Malaria: Developing Drugs for Treatment

Guidance for Industry

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I. INTRODUCTION

This guidance is intended to assist sponsors in the overall development program for drug and biological products[2] for the treatment of malaria, caused by clinically relevant *Plasmodium* species (e.g., *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, and *P. knowlesi* as well as some zoonotic species, e.g., *P. simium* and *P. cynomolgi*). Most of the experience in drug development for the treatment of malaria has been gained from *P. falciparum* trials. This guidance is intended to serve as a focus for continued discussions on the design of malaria treatment trials among the Agency, pharmaceutical sponsors, the academic community, and the public.[3] Some of the trial design issues were discussed at the FDA public workshop on Clinical Trial Design Considerations for Malaria Drug Development held on June 30, 2016.[4]

This guidance does not address drug development pertaining to prophylaxis of malaria. Furthermore, this guidance does not address other aspects of drug development such as pharmacology/toxicology, clinical pharmacology, or manufacturing. The general issues of statistical analysis or clinical trial design are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998), *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021), and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001),[5] respectively.

[1] This guidance has been prepared by the Division of Anti-Infectives in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drug or drugs* include both therapeutic drug and biological products unless specified otherwise.

[3] In addition to consulting guidance documents, sponsors are encouraged to contact the Agency to discuss specific issues that arise during the development of drugs.

[4] Available at https://www.fda.gov/Drugs/NewsEvents/ucm490084.htm.

[5] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

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

Malaria is a parasitic disease primarily transmitted by *Anopheles* species mosquitoes. Rarely, it can also be transmitted by transfusion of blood or blood components. Malaria is caused by several *Plasmodium* species and is endemic in most tropical countries. Clinical manifestations, including the severity of malaria, are dependent on the infecting species and host factors.

Following the inoculation of *Plasmodium* sporozoites through the bite(s) of infected mosquitoes, the sporozoites migrate to the liver and invade hepatocytes (hepatic or exoerythrocytic phase of the life cycle). Merozoites are released from hepatocytes into the circulation and invade and multiply within red blood cells. These red blood cells can rupture, releasing merozoites that invade other red blood cells (erythrocytic phase of the life cycle). Some merozoites mature into male and female gametocytes within the red blood cells. Asexual forms of the erythrocytic stage parasites are responsible for the clinical manifestations of the disease.

P. vivax and *P. ovale* form a dormant stage in the liver, known as hypnozoites, that can cause relapse when released into the circulation weeks or years later; *P. falciparum*, *P. malariae,* and *P. knowlesi* do not form hypnozoites.

The biology of *Plasmodium* species has specific implications for antimalarial drug development. Treatment is directed at the eradication of the erythrocytic and/or exoerythrocytic stages of infection depending on the target *Plasmodium* species.

The terminology used for assessing clinical and parasitological responses includes the following:

- *Clinical cure* is directed at eradication of the parasites in addition to adequate clinical response (i.e., absence of clinical symptom(s) present at baseline).

- *Radical cure* eliminates both erythrocytic and exoerythrocytic stages of infection, including the hypnozoites.

- *Recrudescence* is recurrence of the existing parasitemia due to the survival of the erythrocytic stage parasites of *Plasmodium* species.

- *Relapse* is recurrence of the original parasitemia attributable to the *Plasmodium* parasites that have a hypnozoite stage, that is, *P. vivax* or *P. ovale.*

- *Reinfection*/*new infection* may occur after successful treatment of the initial infection during enrollment in a clinical trial; reinfection/new infection may be with the same or different strain(s) of *Plasmodium* species.

- *Failure of treatment* is persistence, recrudescence, relapse, or new infection regardless of parasite density and/or failure of clinical symptoms to resolve.

III. DEVELOPMENT CONSIDERATIONS

A. General Drug Development Considerations

Considerations for early phase drug development and assessments of efficacy and safety are outlined as follows:

1. Nonclinical Development Considerations

- The activity of an antimalarial drug and its metabolites should be measured using appropriate in vitro and animal models of *Plasmodium* species. Testing should be performed against the erythrocytic and exoerythrocytic stages of the laboratory strains and clinical isolates of *P. falciparum* and other *Plasmodium* species.

