EXECUTIVE SUMMARY

NDA 21-177
New Formulation Isotretinoin

Applicant:	HLR Technology Corporation (Hoffman-La Roche), Nutley NJ
Pharmacologic Category:	Retinoid
Dosage Form:	Soft Gelatin Capsules (7.5 mg, 15 mg, 22.5 mg)
Route of Administration:	Oral
Proposed Indication:	Severe recalcitrant nodular acne (with qualifiers unchanged from currently approved Accutane® labeling)
Summary Date:	August 9, 2000

Introduction

Accutane "NF" is a new formulation of isotretinoin, a drug substance that was approved in 1982. The indication remains severe recalcitrant nodular acne. The Sponsor's stated reason for pursuing this new formulation is that improved bioavailability will allow once daily dosing with or without food, as opposed to twice daily with food as per labeling for the current Accutane® formulation. The Sponsor is aware that the name "Accutane NF" is unacceptable because "NF" is widely recognized as "National Formulary". Nonetheless, for the purposes of this review, the ***new formulation*** *under review will be referred to as "****NF****", and the* ***currently marketed formulation*** *as "****AC****".*

The proposed labeling for NF is based on the "backbone" of tradename AC. The development program for NF was designed to supplement the data already available for AC. There are five pharmacokinetic studies in the application and one multi-center clinical trial. The objective of the clinical trial was to compare the efficacy and safety of the new formulation of isotretinoin administered once daily without food versus currently marketed Accutane® administered twice daily with food. The pharmacokinetic studies are of pivotal importance to this application.

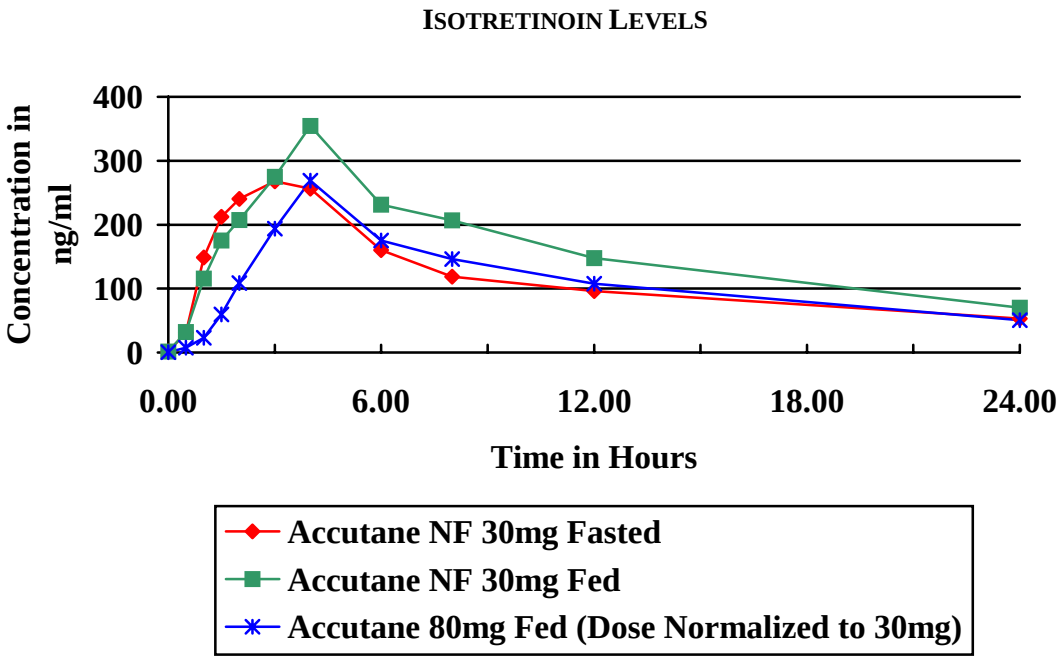
Biopharmaceutics

Formulation

The Accutane NF product is a micronized form of the current Accutane soft gelatin capsules currently marketed. The NDA indicates that by reducing the particle size of isotretinoin, bioavailability was significantly enhanced over the current product. Similar examples of the effect of micronization on bioavailability exist for other drugs such as nitrofurantoin and griseofulvin.

Pharmacokinetic Comparison of Accutane NF and Accutane

Throughout the NDA the Sponsor states that the current Accutane product produces plasma levels 240% greater than those seen with Accutane NF. While true, the doses of drug are *not* comparable: they are comparing 70mg of Accutane to 30mg of Accutane NF or 70mg/30mg *100% = 233%. The micronizing of isotretinoin simply eliminates the need for food to enhance the bioavailability of the drug product. The net result is that if one took 30mg of current Accutane with a high fat meal, it would look like 30mg of Accutane NF (fed or fasted). See figure below for comparison.



