Contains Nonbinding Recommendations

Medical Devices and Clinical Trial Design for the Treatment or Improvement in the Appearance of Fungally-Infected Nails

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Guidance for Industry and Food and Drug Administration Staff

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Food and Drug Administration
Center for Devices and Radiological Health
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Division of Surgical Devices

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Preface

Public Comment

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Guidance for Industry and Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

A variety of diseases can affect the appearance of nails, including fungal infection. This guidance is intended to provide recommendations regarding clinical trial design for medical devices intended either (1) to provide improvement in the appearance of nails affected by onychomycosis, that is, to affect the structure/function of the nails or (2) to treat onychomycosis (fungal nail infection). All marketed devices to date have been 510(k)-cleared for visual improvement, with Indication for Use statements such as "temporary increase of clear nail in patients with onychomycosis (e.g., dermatophytes *Trichophyton rubrum* and *Trichophyton mentagrophytes*, and/or yeasts *Candida albicans*)."[1] Some elements of this guidance will be primarily applicable to non-ablative energy-based devices, although the basic principles may be broadly applicable to all devices.

The Food and Drug Administration (FDA) distinguishes these two conditions as target outcomes. An indication for the treatment of onychomycosis (an infectious disease) requires proof of stable

[1] For brevity, this guidance may use the abbreviated phrases "temporary increase of clear nail" or "temporary increase in clear nail" to refer to the Indication for Use "temporary increase of clear nail in patients with onychomycosis (e.g., dermatophytes *Trichophyton rubrum* and *Trichophyton mentagrophytes*, and/or yeasts *Candida albicans*, etc.).

elimination of the fungal organism, which is a medical endpoint. This outcome is distinct from outcomes limited to "temporary increase in clear nail" in nails which are fungally-infected, which is considered an aesthetic endpoint, and does not necessarily signify successful eradication of fungal infection, but rather an effect on the structure/function of the nails. The Agency recognizes that this endpoint may have functional benefits as well, which may be of some value to the patient if the improvement in appearance or function is clinically significant and if the benefits outweigh potential risks of the treatment. Nonetheless, claims related to appearance remain distinct from claims of eliminating fungal infection.

This guidance addresses patient populations in the United States as the intended demographic for intervention. The recommendations regarding clinical trial design may be applicable for any medical device type that is intended for temporary increase of clear nail or to treat onychomycosis (fungal nail infection). These recommendations would apply to clinical performance data submitted in Premarket Notification (510(k)) Submissions, Evaluation of Automatic Class III Designations (de novo submissions), and Premarket Approval (PMA) applications, as well as for Investigational Device Exemptions (IDEs).[2]

The need for clinical performance data will be dependent on the design and use of the device.[3] Sponsors are encouraged to discuss this with the agency. In addition, we recommend that you contact the Agency through the pre-submission process prior to starting any clinical study for these nail indications. For information on the pre-submission process see FDA's guidance "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff" (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf).

This guidance is not intended to replace the policies described in other guidance documents. In cases where questions arise, consult the appropriate FDA review division directly or the Center for Devices and Radiological Health (CDRH) Division of Industry and Consumer Assistance (DICE).

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

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[2] Currently marketed devices indicated for temporary increase in clear nail have been cleared through the 510(k) pathway. As such, this guidance refers to "clearances" and "devices cleared." However, wherever such terminology is used in this document, the recommendations and considerations may apply to all premarket submission types (e.g., PMA, de novo).

[3] One example of a device type that has been cleared for the indication of "temporary increase in clear nail" is light-based devices. Refer to the Appendix for an example of the information that FDA recommends be submitted in a regulatory application for this device class.

II. BACKGROUND

Nail dystrophy is commonly due to fungal infection (onychomycosis), but approximately 40% of nails which appear abnormal may be due to other clinical conditions.[4] A wide variety of disorders, including inflammatory, metabolic, genetic, and non-fungal infectious diseases, as well as physical trauma to the nail, can create abnormal nail structures. These changes, which include separation of the distal nail from the nail bed, nail thickening, and color changes within the nail, can be visually indistinguishable from onychomycosis.[5] However, it cannot be assumed that treatments that alter the appearance of nails are necessarily effective in eliminating onychomycosis. Conversely, it cannot be assumed that treatments that are effective in treating onychomycosis would necessarily alter the appearance of nails, if the abnormal nail growth or appearance (dystrophy) were caused by a condition other than onychomycosis. It is therefore important to distinguish the indications of "temporary increase of clear nail in patients with onychomycosis" and "treatment of onychomycosis," so as to differentiate the treatment goals.

This guidance is intended to provide information related to both indications, when the device is applied to nails with confirmed fungal infection. The considerations in this guidance may not be equally applicable to nails whose appearance is altered by non-fungal causes. Therefore, prior to pursuing treatment of abnormally structured or dystrophic nails, it is critical to diagnose the underlying cause, and to base treatment decisions on proven therapies for the identified cause.

Temporary increase of clear nail

Historically, devices have been cleared with the Indications for Use (IFU) of "temporary increase of clear nail in patients with onychomycosis (e.g., dermatophytes *Trichophyton rubrum* and/or yeasts *Candida albicans*, etc.)." This indication has been used to highlight that the outcomes for which the device has provided support are limited to visual improvement, an aesthetic endpoint, and not for mycological cure, which would constitute a medical endpoint. Several aspects of this IFU are noteworthy:

1) This IFU is not intended to mean that the treatment eliminates fungal infection. It does, however, convey that clinical studies performed in support of the IFU included nails with confirmed fungal infection.
2) The devices have primarily been assessed for their effectiveness in nails infected with the common fungal organisms; the effectiveness may not be comparable in nails infected with rare species.
3) As stated above, this indication should not be assumed to demonstrate effectiveness in other causes of nail dystrophy. Therefore dystrophic nails should be confirmed as fungally-infected prior to initiation of clinical trials or treatments that employ devices cleared with this IFU.

[4] Gupta AK, Jain HC, Lynde CW, Watteel GN, Summerbell RC. Prevalence and epidemiology of unsuspected onychomycosis in patients visiting dermatologists' offices in Ontario, Canada--a multicenter survey of 2001 patients. International Journal of Dermatology. 1997;36(10):783-7.

[5] Fletcher CL, Hay RJ, and Smeeton NC. Observer agreement in recording the clinical signs of nail disease and the accuracy of a clinical diagnosis of fungal and non-fungal nail disease. British Journal of Dermatology. 2003;148, 558–62.

4) Finally, we recognize that some patients seek total clearing of their nails rather than partial clearance and this expectation should be clarified. Labeling and promotional materials should provide a transparent portrayal of representative results that were achieved in the clinical trials, both in terms of the extent of nail clearance and the timeline of effect.

Treatment of onychomycosis

In contrast to treatments for increase in clear nail, treatments aimed at treating a fungal infection require evidence of an antifungal effect. Specifically, devices marketed with an indication of treating fungal infections of the nail are expected to provide evidence that the fungal infection in the nail has been eliminated. For treatment of toenail fungal infection, this indication, in most cases, will be supported by evidence of visual improvement in conjunction with negative fungal cultures and stains.

Fungal species: geographic and demographic considerations

Clinical studies performed outside the United States may not be applicable to the U.S. population due to different prevailing fungal organisms that may affect the nails. Therefore, studies performed in the U.S. are recommended. Data from clinical studies performed outside the U.S. should include a comprehensive analysis of all fungal species detected in the nails of the population screened for enrollment in the clinical study, and the analysis reveals a similar spectrum and distribution of fungal species.