- Considerations when choosing an appropriate nonclinical model and experimental design should include selecting appropriate *Plasmodium* species relevant to human infection, the similarity of the course of infection and disease in animals and humans, as well as the ability to obtain reproducible parasitemia. Similarly, measurement of activity should be based on relevant endpoints and biomarkers (e.g., survival of the animal, reduction in parasitemia, effect on erythrocytic and exoerythrocytic stages, parasite clearance time, and recrudescence or relapse).

- The ability of *Plasmodium* strains to develop reduced drug sensitivity/resistance when subjected to drug pressure should be examined in appropriate in vitro and/or in vivo models, and efforts should be made to identify the potential resistance markers. Furthermore, the potential for cross-resistance with antimalarial drugs in the same class or in other classes should be evaluated. Investigating the underlying mechanism(s) of resistance would be informative if reduced drug sensitivity is demonstrated. Attempts should be made to evaluate the significance of any changes in phenotype (e.g., in vitro sensitivity to the drug) or genotype observed by correlating such changes with outcome.

2. Early Phase Clinical Development Considerations

- Controlled human malaria infection (CHMI) model studies, usually conducted in malaria-naïve healthy participants from nonendemic regions, may aid in providing preliminary evidence of efficacy for investigational drugs and for selecting doses and a regimen based on pharmacokinetic/pharmacodynamic analysis. Additionally, CHMI studies may provide clinical evidence of the contribution of each drug when investigational drugs are

used in combination. CHMI studies should be performed with well-characterized strains of the parasites (e.g., *P. falciparum* or *P. vivax*). The endpoints may be based on assessment of parasitemia measured by microscopic evidence of parasites on blood smears and/or a biomarker (e.g., *P. falciparum* 18S rRNA/DNA[6]) in addition to clinical signs and symptoms of malaria. Clinical protocols for CHMI studies in nonendemic and endemic regions should be discussed with the Agency.

- Exposure-response relationships should be explored during early phases of drug development to aid in selection of optimal dosing strategies for evaluations in the later trials. Evaluation of the relationship between drug concentration and parasite clearance by integrating the pharmacokinetic/pharmacodynamic information from in vitro and in vivo drug evaluations is recommended to develop dosing strategies that avoid the emergence of resistance to the investigational drug. During early phases of clinical development, a simplified analysis relating exposure and proportion of participants with clinical failure can be used to support evidence of effectiveness and justify dose selection. Additional analyses of the exposure-safety relationship using similar approaches should be performed to assist in evaluating the balance between effectiveness and toxicity of different dosage regimens. Physiologically-based pharmacokinetic modeling integrated with pharmacokinetic/pharmacodynamic information from in vitro and in vivo evaluations can be useful to define dosing strategies for phase 3 development. Evaluations of specific patient populations with different intrinsic factors (e.g., age, body weight, and hepatic or renal impairment) in phase 3 efficacy trials can provide additional information about exposure-response relationships.

3. Efficacy Considerations

- Drugs that are effective against the erythrocytic stages of *P. falciparum* may be effective against the erythrocytic stages of other less prevalent *Plasmodium* species.[7] Sponsors who seek an indication for more than one *Plasmodium* species (e.g., *P. vivax* in addition to *P. falciparum*) should demonstrate the efficacy and safety of the test drug in a subset of participants with monoinfection with the relevant *Plasmodium* species (e.g., *P. vivax* or *P. ovale*).

- If the investigational product contains multiple drugs, or the investigational drug will be given in combination with other antimalarial drugs, the contribution of each of the component drugs to the combination should be demonstrated to address the treatment contribution of each component.[8] Potential approaches include historical evidence of the

[6] See FDA Reviews of Qualified Biomarker: *Plasmodium* 18S rRNA/rDNA, available at https://www.fda.gov/drugs/biomarker-qualification-program/fda-reviews-qualified-biomarker-plasmodium-18s-rrnardna.