True estimates of the bioavailability of isotretinoin are not possible without an intravenous dose. However, using this data in a "relative" comparison between

the products, it appears that the NF formulation is approximately 15% more bioavailable than current Accutane on a mg to mg basis.

Clinical Summary of Trial Design, Procedures, and Analysis Plan

The clinical trial was a randomized, double-blind, parallel group, multicenter design. The study design included a screening/baseline evaluation followed by randomization to receive either AC capsules, twice daily at a total dose of approximately 1 mg/kg, along with placebo capsules, or to receive NF, at a once-daily total dose of approximately 0.4 mg/kg, along with placebo capsule(s), for a period of 20 weeks. Patients in the AC treatment group were dosed as directed in the package insert, twice daily with food (breakfast and dinner), and received placebo in late evening at least 2 hours after dinner. In order to maintain the double-blind status, the patients taking NF received placebos for two meals (breakfast and dinner) and active drug once per day in late evening. No dose adjustments were allowed in this trial.

The safety population consisted of all patients who were randomized and who received at least one dose of medication. This population is therefore identical to the Intent-To-Treat (ITT) population. The Standard (STD) population analysis included patients who (a) did not have any major protocol violations, (b) had complied to the extent of returning $\leq$ 20% of the allocated study drug, (c) had completed at least 12 weeks of treatment, and (d) had not used Ortho Tri-Cyclen as a method of contraception. Comments refer to this as the Per Protocol (PP) population.

The primary efficacy variable was the change from baseline to Week 20 in the total number of nodular lesions. These were counted at baseline and at the completion of treatment. At the final visit (Week 20), the lesion count was performed after the global assessment was done. The minimum duration of treatment required for evaluation for efficacy was 12 weeks. A supportive analysis on the proportion of patients who achieved at least a 90% reduction of baseline total nodular lesion count was also done. Secondary efficacy variables were the change from baseline to Week 20 in the number of non-nodular inflammatory lesions (papules and pustules), and global response at the end of the treatment (Week 20). Summary statistics were provided for need for retreatment and change of total nodular lesion count from baseline at Week 20 for women using Ortho Tri-Cyclen® as contraception.

Safety endpoints were adverse events, prospectively defined as any adverse change from the patient's baseline (pre-treatment) condition, including intercurrent illness, which occurred during the course of the clinical study after

treatment had started, whether considered related to treatment or not. Adverse medical conditions present at baseline that became worse following exposure to study drug were also to be reported as adverse events. Abnormal laboratory test values were also recorded.

The labeling for marketed Accutane served as the safety guide for investigators. Because the trial was designed and implemented prior to the March 1998 labeling change regarding psychiatric adverse events, mood was specifically monitored. The purpose was protection of study subjects; the trial was *not* intended or designed to study the association of isotretinoin and psychiatric symptoms.

The mood evaluation questions were:

1. When you were on Accutane (since your last visit) have you felt depressed, sad or blue much of the time?
2. When you were on Accutane (since your last visit) have you often felt helpless about the future?
3. When you were on Accutane (since your last visit) have you had little interest or pleasure in doing things?
4. When you were on Accutane (since your last visit) have you had trouble sleeping many nights?

Patients who answered "yes" to two or more of these questions while undergoing treatment were asked to complete a Beck Depression Inventory (BDI-II). The Sponsor proposed that If the score was ≤ 30, the patient would be permitted to continue in the study; if the score was ≥ 31, the patient would be discontinued from the study drug. However, the Division advised the Sponsor not to use the BDI as the criterion for discontinuation, but to leave the decision to the investigators' clinical judgment. As will be summarized below under Results, implementation of this protocol procedure appears to have been problematic. This inconsistency in implementation significantly affects interpretation of the safety results in this comparison trial.

Study Results

Population

A total of 657 patients were screened for enrollment at 17 centers: 302 were randomized to receive NF and 300 were randomized to receive AC. Two

randomized patients chose not to participate and returned all medication, therefore the ITT population consisted of 600 patients, 300 in each arm. Eighty-seven percent of patients in the NF group and 85% in the AC group completed the study. Each center enrolled from 7 to 76 evaluable patients. Treatment groups were comparable with respect to age, sex, race, weight and height (dosing was weight adjusted). A total of 244 females were enrolled. About 80% of patients in each treatment group were Caucasian with the remainder distributed among Black, Oriental, Hispanic and Other racial categories.

