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# **Head Lice Infestation: Developing Drugs for Topical Treatment Guidance for Industry**

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

**October 2016  
Clinical/Medical**

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# Head Lice Infestation: Developing Drugs for Topical Treatment Guidance for Industry

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## **Head Lice Infestation: Developing Drugs for Topical Treatment Guidance for Industry<sup>1</sup>**

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**

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of head lice infestation.<sup>2</sup> Specifically, this guidance addresses the Agency's current thinking regarding the overall development program and clinical trial designs of drugs to support approval of an indication for topical treatment of head lice infestation. The information presented will help sponsors plan clinical trials, design clinical protocols, and conduct and appropriately monitor clinical trials. Development plans should be discussed with the review division before initiating trials to ensure that the trial design meets defined objectives.

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.<sup>3</sup> This guidance focuses on specific drug development and trial design issues that are unique to the study of head lice infestation.

This guidance also does not contain discussion of nonclinical or chemistry, manufacturing, and controls issues. See the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.

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<sup>1</sup> This guidance has been prepared by the Division of Dermatology and Dental Products in the Center for Drug Evaluation and Research at the Food and Drug Administration.

<sup>2</sup> For the purposes of this guidance, all references to *drugs* include human drugs and not therapeutic biological products unless otherwise specified.

<sup>3</sup> We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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

## **II. BACKGROUND**

Head lice infestation is characterized by infestation of the scalp and scalp hair by a wingless parasitic insect, the human head louse, *Pediculus humanus capitis*. Head lice live on the hair and feed on the scalp by consuming a blood meal.<sup>4</sup>

Head lice infestation is widespread, affecting both children and adults. In the United States it is estimated that between 6 and 12 million infestations occur each year among children 3 to 11 years of age.<sup>5</sup>

There are many FDA-approved drugs (including prescription and nonprescription drugs) for the treatment of head lice infestation, but genetic resistance of lice to lindane and to the most commonly used treatments, pyrethroids, is not uncommon in the United States;<sup>6,7</sup> thus development of additional drugs for this indication is encouraged.

## **III. DEVELOPMENT PROGRAM**

### **A. General Considerations**

#### *1. Early Phase Clinical Development Considerations*

In early phase clinical development the components of the investigational drug should be defined and all active moieties identified. If two or more active components are identified, it should be demonstrated that each active component makes a contribution to the claimed effects and the dosage of each active component is such that the combination is safe and effective for the intended patient population (see 21 CFR 300.50).

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<sup>4</sup> Jacobson, CC and EA Abel, 2007, Periodic Synopsis: Parasitic Infections, J Am Acad Dermatology, 56:1026-1043.

<sup>5</sup> See the Epidemiology & Risk Factors Web page (located under Parasites – Lice – Head Lice) on the Centers for Disease Control and Prevention Web site at <http://www.cdc.gov/parasites/lice/head/epi.html>.

<sup>6</sup> Lebwohl, M, L Clark, and J Levitt, 2007, Therapy for Head Lice Based on Life Cycle, Resistance, and Safety, Pediatrics, 119:965-974.

<sup>7</sup> Burkhart, CN, CG Burkhart, and DS Morell, 2012, Head Lice, in Dermatology, edited by JL Bologna, JL Jorizzo, and JV Schaffer, 3rd edition, published by Elsevier, Chapter 84, page 1426.

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If the drug contains more than one active ingredient, the sponsor can consider in vitro studies to assess the contribution to efficacy of each of the active ingredients. This issue should be discussed with the Agency early in clinical development.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the drug for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Head lice infestation is primarily a pediatric disease. Sponsors are encouraged to discuss pediatric drug development with the FDA early in the course of clinical development, including appropriate pharmacokinetic (PK) trials in pediatric subjects to support dose selection and the recommended size of the preapproval safety database in children. Under PREA, a waiver to provide a pediatric assessment may be granted if certain criteria are met. Historically, studies in patients younger than 6 months of age for the treatment of head lice infestation have been waived most often because the studies were impossible or highly impracticable. Under certain circumstances, there may be other reasons for waiver (e.g., there was evidence of lack of meaningful therapeutic benefit over existing treatments and was not likely to be used by a substantial number of patients in that age group or there was strong evidence suggesting the drug is ineffective or unsafe in that age group). If studies for any pediatric age group are waived for safety concerns, the safety concern must be included in product labeling.<sup>8</sup> Sponsors are required to submit an initial pediatric study plan no later than 60 days after an end-of-phase 2 meeting.<sup>9</sup> See the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* for information regarding the content of and process for submission of an initial pediatric study plan.<sup>10</sup>

Trials to identify an appropriate (safe and effective) dose are an important component of phase 2 development for topical treatment of head lice infestation. A dose-response trial conducted during early phase clinical development to assess safety and efficacy can help ensure that the most appropriate dose regimen is selected for phase 3 development. For additional information on the FDA's current thinking regarding dose response, see the ICH guidance for industry *E4 Dose-Response Information to Support Drug Registration* and the guidances for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* and *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications*.