[7] See the 2022 WHO Guidelines for Malaria, available at https://reliefweb.int/report/world/who-guidelines-malaria-3-june-2022.

[8] See 21 CFR 300.50; see also the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* (June 2013).

need for combination drug therapy as well as data from the development program such as (1) the mechanism of action of the component drugs in the combination regimen, (2) in vitro studies, (3) animal infection model studies, (4) CHMI studies, or (5) factorial design clinical trials in infected participants living in malaria-endemic areas.

- Efforts should be made to identify markers of drug resistance in participants who fail therapy.

4. Safety Considerations

Approximately 500 or more participants exposed to the intended dose and duration of drug treatment should be included in the safety database; however, a larger safety database may be required depending on the safety profile of the drug(s). Sponsors should discuss in advance the specifics of the safety database with the Agency.

B. Uncomplicated Malaria

Considerations for trial design and evaluation of efficacy in participants with uncomplicated malaria are outlined below:

1. Trial Design

- Use of an active control regimen containing FDA-approved antimalarial drugs is strongly recommended. Non-FDA-approved comparator products may be appropriate if they represent the local standard of care. If a sponsor proposes use of non-FDA-approved comparator products in clinical studies intended to support approval of a marketing application for their proposed drug, they should consult the review division on the scientific acceptability of the proposal. When evaluating the current standard of care, FDA considers recommendations by authoritative scientific bodies (e.g., the World Health Organization, Infectious Diseases Society of America, Centers for Disease Control and Prevention) based on clinical evidence and other reliable information that reflects current clinical practice.

- In trials, sponsors should minimize risk of reinfection by monitoring participants in a hospitalized setting and/or ensuring the use of insecticide-treated nets.

- The optimal duration of follow-up depends on the *Plasmodium* species. FDA recognizes that in rare cases recrudescent or relapse infection may occur more than 28 days after initial therapy. Inclusion of a late follow-up visit at 42 days or more after initiation of therapy should be considered, particularly when antimalarial drugs with prolonged half-lives are being studied.

2. Trial Population

Efficacy trials should be conducted in different geographical regions to address variations in transmission rates, to assess the sensitivity of isolates/strains to existing antimalarial therapy, and

to reflect differences in population host factors. Host factors include immune status (e.g., those living in endemic areas for many years may experience low levels of parasitemia with no ill effects), blood type (e.g., Duffy negative blood types are mostly resistant to infection/disease with *P. vivax*), pregnancy, and age (e.g., pregnant participants and infants have a higher risk of developing complicated malaria). Attempts should be made to study both immune and nonimmune participants.

- Some relevant *inclusion criteria* include the following:

  - Identification of the *Plasmodium* species on peripheral blood smears; parasitemia should be limited to values between 1000/μL and <250,000/μL (0.02 percent and <5 percent).[9] Proposals to study parasitemia outside of this range should be discussed with the Agency before protocol submission (see section III.C).

  - Participants with mixed *Plasmodium* infections can be included in *P. falciparum* treatment studies; however, participants with infection due to more than one *Plasmodium* species should be evaluated in prespecified subgroup analyses.

  - Fever (e.g., oral or tympanic temperature greater than or equal to 38ºC) should be documented at study entry in a participant who reports fever.

  - At least two of the following symptoms or signs of malaria should be present: shivering/chills, malaise, headache, and loss of appetite in adults or irritability, lethargy, and anorexia in children; or malaria-related laboratory abnormalities (e.g., decreased hemoglobin, increased serum creatinine).

- Some relevant *exclusion criteria* include the following:

  - Participants with severe or complicated malaria (which is discussed in more detail in section III.C)

  - Participants with prior antimalarial therapy for the current episode unless the new drug is under development for subjects failing treatment with other drugs

  - Participants with concurrent febrile illnesses (e.g., typhoid fever)

  - Participants who require use of antibacterial drugs with antimalarial activity (e.g., sulfonamides, tetracyclines, and macrolides) for other reasons

- Pregnant participants are at a greater risk of symptomatic malaria and poor birth outcomes. When available data from adult clinical trials indicate that the investigational drug should be studied in pregnant participants, adequate reproductive and developmental

[9] The range of percentage parasitemia is based on a normal red blood cell count of 5 x 10^6 red blood cells per μL of blood. Note: Rapid diagnostic tests should be limited to screening of participants.

toxicity studies in relevant nonclinical models[10] and the standard battery of genotoxicity tests[11] are necessary before enrolling pregnant participants in malaria treatment trials.