Efficacy

According to our biostatistical analysis, NF was marginally less effective than AC as measured by the proportion of patients who had at least 90% reduction in nodules after a 20-week course of therapy (the 95% confidence interval does not quite cover zero and the upper endpoints of the intervals are close to zero). Therapeutic equivalence is, however, supported by equivalent global assessments and relapse rates *in the overall population* (no greater need for retreatment in the NF arm). Furthermore, the need for retreatment [1] in the NF arm was consistent with published figures for marketed Accutane®, about 20%.

The published literature suggests that pediatric-aged patients may have higher acne relapse rates after isotretinoin treatment than older patients. Retreatment requirements are particularly important for pediatric-age patients because they may still be growing and isotretinoin affects the musculoskeletal system. There were 92 patients per arm aged 12-17. While the percentage reduction in total nodules did not show any statistically significant difference between AC and NF in this pediatric population, 77% of subjects in the AC arm had at least 90% reduction in nodular lesions vs. 64% in the NF arm. In addition, about 26% in the NF arm required re-treatment, while about 14% required re-treatment in the AC arm.

[1] The Week 36 assessment was by telephone and 68 subjects were not contacted. In addition, the sponsor reported that 8 patients received additional isotretinoin beyond the Week-20 assessment at the "discretion" of investigators in a "minor protocol violation". Six were in the NF arm (the protocol stated that retreatment with isotretinoin was not allowed after the 20 week treatment period and prior to the 36 week assessment for recurrence). These 8 cases were identified by the Sponsor because of case report form notations about the added medication. It is not known if all investigators who prescribed isotretinoin in the week 20-36 interval entered information that would have alerted the Sponsor. *It is also unknown how many patients received other acne treatments, such as antibiotics, after completion of the 20-week course*.

Relapse is also of particular concern for women of childbearing potential, since retreatment increases the chance of fetal exposure. Although the sample size is too small to allow conclusions (19 and 21 patients per arm), the proportion of women using OrthoTri-Cyclen® who had at least 90% reduction in nodular lesions was 57% in the NF arm, as compared to 84% in the AC arm. This trend was also observed for total inflammatory lesions: 74% of women using AC vs. 33% using NF achieved at least 90% reduction.

While the overall trial supports the therapeutic equivalence of AC and NF, these subset results suggest that AC may have been slightly more efficacious than NF at the dosage tested. The Sponsor stated that isotretinoin exposure from the administration of 0.4 mg/kg/day NF under fed or fasted conditions was calculated to fall within the lower end of the range of the expected drug exposure from the administration of recommended doses of AC with food. The current recommended dosage range for AC for the treatment of severe recalcitrant nodular acne is 0.5 to 2.0 mg/kg/day given with food in two divided doses. The dosage of AC used in the clinical trial in this application was 1 mg/kg with food. According to the Sponsor, it is likely that patients who received AC in the therapeutic study had approximately 240% higher exposure to isotretinoin than the subjects who received NF. Since therapeutic equivalence was demonstrated in the adequately powered total trial population, it would appear that the *currently recommended dosing range for Accutane® may be too high*. This is of considerable clinical importance because many of the side effects of isotretinoin are dose-dependent. Even those that would appear to be “non-serious” (e.g. mucocutaneous effects, transient moderate hypertriglyceridemia) can lead to treatment discontinuation for patients who might otherwise greatly benefit by completing a course. Available dose-ranging studies for Accutane® do not definitively establish that even the lower end of the currently labeled dosage is the *minimum* effective dose.

Safety

The total safety population for NF is 583 subjects, 300 of whom participated in the clinical equivalence study. The remainder participated in the PK studies.

Sixteen patients from each treatment group withdrew because of adverse events. Eight patients in each group “refused treatment”. The lost to follow-up population during the 20 week treatment phase was 3.7% and 6.7% patients, respectively, in the NF and AC groups. At the Week 36 assessment for acne relapse, 68 of the 516 patients who completed the study in the ITT population were lost to follow-up.

While the proportion of patients with early termination was equivalent between arms, the reasons for discontinuation were not. Seven of the 16 for NF involved the nervous system, including 5 with psychiatric symptoms. For AC, 6 of 16 involved elevated triglycerides, 3 for headache, and none for psychiatric events. It should also be noted that 8 additional patients in each arm terminated early for refusal to take medication. The reason for their refusal is unknown. The number of discontinuations for psychiatric symptoms is probably a poor comparative measure of safety due to problems with the criteria for discontinuation. However, there is no readily apparent reason why such problems would be unbalanced between arms. This issue will receive further discussion below.