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<sup>8</sup> See PREA (Public Law 108-155; sections 505B(a)(4)(D) and 505B(b)(2)(D) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); 21 U.S.C. 355c).

<sup>9</sup> See PREA (Public Law 108-155; section 505B(e)(2)(A) of the FD&C Act; 21 U.S.C. 355c) as amended by the Food and Drug Administration Safety and Innovation Act (Public Law 112-144).

<sup>10</sup> When final, this guidance will represent the FDA's current thinking on this topic.

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### 2. *Drug Development Population*

The trial population should be representative of the target population for which the drug is intended for use in clinical practice (e.g., reflective of the age, race, and sex of the population with head lice infestation in the United States). Pediatric subjects should be evenly distributed across age groups. Inclusion of younger age groups would be dependent upon safety findings for the investigational drug. Geographical diversity is also important for the treatment of head lice infestation because resistance patterns to some drugs vary by location.

Although head lice infestation (*P. capitis*) is primarily a disease of the pediatric population, it may be appropriate to obtain safety and efficacy data in adults before proceeding with studies in the pediatric population. See the ICH guidance for industry *E11 Clinical Investigation of Medicinal Products in the Pediatric Population*.

If the sponsor plans to conduct trials outside of the United States, the sponsor should consider factors that may affect the acceptability of such data for drug approval in the United States. Sufficient information should be provided to demonstrate that data from clinical trials conducted outside of the United States are applicable to and will predict the clinical outcomes in U.S. patients (see 21 CFR 314.106). See the ICH guidance for industry *E5 Ethnic Factors in the Acceptability of Foreign Clinical Data* and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials*.

### 3. *Entry Criteria*

For general information regarding the performance of trials to evaluate efficacy, see the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*. See also sections III.A.2., Drug Development Population, and III.B., Specific Efficacy Trial Considerations, for additional discussion. The inclusion and exclusion criteria should be sufficiently broad to allow enrollment of a population that will be representative of that anticipated with proposed labeling (e.g., representative of real-world use).

### 4. *Safety*

Both local and systemic safety information (e.g., adverse events and laboratory data) should be collected during clinical trials. All subjects should be evaluated for safety at the time of each trial visit or assessment, regardless of whether the investigational drug has been discontinued for safety. Generally, all adverse events should be followed until resolution, even if time on clinical trial would otherwise have been completed.

Local safety assessment of the skin/scalp (with careful attention to the adjacent skin such as the forehead, neck, and ears) and eyes should include evaluation for the presence of erythema, edema, pustules, excoriation, and a query for pruritus (at baseline and post-treatment visits). This evaluation should occur at intervals most likely to capture any safety signal. The timing of evaluation may be affected by factors such as the type of drug being studied and the type of reaction that is expected.

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Evaluation of systemic safety should include monitoring for systemic adverse events, laboratory monitoring, physical exam/vital signs, and where appropriate (e.g., for a new molecular entity in the absence of PK data under maximal use conditions) cardiac safety monitoring such as electrocardiogram monitoring.

A maximal use PK trial should be conducted to assess systemic bioavailability and safety. For further information, see section III.A.5., Clinical Pharmacology.

A number of important safety issues for drugs already approved for treating head lice infestation have been identified, for example:

- Neurotoxicity: The treatment may achieve efficacy through effects on the insect's nervous system. Systemic absorption of the drug could raise concern about effects on the human nervous system.
- Neonatal toxicity: The treatment may contain benzyl alcohol. There is a risk of gasping syndrome if benzyl alcohol is used in neonates and low birth weight infants.
- Inhibition of acetylcholinesterase: An approved drug (malathion) inhibits acetylcholinesterase, and its systemic absorption may increase the risk of bradycardia, respiratory distress, and diarrhea.