- The clinical trial population should be representative of the target population expected to take the antimalarial drug with respect to age, sex, and other factors. Sponsors should discuss drug development in the pediatric and geriatric populations with the Agency as early as is feasible.[12,13]

- FDA regulations permit studies performed in foreign countries to be used for drug approval when these studies meet FDA standards for the conduct and design of clinical trials (21 CFR 314.106).

3. Clinical and Parasitological Outcomes

Treatment outcomes can be classified as early treatment failure, late clinical failure, late parasitological failure, or adequate clinical and parasitological response that are mostly consistent with the World Health Organization criteria.[14]

- **Early treatment failure (any of the following)**

  - Development of severe malaria (which is discussed in more detail in section III(C)) on day 1, 2, or 3 of treatment in the presence of parasitemia

  - Parasitemia on day 2 greater than day 0 (i.e., the day of the baseline visit) irrespective of axillary temperature

  - Parasitemia on day 3 with axillary temperature greater than or equal to 37.5ºC

  - Parasitemia on day 3 greater than or equal to 25 percent of the count on day 0

[10] See the ICH guidance for industry *S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals* (May 2021).

[11] See the ICH guidance for industry *S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use* (June 2012).

[12] See the Pediatric Research Equity Act (Public Law 108-155; section 505B of the Federal Food, Drug, and Cosmetic Act; 21 U.S.C. 355c) as amended by the Food and Drug Administration Safety and Innovation Act of 2012 (Public Law 112-144) and the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* (July 2020).

[13] See the ICH guidances for industry *S11 Nonclinical Safety Testing in Support of Development of Pediatric Pharmaceuticals* (May 2021), *E7 Studies in Support of Special Populations: Geriatrics* (August 1994), and *E7 Studies in Support of Special Populations: Geriatrics; Questions and Answers* (February 2012).

[14] World Health Organization, 2009, Methods for Surveillance of Antimalarial Drug Efficacy, available at https://iris.who.int/bitstream/handle/10665/44048/9789241597531_eng.pdf?sequence=1.

- **Late clinical failure (any of the following)**

  - Development of severe malaria after day 3 in the presence of parasitemia without previously meeting any of the factors of early treatment failure

  - Parasitemia any day from day 4 to day 28, with axillary temperature greater than or equal to 37.5ºC without previously meeting any of the factors of early treatment failure

  - Any participant receiving additional antimalarial therapy not specified in the study protocol

- **Late parasitological failure**

  - Parasitemia on any day between day 7 and day 28 with axillary temperature less than 37.5ºC in participants who did not previously meet any of the criteria of early treatment failure or late clinical failure

- **Adequate clinical and parasitological response**

  - Absence of symptoms of malaria and of parasitemia on day 28 in participants who did not previously meet any of the criteria of early treatment failure, late clinical failure, or late parasitological failure

4. Efficacy Endpoints

- *Primary endpoint:*

Clinical Cure: Clinical cure is based on adequate clinical (i.e., absence of clinical symptom(s) present at baseline) and parasitological responses; parasitological response is based on blood smear findings (i.e., uncorrected cure rates) and varies depending on the *Plasmodium* species.

- **In trials of drugs that target the erythrocytic stage parasites of *Plasmodium* species**, the primary efficacy endpoint of clinical cure is typically defined as the absence of parasitemia on day 28 in participants who did not previously meet any of the criteria for early treatment failure, late clinical failure, or late parasitological failure. Therefore, recurrence of parasitemia after initial clearance or persistence of parasitemia during the 28-day period would be considered a failure. Duplicate blood smears should be examined frequently, for example, every 6 to 12 hours until parasitemia has been eradicated; eradication is defined as two successive parasite-negative smears. If parasitological eradication has occurred, subsequent malaria smears should be examined at least once a week until the end of the study on day 28.