Special populations, including individuals with certain chronic diseases, occupational risks, or immune compromise, may have different or additional organisms in the nail, and the effectiveness demonstrated in clinical studies performed in healthy adults may not be sufficiently informative about these populations.

Although indications for use statements in prior clearances have included Candida as an example of an organism that may have been present during treatment, Candida is not a toenail pathogen in healthy individuals and is involved in only approximately half of fingernail infections.[6] Since it is recommended that non-healthy individuals be excluded from clinical studies for these indications, Candida should not be assessed in clinical studies of toenails for the indication of temporary increase in clear nail or of treatment of onychomycosis. An Indication for Use addressing Candida may be considered with specially designed studies assessing the performance of the device in nails infected with Candida species. Future marketing application labeling should reflect this information.

Care and re-use of devices which contact fungally-infected nails

Devices intended for use on infected tissue should be evaluated for design and labeling as described in FDA's guidance "Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling"

[6] Foster KW, Ghannoum MA, and Elewski BE. Epidemiologic surveillance of cutaneous fungal infection in the United States from 1999 to 2002. Journal of the American Academy of Dermatology. 2004;50(5):748-52.

(http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm253010.pdf).

III. TEMPORARY INCREASE IN CLEAR NAIL

A. Regulatory considerations

1. Defining "temporary increase in clear nail"

Normal appearance of nails is the goal for appearance improvement. Historically, for medical devices, FDA has allowed less than fully clear nails as acceptable for a primary endpoint. Although the assessment method for clear nail varied, several medical devices have received 510(k) clearance on the premise that they improve the appearance of nails by an increase in clear nail, observed clinically. These devices have demonstrated that this improvement is maintained or increased when assessed at two timepoints (e.g., 3 months and 6 months) after the last treatment, to reflect growth of clear nail. All studies were performed on toenails, primarily the first toenail.[7]

By way of comparison, pivotal studies performed in support of oral antifungal treatments have shown that the mean time to overall success is 10 months in toenails and 4 months in fingernails.[8] These studies employed multiple endpoints, including complete visual clearance, or for partial responders at least 5 mm increase in clear nail at 36 weeks (9 months) after *completion* of treatment of the toenails and at 18 weeks after *completion* of treatment of the fingernails.

Nails which are structurally abnormal can only clear by outgrowth of the dystrophic component and replacement by newly-created, normal-appearing nail. The mean growth rate for nails in healthy U.S. adults is 1.5 mm per month for toenails and 3-3.5 mm per month for fingernails.[9] Based on this mean growth rate, the ideal effective treatment would be expected to yield a fully replaced, clear fingernail in a healthy adult after approximately 6 months and a fully replaced, clear great toenail approximately 12 months after the *initiation* of treatment. However, given the length of time after the initiation of treatment, it is possible that the nail would be re-infected during this time, in the absence of ongoing treatment.

2. Combining treatment with antifungal drugs or debridement

Historically, device studies have allowed concomitant debridement and/or use of topical or systemic antifungal drug products, aimed at treating the nails or the skin. The combination of debridement and/or antifungal drug therapy confounds the interpretation of the study results in determining the relative contribution of the device to the clinical outcome.

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[7] Refer, for example, to K110370 and K110375

[8] Refer to NDA 020539

[9] Yaemsiri S, Hou N, Slining MM, He K. Growth rate of human fingernails and toenails in healthy American young adults. Journal of the European Academy of Dermatology & Venereology, 2010; 24(4): 420-23.

The Agency will continue to consider submission of clinical performance data evaluating the device with adjunctive interventions, with the exception of oral antifungal drugs. The use of oral drugs will likely confound any device results observed, and as a result, FDA does not believe such data should be used to support a substantial equivalence determination. If topical products (not systemic) are used which can have antifungal activity, they should be administered according to standard of care dosing and route of administration.

For truthful and transparent labeling, the Agency recommends that the device labeling reflect any adjunctive treatment in the Indications and Usage statement. Recommended wording for a device whose clinical trials were performed with topical antifungals and/or debridement, for example, would be:

> "Indicated for adjunctive use in the temporary increase in clear nail in patients with onychomycosis (e.g., dermatophytes - *Trichophyton rubrum* and *Trichophyton mentagrophytes*). This device should be used with manual debridement and/or topical antifungal products, administered according to standard of care dosing and route of administration, whose use may need to be continued after completion of device treatment course, as stand-alone effectiveness of this device for this indication has not been demonstrated;"

or

> "Indicated for the temporary increase in clear nail in patients with onychomycosis (e.g., dermatophytes - *Trichophyton rubrum* and *Trichophyton mentagrophytes*) only when used together with topical antifungalproducts, administered according to standard of care dosing and route of administration for treating accompanying tinea pedis and/or onychomycosis."

For transparency, FDA recommends that the patient and practitioner labeling disclose that the device has been assessed as an adjunct to drug therapy or other intervention.

3. Differentiating aesthetic indications from medical indications

Devices cleared for improvement in the appearance of nails, or an increase in clear nail, could be misconstrued to be intended to treat onychomycosis. To prevent misinterpretation, FDA recommends that the labeling for these devices contain clarifying language, to include:

> "This device has not demonstrated effectiveness in the treatment of fungal infections. It is cleared only for improvement in nail appearance."

4. Special populations

The distinction between aesthetic improvement of the nail and elimination of a fungal infection is of particular clinical relevance for vulnerable populations, who require definitive antifungal treatment, and who may remain at ongoing medical risk by postponing definitive treatment. To protect these populations, the labeling should include the following statement:

"Warning: These devices should be used with caution in patients with diabetes, peripheral vascular disease, or immune-suppression, or with any other medical state which warrants definitive antifungal therapy."

Devices that have not been studied in such populations should receive a similar warning.

B. Clinical trial considerations

The claim of temporary improvement in clear nails is an aesthetic one, but treatments will be performed in nails that are infected with a fungus. Therefore, although the claim is aesthetic, clinical trial design should take into account the medical implications of the proposed protocol.

1. Special populations

Ethical design of clinical studies mandates that risk to special populations be minimized. Special populations may be considered particularly vulnerable and may not be appropriate subjects for clinical studies assessing temporary increase in clear nail. For example, patients with diabetes mellitus, peripheral vascular disease, recurrent cellulitis, lymphatic insufficiency, or immune compromise (whether due to underlying medical disorders or to immunosuppressive treatments), exhibit an increased risk of bacterial infections. In these patients, the skin breakdown induced by a fungus may provide a portal for bacterial infections, which consequently pose a significant health risk. Portals of entry can also be formed at sites of skin breakdown caused by adverse events in the course of a device-based treatment. Furthermore, nails may appear to have an increase in clear area but still harbor fungal organisms; this is the distinction between the "clear nail" indication and an indication of treating onychomycosis. For these reasons, it is recommended that patients with diabetes, immune suppression, peripheral vascular disease, lymphatic insufficiency, recurrent cellulitis, or other compromised states of health be excluded from participating in clinical trials intended to demonstrate improvement in the appearance of nails.

Sponsors and investigators are urged to design clinical studies which enroll a cross-section of subjects that reflects the U.S. demographic. This may include variable age, sex, and Fitzpatrick skin types (if needed).

Treatment with light sources whose wavelength is absorbed by melanin pose increased risk to individuals with darker skin types. In addition, any modality that can induce injury to skin poses an increased risk for post-inflammatory hyperpigmentation in subjects with darker skin. Since the pigmentation of both the nails and the surrounding skin may affect response and treatment tolerance, it is recommended that studies be designed to allow assessment of safety and effectiveness in the target population. If the nature of the treatment mandates restriction in Fitzpatrick skin phototypes in the clinical study, this should be reflected in the device labeling.