During drug development the sponsor should also consider potential safety issues such as:

- Teratogenicity: The risk of teratogenicity should be evaluated. See ICH M3(R2). Measures to reduce the risk for pregnancy exposure should be employed for both caregivers, who administer the investigational drug to pediatric subjects, and subjects who are of reproductive potential.
- Arrhythmogenic potential: See the ICH guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*.
- Medication errors such as ingestion of the intended topical drug: Preventive measures such as child-resistant packaging and/or orifice narrowing should be considered early in drug development.
- Environmental concerns: Because the active ingredients in some head lice drugs are also insecticides, the effect of the introduction of these drugs and their metabolites into the environment should be anticipated and evaluated. See the guidance for industry *Environmental Assessment of Human Drug and Biologics Applications*.

a. Special safety studies

For topical drugs, dermal safety studies with the to-be-marketed drug may be needed to provide information regarding cumulative irritancy, contact sensitization, phototoxicity, and photo-contact allergic potential.

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### b. Drug-drug interactions

The potential for drug-drug interactions should be adequately addressed during development. For further information, see the draft guidance for industry *Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*.<sup>11</sup>

### 5. *Clinical Pharmacology*

PK trials to assess systemic absorption may be needed unless there is a waiver of in vivo bioavailability studies, which is rarely granted. Because of the variable dosing nature of topical drugs, the FDA recommends that trials of the in vivo assessment of systemic exposure be done under so-called *maximal use conditions*.<sup>12</sup> The recommended elements of such a maximal use PK trial are as follows:

1. A formulation identical to the clinically studied/to-be-marketed formulation should be used.
2. The trial should be done in an adequate number of subjects at upper end of severity of lice infestation (e.g., at least three live lice present at enrollment and moderate pruritus/excoriation of scalp) that is expected to be included in both the clinical program and the anticipated approved indication. Steps should be taken to ensure that the target patient population (e.g., age, sex, race) is adequately represented. The FDA recommends enrollment be stratified by age to ensure a sufficient number of younger subjects are enrolled.
3. The topical dosing regimen selected should represent the maximal dosing anticipated in both phase 3 trials and in the proposed labeling for the following:
  - Use of highest proposed strength
  - Amount applied
  - Method of application and site preparation
  - Frequency of dosing
  - Duration of treatment
4. The analytical method should be properly validated for both parent compound and metabolites.

The objective of this trial is to maximize those elements affecting dermal penetration to assess systemic bioavailability and systemic safety of the drug. The FDA recommends, when possible, that the resulting PK data be analyzed using standard PK metrics (e.g., area under the

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<sup>11</sup> When final, this guidance will represent the FDA's current thinking on this topic.

<sup>12</sup> Bashaw, ED, T Tran, C Shukla, and X Liu, 2015, Maximal Usage Trial: An Overview of the Design of Systemic Bioavailability Trial for Topical Dermatological Products, *Therapeutic Innovation & Regulatory Science*, Vol. 49(1) 108-115.

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concentration versus time curve, maximum concentration ( $C_{\max}$ ), time at which  $C_{\max}$  occurs, half-life). It is also recommended that the trial protocols incorporate evaluations for cutaneous safety.

### **B. Specific Efficacy Trial Considerations**

The trial protocol should take into consideration the following elements.

#### *1. Trial Design*

In general, sponsors should conduct two randomized, double-blinded, controlled trials to establish efficacy and safety of a drug for the treatment of head lice infestation in the intended population. A commonly used design compares the investigational drug to vehicle alone. In a vehicle-controlled design, potential influences on the course of the disease other than those arising from the pharmacologic action of the investigational drug can be controlled via randomization and blinding. See also section III.B.9., Trial Procedures and Timing of Assessments, for additional comments relating to trial design, and refer to the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

If the investigational drug has clinically significant potential risks (e.g., neurotoxicity), an active control may be appropriate to ensure that the investigational drug has a clinically meaningful benefit (e.g., superior efficacy or comparable efficacy with more favorable safety profile) when compared to an approved topical treatment for head lice infestation. In active-controlled clinical trials, the comparator should be an FDA-approved drug, used according to approved labeling.

Use of a lice comb device as part of the treatment regimen could affect efficacy. When a device such as a dedicated comb is to be used, the sponsor should submit its specifications to the investigational new drug application as early as is feasible.

#### *2. Trial Population*

The population studied should include pediatric subjects with an age group distribution reflecting the fact that the highest incidence of head lice infestation is found in children aged 3 to 11 years. Depending upon safety findings, the lower boundary of age studied, generally younger than 6 months, should be as low as that in which use is intended to occur. See also sections III.A.1., Early Phase Clinical Development Considerations, and III.A.2., Drug Development Population.

#### *3. Entry Criteria*

Entry criteria should specify a minimum baseline level of infestation. Index subjects are the primary population to be evaluated for efficacy and should have an active head lice infestation, defined as at least three live lice (adults and/or nymphs) present on the scalp and/or hair. *Index subjects* are defined as the youngest household members presenting with an active head lice infestation. Household members, to be considered for trial entry, should have an active head lice infestation defined as at least one live louse present on the scalp and/or hair.

