have not been previously used should be subject to the Agency approval before using them as botanical raw material for mass production of marketing drug substance batches. Cultivars of *Camellia sinensis* may have significant chemical variations, and newly introduced taxa from interspecific hybridization will further bring variation in addition to the differences of Assam tea and China tea. Thus, only the established cultivars that have already been tested in the drug development process should be used in manufacture to maintain the consistency of the botanical raw material and the botanical drug substance.

If other tea farms are going to be added as new providers of green tea, select only tea farms with the same cultivars that have been identified and previously used as the botanical raw material. In addition, natural/environmental conditions related to the geographical locations (climate, soil, etc.) should also be taken into consideration. The Agency review and approval is requested for changing the suppliers of the botanical raw material.

It is recommended that International or local GAP (e.g., WHO Guidances on Good Agricultural and Collection Practices (GACP) for Medicinal Plants; GAP for Traditional Chinese Medicine, People's Republic of China) procedures for medicinal plants to be followed in addition to the tea growing guidelines issued by the local authority for tea production for food/beverage uses, as appropriate. Through proper raw material control and manufacturing control, and specification, drug product and clinical effect consistency is expected to be met with no major practical difficulties.

Bioassays should be further developed and validated. They can be useful in assessing the similarity of botanical raw material and different batches of Polyphenon® E drug substance according to their bioactivities in combination with established CMC specifications when selecting new sources of botanical raw material.

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