2. Inclusion/exclusion criteria: recommendations

<u>Clinical involvement</u>

Nails with 100% dystrophy or with involvement of the lunula can be very resistant to treatment due to permanent damage to the nail matrix ("root"); this may reduce the mean effectiveness assessed across a group of subjects.[10] Conversely, nails with minimal distal changes may not be representative of the target populations for this procedure. Therefore, it is recommended that the study population include nails with at least 25% involvement of the nail area and no more than 75% involvement of the nail area.

Clinical presentations of onychomycosis

There are several clinical forms of onychomycosis, differentiated by their appearance. Some are appropriate for inclusion in device clinical trials, while others may be less appropriate for inclusion in clinical studies intended to demonstrate improvement in the appearance of nails.

- *Distal subungual onychomycosis (DSO)*: This type of onychomycosis is the most common clinical presentation, in which the distal nail plate is separated from the nail bed. This infection is visualized as nails with normal surface texture and thickness but variable "bays" of white nail that extend from the distal nail tip proximally into the area of the nail bed. This form has been the cornerstone of antifungal drug studies. Since it generally does not involve the nail matrix, it is more amenable to improvement in clinical appearance than some other forms.

- *Proximal subungual onychomycosis (PSO)*: PSO is an uncommon form of onychomycosis that appears as a white discoloration below the nail plate at the base of the nail, near the lunula. The distal nail retains normal appearance and texture. PSO involves infection near the matrix, deep to the nail. It may be associated with trauma to the nail or to immune compromise. Therefore, the clinical presence of PSO may hint at an underlying medical disorder. In addition, PSO may reflect different species of fungus. Moreover, obtaining samples for mycology studies prior to enrollment is not possible without piercing or removing the nail. It is therefore recommended that this form of onychomycosis not be included in device clinical studies.

- *Superficial white onychomycosis (SWO)*: This form of onychomycosis is defined by the appearance of a white coating on the nail surface. This clinical form can be eliminated by filing or buffing the surface of the affected portion of the nail. Since subjects might buff or file the nails during the study and confound the results, and since this form does not generally require any other treatment, SWO is not an ideal clinical form of onychomycosis for device trials or for post-market treatments.

- *Complete dystrophy*: Nails which are 100% dystrophic are manifested by yellowing and thickening of the entire nail unit. These nails may be difficult to treat due to irreversible damage to the nail matrix. In such cases even complete eradication of the fungus may not lead to normal nail growth rate or appearance. Such nails may provide data that is relevant for subsequent clinical use, but these cases may also be more difficult targets for

[10] Gupta A and Daniel III C. Factors that may affect the response of onychomycosis to oral antifungal therapy. Australasian Journal of Dermatology. Nov98, Vol. 39 Issue 4, p222-224

treatment. If enrolled, it is recommended that this clinical form of onychomycosis be evaluated for improvement in appearance separately from other clinical forms, whose appearance may improve more readily with treatment.

- *Other nail changes*: Nail changes that appear as parallel lines, small pinpoint depressions, brown spots, black or brown linear streaks, complete yellowing of all nails without textural change, green debris below the nail, or notches in the nail margin may represent causes of nail dystrophy that are not fungal. It is therefore recommended that all nails be evaluated by an expert in nail disease prior to enrolling such subjects in device clinical trials or post-market treatments.

Confirmation of fungal infection underlying nail appearance

To support an Indication for Use of "temporary increase of clear nail in onychomycosis," it is appropriate that all enrolled subjects be confirmed to have nails infected by the common fungal organisms implicated onychomycosis. In the United States, *Trichophyton rubrum* accounts for roughly 80% of toenail onychomycosis, with additional infections caused by *Trichophyton mentagrophytes* or *Epidermophyton floccosum*; other observed but less common fungal infections of the toenails include *Candida parapsilosis*, and Fusarium species.[11] In fingernail onychomycosis, *Candida albicans* accounts for over 50% of cases, with another 25% accounted for by *Trichophyton rubrum*; other *Candida* species comprise most of the remaining cases.[10] By enrolling subjects whose nails have been demonstrated to harbor these organisms, studies are more likely to generate data that is clinically meaningful. It is recommended that nails infected by rare fungal species or non-fungal organisms such as mold or bacteria be excluded, as their data is unlikely to provide information that is widely applicable.

Common methods for identifying the presence and type of fungus present in nails include stains (e.g. periodic acid Schiff (PAS); silver stains; potassium hydroxide (KOH)) and fungal culture.) Negative stains, particularly PAS and silver stains, provide convincing evidence that the sampled portion of the nail is free of fungal organisms. However, while finding fungal organisms within the nail plate using fungal stains provides convincing evidence of the presence of fungus, it does not speak to the organism's viability, and it does not identify the type of fungus. Identification of the organism and determination of its viability, both of which are critical pre-treatment data, are accomplished by culture.

The best evidence that a nail is suitable for a clinical study would be a concurrent positive stain showing septate hyphae and positive culture demonstrating the growth of *T. rubrum* or other common dermatophyte. Therefore, it is suggested that prior to enrollment, both a stain and culture be obtained.

It is known that cultures may yield false negative results. If the stain exhibits septate hyphae but the culture fails to grow a fungus, the culture may be repeated. If two sequential cultures are negative, it is recommended that the nail not be included in the study, as the fungus may be partially treated, fastidious, or otherwise not representative of the target strains. Sponsors may

[11]Foster KW, Ghannoum MA, and Elewski BE. Epidemiologic surveillance of cutaneous fungal infection in the United States from 1999 to 2002. Journal of the American Academy of Dermatology. 2004;50(5):748-52.

wish to stain and culture material from two nails from an affected foot or hand in parallel to expedite this process. The finding of positive stains with negative cultures from two nails would suggest the subject is not a good candidate for the study.

Co-morbidities

Subjects with psoriasis, lichen planus, or other medical conditions known to induce nail changes may also have superimposed fungal nail infections. Trauma from ill-fitting shoes, running, or overly-aggressive nail care can also induce changes visually indistinguishable from onychomycosis. These causes of nail breakdown can predispose to secondary fungal infection. However, it cannot be predicted whether treatments aimed at increasing clear nail in patients with onychomycosis would also improve the appearance of nail changes when those nail changes are due to an additional causative condition. It is therefore advisable to avoid inclusion of subjects known to have such medical conditions, as their response may not be indicative of the effects of the device on nails that are infected by fungus but are otherwise normal.

Prior or ongoing antifungal drug therapy

Systemic antifungal drugs are deposited in the nail substance and remain in the nail until the nail grows and is trimmed. Based on the known rates of nail growth in healthy adults, it is expected that nails exposed to even one dose of an antifungal drug may contain the drug for 1 year in the case of toenails and 6 months in the case of fingernails. Enrollment of subjects who have been exposed to antifungal drugs in the 12 months prior (in the case of toenails) or 6 months prior (in the case of fingernails) could confound interpretation of the study data, and it is therefore recommended that these subjects be excluded from any device study.

Topical antifungal drugs are less effective in providing clinical clearance of onychomycosis. However, their presence can reduce the sensitivity of fungal cultures, even if applied only to the skin of the affected hand or foot. It is therefore recommended that a significant washout period be applied when enrolling patients who have undergone topical treatment of the skin or nails, and that such treatments be avoided during the clinical trial and follow-up period.