- **In trials of drugs that target the liver stage parasites of *Plasmodium* species with a hypnozoite stage**, such as *P. vivax* and *P. ovale*, clinical cure is defined as the

absence of parasitemia on blood smears (i.e., uncorrected or unadjusted cure rates), clinical signs and symptoms, and laboratory abnormalities without recurrence after completion of treatment for an interval consistent with the natural history of the local parasite strains (e.g., 6 to 12 months for radical cure). As recurrence patterns vary geographically with the strain of *P. vivax* and *P. ovale*, documentation of the malaria local relapse patterns should be provided and justification for the selected recurrence monitoring period should be included in the protocol submission.

If test(s) other than blood smears are used for assessing parasitemia, then details of the method(s) to be used should be discussed with the Agency.

Rescue therapy with alternative antimalarial therapy or loss to follow-up should be considered as lack of clinical cure.

- *Secondary endpoints:*

  - Parasite clearance time
  - Fever clearance time
  - Corrected/adjusted cure rates

    - The cure rates adjusted for new infections based on genotypic and phenotypic markers should be considered as secondary or exploratory endpoints. Attempts should be made to characterize the genotype(s) of parasite isolates, collected at baseline (pretreatment) and at the time of recurrent parasitemia, to differentiate recrudescence/relapse due to the same genotype (homologous) of the blood stage parasites from a new infection with a different genotype (heterologous). The specimens should be stored appropriately and analyzed at the same time using appropriate methods.

    - Differences in *Plasmodium* parasite genotyping methods can affect estimates of corrected cure rates in clinical trials across different epidemiological settings. It is recommended that the performance of the genotyping assay(s) be assessed across different geographic regions with a range of transmission intensities (e.g., low, moderate, and high), multiplicity of infection (e.g., variation in the prevalence and number of genetically distinct dominant and minority/low-density parasite clones/strains) and allelic frequencies; such information will be useful in understanding the epidemiological settings and the diversity of genotyping markers in the study population. The validity of the genotype results depends on systematic analysis of the test performance including but not limited to sensitivity, specificity, and reproducibility, as well as effective quality control assessments. The details of the methods used, the performance characteristics of the assays, and quality control parameters implemented in the laboratory where testing of clinical specimens will be conducted should be well documented. The performance of the laboratory should be in accordance with Clinical Laboratory Improvement Amendments. The data elements to be collected should be discussed with the Agency.

- *Exploratory endpoint:*

  - Efforts should be made to identify markers of drug resistance in isolates from participants failing treatment.

C. Severe or Complicated, Including Cerebral Malaria

Considerations for trial design and evaluation of efficacy in participants with complicated malaria are outlined below:

1. Trial Design

Trial design aspects for severe complicated malaria are similar to those for uncomplicated malaria (see section III.B).

2. Trial Population

Some relevant inclusion and exclusion criteria for adults and/or pediatric participants with severe or complicated malaria include the following:

- *Inclusion criteria*:

  - Participants with hyperparasitemia based on one of the following criteria:

    - Parasitemia of greater than or equal to 10 percent (i.e., 500,000/µL)

    - Parasitemia of greater than or equal to 5 percent (i.e., greater than or equal to 250,000/µL) accompanied by at least one or more major complications of severe malaria such as impaired consciousness, seizures, hypoglycemia, circulatory collapse/shock, pulmonary edema or acute respiratory distress syndrome, acidosis, acute kidney injury, abnormal bleeding or disseminated intravascular coagulation, jaundice, and/or severe anemia.

    Inclusion of participants with parasitemia of greater than or equal to 5 percent, without any of the major complications listed above, should be discussed with the Agency.

- *Exclusion criteria*:

  - Participants with uncomplicated malaria

The inclusion and exclusion criteria or other design aspects for special populations such as pediatric participants with cerebral malaria or pregnant participants should be discussed with the Agency.