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Subjects with the following characteristics should be excluded from trials for head lice infestation:

- Presentation at the treatment site with visible skin/scalp condition(s) that are not attributable to head lice infestation and that in the opinion of the investigative personnel will interfere with safety and/or efficacy evaluations
- Recent (e.g., within 7 days) treatment for head lice, including nonprescription, home remedy, and/or prescription treatments

Because the population studied is expected to include pediatric subjects, the sponsor should employ age-appropriate assent/informed consent.

### *4. Randomization, Stratification, and Blinding*

Ideally, trials should be multicenter, well-controlled, and double-blinded. Randomization and blinding are important to minimize biases. If blinding of both subject and evaluator is not possible, sponsors should discuss potential biases with the FDA and how these biases will be addressed.

If an active-controlled trial design is chosen, challenges to blinding may occur and the following additional processes may be needed to minimize bias:

- If the labeled treatment regimen for the active control is different from that for the investigational drug, the time and geographical place of drug application can be masked from the evaluators of the trial
- If the active control treatment involves a procedure, such as combing, that is not part of the proposed treatment regimen under study, or if the proposed drug treatment involves a procedure that is not part of approved labeling for the active control, an additional treatment arm that involves use of both the procedure and the relevant drug (proposed treatment or active control, respectively) can be included

For details of randomization and stratification, see section III.B.11., Statistical Considerations.

### *5. Specific Populations*

#### *a. Pediatric*

See section III.A.1., Early Phase Clinical Development Considerations, for information relating to pediatric considerations.

#### *b. Pregnant and lactating women*

Fertility and embryo fetal development studies in animals should be completed before phase 3 trials are initiated. Results of such studies generally should be included in labeling. Additionally, available information regarding the use of the drug in pregnant women should be

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included in labeling. Sponsors should be advised of labeling requirements in other guidance for pregnancy, lactation, and females and males of reproductive potential.<sup>13</sup>

Information on the safety of the drug during lactation also should be included in labeling. Information on conducting lactation studies, when necessary, is addressed in other guidance.<sup>14</sup>

Caregivers may be exposed to the drug during application to younger pediatric subjects. Risks of exposure to caregivers who are pregnant or lactating should be addressed and included in labeling, if appropriate.

### c. Geriatric

If conclusions are to be made regarding drug safety and efficacy in the geriatric population, a sufficient number of subjects 65 years of age and older should be evaluated at the level of exposure (dose and duration) proposed for use. See the ICH guidance for industry *E7 Studies in Support of Special Populations: Geriatrics*.

### 6. Dose Selection

See section III.A.1., Early Phase Clinical Development Considerations, for a more detailed discussion of dose-ranging.

### 7. Choice of Comparators

See section III.B.1., Trial Design, for a discussion of comparators.

### 8. Efficacy Endpoints

The primary efficacy measure should be the presence or absence of live lice in index subjects.

The primary efficacy endpoint should be dichotomized to success or failure with success defined as the absence of live lice and failure defined as the presence of live lice. Specifically, success should be defined as follows:

- The proportion of index subjects in the enrolled households who are lice free (no live lice, adults or nymphs) 14 days after the last treatment

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<sup>13</sup> See the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format*. When final, this guidance will represent the FDA's current thinking on this topic.

<sup>14</sup> See the draft guidance for industry *Clinical Lactation Studies — Study Design, Data Analysis, and Recommendations for Labeling*. When final, this guidance will represent the FDA's current thinking on this topic.

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### *9. Trial Procedures and Timing of Assessments*

The time point to evaluate efficacy should be based on the life cycle of the head louse. Because nits hatch in a range of 6 to 12 days after being laid,<sup>15,16</sup> selection of a time point 14 days after the last treatment to evaluate for efficacy minimizes the likelihood of missing late-hatching lice.

The assessment of presence or absence of live lice should be performed by a trained evaluator, with a minimum agreed-upon time for lice examination in the event that lice are not immediately identified. The actual time spent in examination should be documented on the case report form.

Because approved drugs for head lice treatment are available, if a vehicle-controlled trial will be conducted, its design should include an early removal option for rescue treatment of subjects who have live lice after the last treatment and evaluation. Household members who have active head lice infestation, defined as at least one live louse present on the scalp and/or hair, should receive the same treatment as index subjects.

Trial procedures in phase 3 trials should conform as closely as possible to expected real-world use (e.g., the caregiver should apply the medication at home rather than investigator application in the clinic) so that results from pivotal trials will be generalizable to the postmarketing setting.