Demographics

It is recommended that the enrollment include adequate US demographic representation of the intended population with regard to sex, age, ethnicity, race, and skin phototype.

3. Adjunctive therapies

Adjunctive therapies in clinical trials of devices are suboptimal as they may mask the true performance of the device. Nonetheless, if a clinical trial is designed in which antifungal drug therapy or other intervention is administered in parallel to the device treatment, the adjunctive intervention should be consistent across all study subjects, and the full regimen should be included in the recommended treatment protocol as well as the device labeling. Sponsors might consider including a control which utilizes only the adjunctive therapy, in order to identify the incremental benefit provided by the device. For example, studies that include a topical antifungal product may be able to provide additional data in support of device effectiveness by performing a contralateral controlled study, in which both feet (or hands) are exposed to the

topical antifungal agent, but only one side is exposed to the device treatment. Such a study design would require special considerations if blinding or placebo were to be incorporated.

It is recommended that debridement not be carried out more proximally than the most proximal margin of the dystrophic nail, as this can interfere with assessment of clear nail area attributable to the device intervention. If debridement is used in clinical studies performed in support of a device, the debridement procedures should be well described in the clinical protocol, used consistently in study subjects, and included in the recommended treatment protocol as well as the device labeling.

4. Endpoints

Based on the nail growth rates described in the "regulatory considerations" section above, and to provide a fair and informative guideline for assessment of the success of a treatment, FDA recommends the following effectiveness endpoints be used in a study to demonstrate temporary increase in clear nail. Although these endpoints differ from those historically provided for this device type for this indication, we believe that the use of data at time points measured after the first treatment, rather than the last treatment, provides a more clinically relevant result than assessment of nails after treatment has been discontinued. Further, to address variability in nail length among different digits, the longest nail (thumb or first toe) is recommended as the target nail for measurement.

The 95% one-sided confidence interval (i.e., lower bound only) around the observed response rate as described below should be ≥50%.

Toenails: (based on assessment in the first toe nail)

- To be defined as a responder, a nail would need to meet one of the following measurements of clear nail increase:
  - at least 6 mm increase in clear nail measured from the proximal nail fold to the most proximal area of nail dystrophy, with evidence of distal growth of the affected area, 6 months after the *first* treatment;

  or
  - an additional 60 mm^2 of clear nail (based on width of the first toenail), with evidence of outward growth of the affected area, 6 months after the *first* treatment;

  or
  - complete clearance 6 months after the *first* treatment if less than 6 mm distal nail was involved prior to treatment.

- Treatments may be continued, as the clear nail will be measured 6 months after the *initiation* of treatment.

- The response should be progressive in at least 2 sequential timepoints that are at least 3 months apart, with a projected increase in clear nail of at least 1 mm per month.

Fingernails: (based on assessment in the thumb nail)

- Measurement of clear nail increase:
  - at least 12 mm increase in clear nail, with evidence of distal growth of the affected area, 6 months after the *first* treatment;

  or
  - an additional 90 mm^2 of clear nail (based on width of the thumb nail), with evidence of outward growth of the affected area, 6 months after the *first* treatment;

  or
  - complete clearance 6 months after the *first* treatment if less than 12 mm distal nail was involved prior to treatment.

- Treatments may be continued, as the clear nail will be measured 6 months after the *initiation* of treatment.

- The response should be progressive in at least 2 sequential timepoints that are at least 3 months apart, with a projected increase in clear nail of at least 2 mm per month.

These recommended endpoints arise from the combined consideration of the expected response to an effective treatment (in which the majority of nails would respond) with the known slower nail growth rate in older individuals and in certain disease states. It is anticipated that at least half the treated nails would show a response within the designated time frame for assessment, while slower-growing nails would achieve the response later.

FDA may consider alternate endpoints and/or response rates for devices which pose very high or very low risk. If alternate endpoints are being considered, FDA recommends that you contact the Agency through the pre-submission process to discuss these endpoints.

Studies performed on fingernails only should only be used to support an IFU in the fingernails. Studies which include the toenails can be used to support an IFU of all nails.

The indication of "temporary increase in clear nail" is an aesthetic endpoint, and as such study endpoints will reflect visual improvement in clear nail. A number of methods can be employed to assess the improvement. In some trials, multiple methods may be employed to offer the most accurate assessment.

- Millimeters of clear nail: The simplest method of assessing increase in clear nail is sequential measurements of the distance from the proximal nail fold to a predefined distal mark, such as the most proximal edge of the nail change. Effective therapy will allow normal nail to replace the affected nail as it grows, leading to a progressive increase in the distance from the proximal nail fold to the most proximal portion of the nail change. Measurement to the distal margin of the nail is not recommended as nail trimming can introduce artifact into the measurement. The drawback of this technique is that the nail

dystrophy may not form a well-demarcated line, nor will it necessarily be parallel to the proximal nail margin. Furthermore, such techniques do not account for variable rates of nail growth. Variations on this method can overcome this limitation. For example, a nail file can be used to etch a shallow horizontal line parallel to the horizontal portion of the proximal nail fold; this line would be placed at the most proximal portion of the dystrophic nail. This line can serve as both a marker for nail growth rate, to confirm the nail is growing, as well as for marking the most proximal point of the nail dystrophy.

- Clear nail area (mm^2): An increase in the area of the nail that is clear can provide clinically-meaningful data, and this method overcomes the limitations imposed by uneven margins of a dystrophic nail segment. This method suffers from more complex evaluation methods with standardized photography equipment and dedicated software. Providing that methods can be validated, a measurement of area, presented as millimeters squared, can yield objective data. Presentation of the same data as percentage is less desirable, as nail trimming or debridement can artificially increase the percent of the nail which is clear. Therefore, measurement of clear nail area in square millimeters provides a more reliable, stand-alone objective measurement than percent clear nail.

- Photographic assessment: Visual evidence of improvement underlies all aesthetic treatments, including the indication of "temporary increase in clear nail," and therefore will represent the bulk of the study data. FDA recommends submission of all photographic data gathered in the performance of a clinical study for this indication, in order to assess the visual change. To ensure adequate photographic quality and to maximize the ability to compare photographs across timepoints and across subjects, a standardized photography protocol should be put in place. Photographs should be of high quality and high resolution. An internal scale (e.g. ruler) should be included in all images to allow objective measurement of millimeters of clear nail regardless of magnification of the image. Unedited and unretouched photographs are necessary in order to perform an accurate assessment. Images should be assembled and presented in an organized fashion, for example pre-treatment and post-treatment images side by side, to facilitate FDA review. Sponsors may choose to score the nail appearance on a numerical scale or use another categorization tool. When such tools are used, they are most reliable when photographs are evaluated in a blinded manner and when the scores of multiple independent, blinded observers are combined. The use of training aids, such as representative photographs for each score or category, add to the accuracy and reduce inter-observer variability and should therefore be considered.

- 3-Dimensional improvement: Dystrophic nails may also be thickened. Means of assessing nail thickness, using calipers or photography from an appropriate angle, may be used as additional tools in assessing improvement in nail appearance. Such assessment would be less relevant if debridement were used in the treatment protocol.

- Composite endpoints: Methods of assessing "overall improvement" or multi-axis scoring systems can be of use in some aesthetic indications. However, these endpoints should be used with caution as they can be subjective or easily affected by non-quantifiable factors. Furthermore, such scales may lack clinical validation. If a composite endpoint is chosen,

it is recommended that it be a secondary endpoint and that it be discussed with the FDA prior to commencement of the study.