3. Efficacy Endpoints

- *Primary endpoint:*

  - All-cause mortality

- *Secondary endpoints* may include the following:

  - Incidence of neurological sequelae
  - Combined death or neurological sequelae
  - Duration of signs/recovery times (times to eat, speak, sit)
  - Time to discharge
  - Development of other severe complications
  - Health-related quality of life measure(s)

- *Other endpoints* may include the following:

  - Brain volume score on magnetic resonance imaging

  - Duration of electrographic seizures as measured by continuous electroencephalogram monitoring

  - Electroencephalogram amplitude, frequency, and power analysis

  - Transcranial doppler ultrasound phenotype, and flow velocities

  - Cerebrospinal fluid metabolic profile of the drug

D. Statistical Considerations

- Justification of a noninferiority margin will be essential for all trials assessing efficacy using a noninferiority design.[15] Although effective antimalarial regimens that would be appropriate active controls are generally thought to have large effects over a hypothetical placebo, the noninferiority margin justification may depend on the active control arm, the possible combination regimen to be evaluated in the investigational treatment arm, and the planned population and parasite species of interest.

- Sponsors should consider the following definitions of analysis populations:

  - **Intent-to-treat population:** All randomized participants. If participants are randomized before parasitological confirmation, they should be included in the intent-to-treat population regardless of subsequent confirmation or nonconfirmation of malaria. A secondary or supplementary analysis of the primary endpoint should be conducted in the intent-to-treat population.

[15] See the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness (*November 2016).

462
463 – **Modified intent-to-treat population**: All randomized participants with a
464 microbiologically confirmed *Plasmodium* species at baseline. For both noninferiority
465 and superiority trials the primary efficacy assessment is typically conducted on a
466 modified intent-to-treat analysis population. In noninferiority trials the modified
467 intent-to-treat population should exclude participants if the control is not effective
468 against the baseline pathogen(s). In superiority trials the modified intent-to-treat
469 population may or may not exclude participants based on the activity of the control
470 against the baseline pathogen(s). Participants should not be excluded from this
471 population based on events that occur after randomization (e.g., lost to follow-up).
472
473 – **Safety population**: All participants who received at least one dose of the study
474 treatment during the trial.
475
476 • New infections should be considered treatment failures in the primary efficacy analyses
477 for the following reasons: Firstly, from a patient perspective, any new infection is a
478 failure. Secondly, there is a possibility that the new *Plasmodium* strain was present in
479 low density at baseline. Lastly, a new infection requires treatment, thus confounding an
480 assessment of relapse/recrudescence. Additional analyses separating failures by
481 relapse/recrudescence and new infection should be conducted.
482
483 • To improve the precision of treatment effect estimation and inference, sponsors may
484 consider adjusting for prespecified prognostic baseline covariates (e.g., age under 5 years,
485 pregnancy, nonimmune traveler status) in the primary efficacy analysis and propose
486 methods of covariate adjustment.[16]
487
488 • The trial should aim to minimize missing data. The protocol should distinguish between
489 discontinuation from the study drug and withdrawal from study assessments. Trial
490 participants may choose to discontinue treatment during the trial for various reasons, such
491 as experiencing adverse events or perceived lack of efficacy. Unless the participant
492 withdraws consent, sponsors should encourage participants who discontinue therapy to
493 remain in the study and to continue follow-up for key safety and efficacy assessments.
494
495 • Participants who are lost to follow-up or withdraw consent will have missing data for
496 outcomes occurring after that event. For a primary analysis, these participants should be
497 imputed as failures/non-cures; however, additional analyses should be proposed and
498 conducted to assess the overall impact of missing data on the study results. The study
499 protocol should address how missing laboratory samples or other missing information
500 should be handled in the analysis.
501
502 **E. Labeling Considerations**
503
504 The labeled indication should reflect the patient population (e.g., uncomplicated or complicated
505 malaria) and *Plasmodium* species evaluated in the clinical trials.

[16] See the guidance for industry *Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products* (May 2023).