The use of drugs for the treatment of head lice infestation occurs within the context of an overall lice management program. Trial design should include appropriate instructions to subjects such as:

- Wash (in hot water) or dry-clean all recently worn clothing, hats, used bedding, and towels
- Wash (in hot water) personal care items such as combs, brushes, and hair clips
- Use a fine-tooth comb or special nit comb to remove nits and dead lice

### *10. Endpoint Adjudication*

In general, endpoint adjudication is not needed for topical drugs intended for the treatment of head lice infestation.

### *11. Statistical Considerations*

Because treatment efficacy could be affected by household members with an active head lice infestation, randomization should be done at the household level, where the index subject and all eligible household members would receive the same treatment. The primary population for the

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<sup>15</sup> Lebowhl, M, L Clark, and J Levitt, 2007, Therapy for Head Lice Based on Life Cycle, Resistance, and Safety, *Pediatrics*, 119:965-974.

<sup>16</sup> van der Wouden, JC, T Klootwijk, L Le Cleach et al., 2011, Interventions for Treating Head Lice (Protocol), *The Cochrane Library*, Issue 10.

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evaluation of efficacy is the index subjects; therefore, the intent-to-treat population should be defined as all index subjects randomized and dispensed treatment medication.

Because there may be regional or investigator-related factors that may affect assessment of efficacy (such as drug resistance patterns of head lice or investigator skill), evaluating center-to-center variability is recommended for appropriate interpretation of trial findings. Therefore, centers should enroll a reasonable number of subjects to allow for a meaningful assessment of center-to-center variability.

### ***12. Accelerated Approval (Subpart H) Considerations***

Head lice infestation is not a *serious or life-threatening condition*; therefore, accelerated approval is not appropriate for drugs intended to treat this condition.

### ***13. Risk-Benefit Considerations***

Assessment of risks and benefits involves an evaluation of the effect of the investigational drug on head lice infestation. The primary efficacy analysis should demonstrate a clinically meaningful and statistically significant result. If present, toxicities related to the pharmacologic effects of the investigational drug (e.g., neurotoxicity) also should be considered as part of the overall risk-benefit assessment.

## **C. Other Considerations**

### ***1. Relevant Nonclinical Considerations***

It is recommended that *in vitro* studies be conducted using head lice and their eggs to investigate the mechanism of action and identify the active ingredient(s) of the drug. Such studies should be designed to evaluate the mortality/hatchability of head lice/eggs treated with the drug.

If the mechanism of action of the drug is related to the head louse nervous system, the potential for human neurotoxicity should be adequately addressed in nonclinical safety pharmacology and toxicology studies. Other safety concerns for topical pediculicide drugs that should be adequately addressed in nonclinical studies include, but are not limited to, dermal irritation, ocular irritation, dermal sensitization, and phototoxicity. Dermal irritation can be evaluated in conjunction with repeat-dose dermal toxicity studies. The *in vivo* rabbit ocular irritation test is not recommended for the evaluation of ocular irritation. Ocular irritation can be evaluated by conduct of appropriate *in vitro* or *ex vivo* tests (e.g., the bovine corneal opacity and permeability assay). *In vitro* assays can be used as a screen for clinical assessment of dermal sensitization and phototoxicity. See ICH M3(R2) for additional information regarding the recommended nonclinical studies to support the proposed clinical dose and treatment regimen of the drug.

### ***2. Labeling Considerations***

A representative indication statement for a topical drug intended to treat head lice infestation should be:

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*[Drug X] is indicated for the topical treatment of head lice infestation in patients (age) and older*

The INDICATIONS AND USAGE section of labeling for drugs for the treatment of head lice infestation generally should also include information about adjunctive measures, such as:

*[Drug X] should be used in the context of an overall lice management program:*

- *Wash (in hot water) or dry-clean all recently worn clothing, hats, used bedding, and towels*
- *Wash (in hot water) personal care items such as combs, brushes, and hair clips*
- *Use a fine-tooth comb or special nit comb to remove nits and dead lice*

The risk of accidental ingestion should be discussed in the WARNINGS AND PRECAUTIONS and PATIENT COUNSELING INFORMATION sections.<sup>17</sup> To prevent accidental ingestion, the discussion of the risk should include a recommendation to use the drug on pediatric patients only under direct adult supervision.

Safety concerns, especially with respect to use in the pediatric age group (e.g., accidental ingestion, misapplication), generally support the inclusion of FDA-approved patient labeling (i.e., Patient Information). For those drugs having complex application procedures, FDA-approved Instructions for Use would be beneficial to enhance compliance.

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<sup>17</sup> See the guidances for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* and *Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*.