- Nested studies endpoints: The endpoints for an indication of clear nail may later be used to support an indication for treatment of onychomycosis, when combined with appropriate mycology studies and controls. As will be discussed below, a study can be designed to provide data in support of a clear nail indication in the first phase, and after continued follow-up and analysis of the relevant additional data, further endpoints can be used to support an indication of treating onychomycosis in a second phase of the study.

5. Follow-up

In the absence of fungal re-infection or recurrence, it is anticipated that successful treatment will result in stable and progressive increase in clear nail. To assess the effectiveness of the response to treatment, an ideal study would follow the nails until they are completely replaced by clear nail. As discussed above, based on the average growth of nails this follow up duration would translate to roughly 6 months after the *first* treatment for fingernails and 12 months after the *first* treatment for toenails.

The FDA recognizes that there is an inherent rate of re-infection or recurrence, and that the goal of studies in support of clear nail indications is to assess the improvement in appearance in response to treatment, rather than the ability to prevent re-infection. However, sponsors are reminded that prospective patients and providers will have interest in data about recurrence rates.

6. Controls

When possible, clinical trials benefit from the use of well-selected controls. In the design of trials assessing body sites which are symmetric, such as the hands and feet, the use of a contralateral untreated control can be of great value, provided the two sides have similar involvement at baseline. This type of control is of particular value in studies whose design includes the concomitant use of a topical antifungal drug. When the baseline severity of the two sides is not similar, a contralateral control with crossover may allow maximal use of the contralateral side as control.

Using the "before" status or photos of a nail as a control may not be sufficient. Sponsors are encouraged to consider contralateral control design when possible, as this approach reduces inter-subject variability. Additional controls that have been employed include untreated individuals or historical controls. These approaches suffer from multiple limitations; the use of such data may not provide adequate comparator data or may necessitate a larger number of subjects for adequate statistical power. Sponsors and investigators are advised to consult with a statistician and with the Agency.

7. Blinding

The use of blinding in clinical trials that assess visual improvement strengthens the data by removing conscious or unconscious bias by the observer and by reducing placebo effect in the

subject when patient reported outcomes or unblinded photographic analysis is used. When possible, the use of a sham strengthens study design. This may only be possible for treatments which cannot be felt by the treated subject, as may be the case in low level laser therapy, for example. Blinding may be difficult when a laser or other energy-based treatment can be distinguished by the subject if the active intervention leads to heating or discomfort. However, blinding of the observer is possible and recommended. This blinding can be accomplished by providing unmarked before and after photographs, or by providing unlabeled "treated" and "control" photographs to independent observers. The FDA recommends use of blinded assessment to provide maximally objective data.

8. Dose considerations

The Indication for Use of "temporary increase in clear nail" does not distinguish between different nails. Historically, studies in clear nail were performed on the first toe, which has the largest nail, and which nail is most often affected. However, in practice the treatment will be applied to the smaller toenails as well as to fingernails. The differing thickness and area of these nails, together with potential differences in heating of underlying neural and vascular structures, may require that different doses of energy be applied to the first versus other toenails and to the toenails versus the fingernails. Clinical trials and labeling should address dose considerations so as to assess and ensure substantially equivalent safety and effectiveness in these different body sites.

9. Data analysis

Clinical trial data can be analyzed in several different manners in order to evaluate whether a device is as safe and effective as a predicate device, to confirm a response to a particular regimen, to identify a dose-response relationship in both safety and effectiveness, to test whether different nail changes respond differently, and to unmask sources of confounding. For trials that study the response of a nail whose appearance has been altered by fungal infection, several different analyses may be relevant. Analysis of data as a function of each of these may provide information that will assist FDA in evaluating the performance of the device. Such analyses may also provide valuable information to the sponsor with respect to training, marketing, and development of devices for clear nail indications. Suggested analyses include:

- Increase in clear nail at each timepoint of evaluation after the last treatment
- Increase in clear nail as a function of the number of treatments, energy dose, or other controllable variable
- Subgroup analysis of response by clinical subtype (e.g., distal subungual onychomycosis, total dystrophy)
- Subgroup analysis by fungal species isolated prior to enrollment
- Subgroup analysis by baseline severity
- Subgroup analysis by degree of response (e.g., complete response or clearing, >75% clear, 50-75% clear)
- If multiple nails are affected, subgroup analysis of toenails vs. fingernails, or first nail vs. smaller nails

- If relevant, device alone vs. device with adjunctive topical antifungal product or debridement

When responder analysis is reported on a per nail basis, per subject analysis should be included.

10. Adverse event monitoring

Post-market monitoring of devices cleared for temporary increase of clear nail has identified several adverse events which may be device-related. These adverse events include edema, burn/blister, disfigurement of nails, infection of soft tissue, infection of the underlying bone, deep tissue damage and nerve damage, and delayed wound healing. Some of these events were associated with device output failure or use error, while others occurred when the device was used and operating within specifications.

In light of these reports, sponsors, investigators, and practitioners are urged to be mindful that energy-based treatments do pose risks. In the context of the aesthetic Indications for Use of "temporary increase in clear nail," the benefit-risk analysis is particularly important. All adverse events related to such procedures should be reported by type, severity, duration, outcome, and relationship to the device or procedure in order to develop an accurate understanding of the risks and benefits of these procedures.

C. Statistical Considerations

Like studies for other medical products, clinical studies for devices aimed at treating or improving the appearance of fungally infected nails should be well designed with valid statistical analysis plans. Many general statistical principles such as study design, objective (e.g., superiority or non-inferiority), randomization, prespecification of analyses (e.g., method, covariates), multiplicity control of type I error due to multiple endpoints or analyses, determination of analysis populations (e.g., ITT, per protocol), handling of missing data, use of interim or subgroup analyses, etc., are issues that need to be addressed for devices intended to treat nails in the same way as for other medical devices. As such, these topics will only be briefly discussed here.

1. The **study objective(s)** should be clearly stated as superiority, non-inferiority. The null and alternative **hypotheses** should be stated in text and in statistical notation, including the non-inferiority margin (delta), along with appropriate justification if the study is a non-inferiority trial.

2. Study designs with randomized, **concurrent controls** are recommended whenever possible. For products not expected to have systemic effects, the most efficient design would be a within-patient controlled design, where nail(s) on one foot get the investigational treatment and nail(s) on the other foot get the control treatment. This "split-foot" design reduces the patient to patient variability and thus requires a smaller sample size. Another strong design is the controlled parallel group design, where treatment (investigation or control) is randomly assigned to subjects in two independent

groups. FDA recognizes the inherent limitations with historically controlled studies and recommends other study designs be utilized when appropriate.

3. There should be a **statistical justification of sample size,** which is typically based on type I error, power, and expected outcomes considerations. In some cases, there may be a need to power the study for safety as well, as there may be a low tolerance for serious or bothersome adverse reactions. The final sample size is a judgment and depends upon prior experience with the class of products. If a performance goal is being used, such as a 50% response rate, then the (lower bound) 95% one-sided confidence interval around the observed success rate in the study population should be ≥50%.

4. The **randomization scheme** should be fully described, including the randomization ratio, and any use of stratification or block size. It should also be specified whether the randomization is centrally controlled or managed at each site.

5. The **level of blinding** (patient/investigator/evaluator) should be carefully considered. Double-blinded studies should be conducted whenever possible. However, when this is not possible, investigator- or evaluator-blinding should be considered. The use of photographic evaluations may also be used to maintain the blind; however, assessment of depth is typically compromised with photographs. It is prudent to have as much blinding as possible due to the degree of subjectivity in assessing endpoints with nail products.

6. Studies for devices intended to treat nails may have a number of assessments that are used to define the **primary and secondary endpoints.** The number of assessments may be due to the multifaceted nature of the condition (e.g., color, area, thickness, texture), the number of assessors (e.g., investigator, subject, or blinded evaluator), or the timepoints for assessment. When appropriate, scales should allow for worsening of the condition as well as improvement. Studies may evaluate efficacy, safety, or patient satisfaction outcomes. All scales used should be validated to the extent possible.

7. If efficacy is based on the number of patients responding to treatment (i.e., a responder analysis), then the **patient success decision rule** should be described. This may involve meeting a single criteria or meeting all components of a composite endpoint.

8. The overall **study success decision rule** should be prespecified. Study success should depend on both clinical significance and statistical significance. The protocol should include a plan for adjusting for **multiplicity** in cases with more than one endpoint to control the type I error.

9. The **follow-up schedule** should be fully described. Long-term follow-up may be needed to assess duration of effect (i.e., for one-time use or intermittent use products). Protocols should include plans to minimize loss to follow-up, especially in cases where subjects may not be motivated to return for follow-up after receiving treatment or complying with only some of the post-treatment visits.

10. The **length of treatment** or the number and spacing of treatments should be specified. Data should be collected on dosing or volume of product administered.

11. The **statistical methods** to be used for the analysis of all endpoints should be specified in the statistical plan, and should be appropriate for the type of data collected. If the statistical method will incorporate **important covariates,** such as with various regression methods or subgroup analyses, the covariate list should be prespecified. How the covariates will be used should be spelled out in the statistical plan.

12. The **primary analysis cohort** (e.g., ITT, modified ITT, per-protocol) should be pre-specified. If other analysis cohorts will be used, these should be prespecified as well.

13. For some types of treatments administered by the investigator, the investigator technique may impact the results. Studies should be designed to enroll sufficient numbers of subjects per center so that investigator-to-investigator variability and **treatment-by-center interactions** can be adequately assessed. Number of investigational centers planned (#US and #foreign) should be carefully considered.

14. If the study is a **non-inferiority** study, the control treatment should be shown to be **effective** at the primary analysis time point. It would be inappropriate to evaluate non-inferiority/equivalence to an ineffective treatment.

15. Primary and secondary endpoints intended for **labeling** should be clinically relevant and supported by appropriate prespecified statistical hypotheses. The labeling should only reflect what was demonstrated in the clinical trial.

16. There should be a plan for handling **missing data** which includes the type of imputation that will be used for missed observations and a plan for a sensitivity analyses.

17. Any planned **subgroup analyses** should be prespecified or they will be considered exploratory. In some cases a multiplicity adjustment is needed.

18. Any planned **interim analyses** (i.e., early stopping for futility or effectiveness) should be prespecified. The purpose of the analysis should be clearly stated as well as the alpha spending function to be used to control the overall type 1 error.

19. The **kappa statistic, weighted kappa, or intra-class correlation coefficient (ICC)** may be used to measure inter-rater agreement, intra-rater agreement, or reliability depending on the nature of the data (e.g., dichotomous, ordered categorical, continuous). It is reasonable to obtain more than one opinion on the amount of clear nail.

20. Some trials require the use of a Data Safety Monitoring Board (DSMB). An interim analysis of safety may be needed if the risk of the medical device is high.

D. Labeling Considerations

Devices which are cleared for "temporary increase in clear nail in patients with onychomycosis" should be clearly labeled for this indication. Specifically, claims should be limited to aesthetic improvement.

Since the IFU specifies visual improvement in fungally-infected nails, appropriate labeling should include language which states this clearly by conveying both components of the IFU:

1) Target nails are those whose appearance is altered due to fungal infection. Physician labeling should list the species assessed, and should recommend that physicians confirm fungal etiology.
2) The physician labeling should indicate that the device has not been cleared to treat fungus, as discussed in the "Regulatory Considerations" section above.

As discussed in the "Regulatory Considerations" section above, due to the potentially increased risk of these treatments in patients with diabetes, peripheral vascular disease, immune suppression, and other compromised medical states, the labeling should include a warning in both the physician and patient labeling stating that these devices are to be used with caution in these populations.

The labeling for devices cleared for a "clear nail" indication should contain details regarding the clinical study data, including:

<u>Physician labeling:</u>

- Representative before and after photos of nail with various severities prior to treatment
- Description of the treatment protocol used, including any adjunctive interventions such as topical antifungal products or debridement
- Potential and observed adverse events, and frequency as available
- A table summarizing the percent complete responders, partial responders (which may be further stratified), and non-responders.
- Fungal species assessed, and response rates for each species.
- Clinical presentations of onychomycosis assessed (e.g., DSO).
- If a controlled study, results should be reported for both treated and control data with p-values for any statistical comparison tests performed.
- Caveat that the results represent the US population, and that these data may not be extrapolatable to other strains or other geographic areas.

<u>Patient labeling:</u>

- Representative before and after photos of nail with various severities prior to treatment.

- Description of the treatment protocol used, including any adjunctive interventions such as topical antifungal products or debridement.
- A table summarizing the percent complete responders, partial responders (which may be further stratified), and non-responders.
- Potential and observed adverse events and frequency as available.
- If a controlled study, results should be reported for the untreated group (p-values need not be included here).

IV. TREATMENT OF ONYCHOMYCOSIS

A. Regulatory considerations

1. Defining "treatment of onychomycosis"

In contrast to the indication of "temporary increase in clear nails in patients with onychomycosis," which provides support only for aesthetic improvement, the IFU of "treatment of onychomycosis" is a medical indication, based on reduction or elimination of fungal organisms as assessed by mycological testing. As discussed in section III.A.1 (Defining "temporary increase in clear nail"), stains may be used to assess the presence or absence of fungal organisms, while culture is needed to assess whether the organisms are viable and to identify the species. Mycological cure is therefore defined as simultaneous occurrence of negative stain and negative culture. However, in slow-growing nails, there may be residual fungal forms detectable by staining which are not viable. In such cases, two serial negative cultures from the same nail may provide evidence of mycological cure.

Mycological cure may be assessed in parallel to clear nail. Antifungal drug studies have also assessed overall response rate using an endpoint of "effective treatment" which was defined as mycological cure plus 0% nail involvement or a pre-defined minimum distance of unaffected nail growth, to allow inclusion of nails which are mycologically cured but whose slow growth precludes complete nail replacement within the anticipated timeframe.

As discussed above, nails which are structurally abnormal can only clear by outgrowth of the dystrophic component and replacement by newly-created normal-appearing nail. Based on the mean growth rate for nails in healthy U.S. adults, the ideal effective treatment would be expected to yield a fully clear fingernail after approximately 6 months and a fully clear great toenail approximately 12 months after the *initiation* of treatment.[12] In contrast to the IFU of "temporary increase in clear nail," it is anticipated that effective treatment of the fungus underlying onychomycosis will lead to durable changes in the nail after 6 and 12 months, respectively. Any regression could indicate incomplete or unsuccessful elimination of the fungus or recurrent fungal infection.

[12]Yaemsiri S, Hou N, Slining MM, He K. Growth rate of human fingernails and toenails in healthy American young adults. Journal of the European Academy of Dermatology & Venereology, 2010; 24(4): 420-23.

2. Combining treatment with antifungal drugs or debridement

Due to the nature of the indication, the use of antifungal drug therapy of any kind in studies performed in support of "treatment of onychomycosis" could compromise assessment of device effectiveness and are therefore not recommended. Debridement may be offered for functional improvement, but such interventions should be used uniformly across study subjects with given severities and should be disclosed in labeling.

3. Species-dependent outcomes

Clinical studies may reveal that different organisms respond differently to the procedure, or may require varying doses or treatment protocols. However, the Indication for Use of "treatment of onychomycosis" is worded broadly. A sponsor may choose to specify within the IFU what species can be treated effectively, or may provide this information in the labeling. The goal in either case is to ensure that the device be used to treat only nails which are likely to respond to the treatment protocol.

4. Special populations

As discussed in section III.A.4 (Special populations), effective treatment of a fungal infection is of particular clinical relevance for vulnerable populations, who may remain at ongoing medical risk with partially-treated or unsuccessfully-treated onychomycosis. Furthermore, in these populations, trauma to the nail due to potential adverse events during the procedure may result in delayed wound healing or may predispose to severe or life-threatening infections. To protect these populations, the labeling should include the following statement:

> "Warning: These devices should be used with caution in patients with diabetes, peripheral vascular disease, or immune-suppression, or with any other medical state that renders the foot at risk of infection or delayed wound healing."

A device whose labeling includes an Intended Use or Indication for Use for treating onychomycosis and which has not been studied in such vulnerable populations should be labeled with a similar warning.

B. Clinical trial considerations

1. Special populations

As discussed above (section III.B.1 (Special populations)), risk to special populations should be minimized. Special populations may be considered particularly vulnerable and may not be appropriate subjects for clinical studies assessing treatment of onychomycosis in lieu of definitive therapy, until such procedures are demonstrated safe and effective. It is recommended that subjects with diabetes mellitus, peripheral vascular disease, recurrent cellulitis, lymphatic insufficiency, or immune compromise (whether due to underlying medical disorders or to

immunosuppressive treatments), or other compromised states of health be excluded from participating in clinical trials intended to treat onychomycosis.

Investigators are urged to design clinical studies which enroll a cross-section of subjects that reflects the U.S. population by including subjects with varying age, sex, race, and Fitzpatrick skin type, if applicable, in which it is anticipated the device will be used.

2. Inclusion/exclusion criteria: recommendations

Clinical involvement

The recommendations discussed above (section III.B.2 (Clinical involvement) will also apply to studies performed in support of the treatment of onychomycosis.

Clinical presentations of onychomycosis

The different clinical forms of onychomycosis, which are differentiated by their appearance, are discussed in section III.B.2 (Clinical presentations of onychomycosis). Certain clinical forms are associated with particular species of fungus. As such, some clinical forms may be more resistant to treatment, both due to anatomical factors and due to variably sensitive organisms. It may therefore be of value to evaluate various clinical forms separately, or to analyze and report the outcomes obtained in the treatment of different clinical forms of onychomycosis separately.

Confirmation of fungal infection

As described section III.B.2 (Confirmation of fungal infection underlying nail appearance), a small number of fungal strains are the predominant causes of toenail and fingernail onychomycosis. To maximize the clinical relevance of trial results, and to provide data that is most predictive of treatment response in the population of patients with onychomycosis, it is recommended that studies include only subjects whose nails have been demonstrated to harbor the common causative organisms and exclude subjects whose nails are infected by rare fungal species or non-fungal organisms such as mold or bacteria.

To support an IFU of "treatment of onychomycosis," it is appropriate that all enrolled subjects have confirmed nail infection by one of these fungal organisms prior to treatment and that the nails be definitively assessed for cure of the fungal organism at the relevant timepoint after treatment. Mycological cure is defined as negative stain (e.g. periodic acid Schiff (PAS); silver stains; potassium hydroxide (KOH)) concurrent with negative fungal culture. The concurrence of a negative stain and a negative culture from the same nail may be considered definitive. In the event that the stain and the culture provide conflicting results, i.e., one is positive and the other negative, resolution may be obtained by several approaches. A nail which shows fungal organisms by staining may yield a negative culture. It is known that cultures may yield false negative results in up to 30% of cases due to partially-treated organisms, fastidious organisms, nuances in laboratory methodology, or recent contact with a topical microbicidal agent (including alcohol or acetone applied to the nail prior to collecting the specimen).[13] Conversely,

[13]Fletcher CL, Hay RJ, and Smeeton NC. Onychomycosis: the development of a clinical diagnostic aid for toenail disease. Part I. Establishing discriminating historical and clinical features. Br J Dermatol. 2004 Apr;150(4):701-5.

in slow-growing nails the distal nail margin may contain non-viable organisms, leading to a true negative culture and a positive stain. In this case also, two serial negative cultures from the same nail may provide evidence of mycological cure.

Co-morbidities

Many non-fungal conditions can affect nail appearance, including psoriasis, lichen planus, trauma from ill-fitting shoes, running, or overly-aggressive nail care. These conditions may be the primary cause of nail dystrophy but may also predispose a subject to secondary fungal infection. While these subjects may benefit from procedures which can treat the secondary onychomycosis, it is recommended that they not be included in clinical studies, as the nail appearance may remain abnormal despite successful eradication of the fungus.

Prior or ongoing antifungal drug therapy

Because systemic antifungal drugs are deposited in the nail substance and remain in the nail until the nail grows and is trimmed, enrollment of subjects who have been exposed to antifungal drugs in the 12 months prior (in the case of toenails) or 6 months prior (in the case of fingernails) could confound interpretation of the study data and is not recommended.

While topical antifungal drugs are less effective in providing clinical clearance of onychomycosis, their application can interfere with fungal cultures, even if applied only to the skin. It is therefore recommended that such treatments be discontinued prior to screening and enrollment and for the duration of the clinical trial and follow-up period.

3. Adjunctive therapies

Adjunctive medical therapies may mask the true performance of the device. The use of a topical or systemic antifungal therapy would preclude the ability to assess true safety and effectiveness of a device in treating onychomycosis and are therefore not recommended. If a sponsor or investigator wishes to assess the ability of a second intervention to work in synergy with a device, for example, a topical product that would increase the absorption of laser light, appropriate study design could be established in support of the combination, by providing properly-controlled comparative data of the product alone, the device alone, and the combination. Sponsors are urged to discuss such study designed with the Agency in advance, and to address whether such combinations would be drug-device combination products.[14]

4. Endpoints

Based on the average nail growth rates discussed above, and to provide a fair and informative guideline for assessment of the success of a treatment, FDA recommends the following effectiveness endpoints for treatment of onychomycosis, based on achieving endpoints of both clear nail and mycology.

[14] See 21 CFR 3.2(e).

Clear nail: The specifications for clear nail are described below. The 95% one-sided confidence interval (i.e., lower bound only) around the observed response rate as described below should be ≥50%.

Mycology: Among toenails and fingernails which are deemed responders based on the "clear nail" criteria, at least 80% should demonstrate negative mycology (negative stain with concurrent negative culture, or two negative cultures from the same nail).

Toenails: (based on assessment in the first toe)

- Measurement of clear nail increase:
  - at least 12 mm increase in clear nail, with evidence of distal growth of the affected area, 12 months after the *first* treatment;

  or
  - an additional 120 mm^2 of clear nail (based on mean width of the first toenail), with evidence of distal growth of the affected area, 12 months after the *first* treatment;

  or
  - complete clearance 12 months after the *first* treatment if less than 12 mm distal nail was involved prior to treatment.

- The response should be progressive in at least 2 sequential timepoints that are at least 3 months apart, with projected increase of at least 1 mm per month.

Fingernails: (based on assessment in the thumb)

- Measurement of clear nail increase:
  - at least 12 mm increase in clear nail measured from the cuticle to the most proximal area of nail dystrophy, with evidence of distal growth of the affected area, 6 months after the *first* treatment;

  or
  - an additional 90 mm^2 of clear nail (based on mean width of the thumb nail), with evidence of distal growth of the affected area, 6 months after the *first* treatment;

  or
  - complete clearance 6 months after the *first* treatment if less than 12 mm distal nail was involved prior to treatment.

- The response should be progressive in at least 2 sequential timepoints that are at least 3 months apart, with projected increase of at least 2 mm per month.

Studies performed on fingernails only should only be used to support an IFU in the fingernails. Studies which include the toenails can be used to support an IFU for all nails.

As stated earlier, these recommended endpoints arise from the combined consideration of the expected response to an effective treatment (in which the majority of nails would respond) with the known slower nail growth rate in older individuals and in certain disease states. It is anticipated that at least half the treated nails would show a response within the designated time frame for assessment, while slower-growing nails would achieve the response later. FDA may consider alternate endpoints and/or response rates for devices which pose very high or very low risk. If alternate endpoints are being considered, FDA recommends that you contact the Agency through the pre-submission process to discuss these endpoints.

The indication of "treating onychomycosis" should include demonstration of mycological cure, defined by the concurrence of a negative stain and a negative culture. Sponsors and investigators may choose to apply a nested study design, in which early endpoints are applied and discussed for the clear nail indication (section III.A.1 (Defining "temporary increase in clear nail")) in the first phase, and to pursue a subsequent IFU of "treatment of onychomycosis" with the data generated in a second phase of the study, in accordance with the recommended endpoints (section III.B.4 (Endpoints)). If such a study design is used, pre-specified statistical considerations should be included in the study design to account for the interim data analysis and unblinding.

To evaluate the overall response rates, it is recommended that the study report be written in a tiered fashion, citing the success rate for the subjects exhibiting mycological cure concurrent with clear nail, with separate presentation of the data for subjects exhibiting mycological cure with residual nail dystrophy.

5. Follow-up

The goal of treatments for onychomycosis is complete elimination of the fungal organism and full clearance of the nail. Follow-up for this indication should be based on the anticipated time for complete nail regrowth, which is approximately 6 months for fingernails and 12 months for toenails as discussed above. Longer follow-up times will be helpful for assessing recurrence rates. To control for loss of subjects who do not exhibit the desired visual outcome, it is recommended that subjects who drop out or are lost to follow-up be considered as treatment failures for this indication. This restriction should be incorporated into the statistical analysis plan.

6. Controls

The controls discussed in the "clear nail" section above (section III.B.6 (Controls) are relevant and can be applied to studies in support of the treatment of onychomycosis. These controls may be complemented with mycological studies from the control nails.

7. Blinding

The blinding considerations discussed in the "clear nail" section above (section III.B.7 (Blinding)) are relevant and can be applied to studies in support of the treatment of

onychomycosis. Blinding should be applied to mycological specimen assessment in addition to clinical assessments.

8. Dose considerations

The dosimetry of energy for different toes and for toenails versus fingernails is addressed in section III.B.8 (Dose considerations). It is not known whether elimination of fungal organisms to support the IFU of treatment of onychomycosis would require similar or higher doses of energy than those used for "temporary increase in clear nail," nor whether a higher dose would be tolerated if needed. Clinical trials and labeling should address dose considerations if a device is used to treat both the "temporary increase in clear nail" and "treatment of onychomycosis" IFU, and if it is to be used on different nails, so as to assess and ensure adequate safety and effectiveness in these different body sites.

9. Data analysis

General considerations for data analysis are discussed in section III.B.9 (Data analysis). Given the antifungal nature of the IFU of "treatment of onychomycosis," there is particular importance in identifying dose-response relationships and species-specific response rates. Sponsors and investigators may utilize bench testing to identify target parameters prior to human studies. However, the ability of an energy source to penetrate a living nail overlying complex structures will in most circumstances necessitate clinical studies. Such studies would also provide information about the ability of the nail to resume normal growth after treatment.

10. Adverse event monitoring

As discussed in section III.B.10 (Adverse event monitoring) post-market monitoring of devices cleared for temporary increase in clear nail has identified several adverse events which may be device-related. In the absence of dose-response data about such adverse events, sponsors, investigators, and practitioners are urged to monitor and report all adverse events in order to develop an accurate understanding of the risks and benefits of these procedures. FDA will review adverse events and provide a benefit-risk analysis.

C. Statistical Considerations

These are the same as those discussed in III.C (Statistical Considerations) above.

D. Labeling considerations

Devices which are cleared for "treatment of onychomycosis" should be clearly labeled for this indication, provided they have demonstrated effectiveness in eliminating nail fungus. No devices have been cleared or approved for this indication as of the publication of this guidance. Therefore, much is not yet known, including potential response rates, adverse events, etc. for these studies, and FDA cannot make specific recommendations for labeling at this time. However, general labeling considerations will follow best practices and provide transparency to

the provider and patient. It is anticipated that the recommendations will be similar to those detailed in section III.D (Labeling Considerations) above.

Appendix: Light Sources for Nail Indications

FDA recommends that the following information be included in marketing submissions for devices incorporating a light source intended for a nail indication, with specific attention to the parameters applicable to the IFU. This example may serve as a paradigm for other energy-based devices, in which comparable relevant parameters will be evaluated.

For 510(k) submissions, this information will be taken into consideration along with any performance data (non-clinical or clinical) when comparing the proposed device to a predicate device for purposes of determining substantial equivalence. For devices that differ significantly from those already on the market, additional information may be necessary to evaluate those differences.

I. Wavelength: The submission should identify the individual wavelength(s) or the range of wavelengths of light that will be delivered to the nail by the proposed device.

II. Laser or Light Generation: If the device is a laser, the details of the laser generation method should be submitted. This description may include the gain medium, pumping source, and the method used for pulsing (q-switch or other). If the laser is generated without a gain medium, e.g., by laser diodes, detailed specifications and engineering drawings of the diodes or other laser source(s) may be requested. If the device is an intense pulsed light or any other kind of light source, a description of the light source and the method of light generation will be requested.

III. Fluence: The submission should identify the total fluence (energy per area), delivered at each spot. If the clinical procedure for the nail includes multiple steps, the submission should identify the energy delivered to a spot at each step as well as the total energy delivered to a spot.

IV. Spot Size: The submission should include the spot size(s) that will be used for the procedure.

V. Output mode: The submission should detail whether the light output is pulsed or continuous wave (CW).

VI. Power: Submissions should identify the power that will be delivered during the procedure. For pulsed light, the average power should be provided.

VII. Pulsed laser and light sources: The following parameters should be submitted for pulsed lasers and light sources.

- Pulse duration
- Energy per pulse

- Fluence per pulse
- Duty cycle
- Repetition rate (pulses per second)

VIII. Directions for use: The directions for use should include the following information:

- The size and the shape of the area on the nail that will be illuminated by light during the clinical procedure
- The spatial distribution and number of spots per unit area, if the light is to be delivered at discrete spots
- The dwell time at each spot and the time interval between spots, as well as the direction of movement to complete the spot pattern, if the light is delivered in discrete spots, or in a stacked or "paintbrush" fashion
- The movement velocity and the direction(s) of the movement, if a "paintbrush" fashion is employed
- The number of procedures per session, number of sessions per week, and the total number of sessions
- Nail that will be treated per procedure and per session
- Patient preparation, pre- and post-operative evaluation and post-operative care instructions
- Warnings or contraindications for the proposed device