In the NF group, a total of 1362 adverse events were reported involving 296 of 300 patients. In the AC group, 1450 adverse events were submitted involving 293 of 300 patients. Over 95% of all patients experienced adverse events that were considered as probably related to the study drug. Approximately 15% of all adverse events were coded as unrelated to study drug. The majority of adverse events (about 90%) were mild or moderate in intensity. Of the 1362 adverse events reported by patients in the NF group, 10.7% were *severe*; in the AC group, the corresponding number was 11.6%. Thirty-four percent of subjects in the NF group experienced *severe* adverse events compared with 35% of patients in the AC group. The Sponsor has stated that the adverse event profile of NF in this trial did not reveal any events not previously observed in the safety database for marketed Accutane®.

Mucocutaneous Adverse Events

Cheilitis occurred in over 90% of patients in both NF and AC treatment groups. Epistaxis and nasal dryness together with dry and irritated eyes were reported by approximately one third of the patients in both groups. The mucocutaneous adverse event profile is important because it is a frequent cause for treatment discontinuation, which can have serious consequences (disfiguring scarring) for patients with severe cystic acne. The trial indicates that the mucocutaneous safety profile for NF is comparable to AC at the dosages tested.

Headache

Headache was reported for 16% of patients in the NF arm compared with 13.3% of AC patients, and headache duration at all levels of intensity was longer in the NF group (2-5 days). Both cases characterized as “migraine” in the trial occurred

in the NF arm, as did the one suspected case of pseudotumor cerebri. However, the 3 discontinuations in the trial for headache occurred in the AC arm.

Psychiatric Adverse Events

As reported in the NDA, there were 11 psychiatric adverse events in the NF arm, and only 1 in the AC arm. Although none were deemed "serious" by investigators, this disproportion is statistically significant and would be cause for concern if verified. It appears, however, that the psychiatric adverse event numbers refer *only* to subjects who complained of symptoms verbally, regardless of their answers to the screening questionnaire or the Beck's Depression Inventory (BDI-II). The final study report submitted in the NDA states that patients were "required to answer four specific questions to determine whether or not they had experienced any significant depression or insomnia since the last visit that affected their work or ability to perform normal daily activities". It is unclear why neuropsychiatric symptoms gathered in this manner that were severe enough to interfere with the conduct of normal activities did not qualify as an adverse event. Furthermore, it does not seem reasonable to exclude patients' events because they did not verbally report psychiatric symptoms when they had just finished filling out a questionnaire about them. Indeed, there were several subjects in this trial who answered "yes" to the self-injurious behavior question on the BDI-II, who answered "yes" to all four screening questions, and/or had BDI-II scores only one point below that considered "severe" who had *no* psychiatric adverse event recorded.

The issue of case ascertainment will not be expanded because the trial was *not* designed to evaluate the psychiatric effects of isotretinoin. When all of the cases with a possible psychiatric adverse event are included, the numbers are approximately equal in the two arms (9 or 10 cases with AC and 11 cases with NF). The disproportion in *reporting* of adverse events between the arms, however, is not explained.

The inconsistencies in follow-up of positive survey responses, recording of psychiatric events, and implementation of discontinuation rules preclude reliable estimates of the incidence of psychiatric adverse events in the trial. In addition, bias against reporting of mood changes was likely a factor in this trial. Unlike a trial for a new drug of unknown effectiveness, it is likely that most patients were very aware of the expected benefit. Answering "yes" to bad mood and feelings at any time on-study would logically be viewed as a liability by a patient who wanted to complete treatment. Likewise, investigator bias may have also contributed to under-reporting by affecting the risk-benefit analysis for continuing the study

drug, since all subjects in the trial were receiving isotretinoin and expected to derive significant benefit.

The baseline BDI-II scores in the trial were low (the mean at baseline was 3.5 $\pm$ 4.6, which is significantly lower than the mean reference score reported in the NDA for college students, 12.56). In addition to low baseline scores, there was no correlation between follow-up scores and acne resolution in the trial. These observations are consistent with published studies on acne as a risk factor for depression[2].

Twelve cases in the trial with "spontaneously" reported psychiatric adverse events and 5 additional cases with increases on BDI-II were reviewed for the Sponsor by two consultants: Douglas Jacobs, MD, Associate Clinical Professor of Psychiatry, Harvard Medical School, and Robert Nelson[3], PhD, pharmacoepidemiology consultant. Since the trial was neither intended nor designed to study the issue, the consultants' reports will not be reviewed in this Summary. The association of isotretinoin with psychiatric adverse events is on the agenda for panel discussion in the context of currently marketed Accutane®.

Pregnancy

[2] While the literature suffers from significant methodological limitations, the studies tend to confirm an intuitive perception that significant acne is associated with some degree of *psychological distress,* but do *not* demonstrate that severe nodular acne *causes* depression; in fact, a prospective study supported the opposite conclusion. Rubinow et al. (J Am Acad Dermatol 1987, 17:25-32) reported that severe recalcitrant nodular acne patients had evidence of "moderate psychological distress" prior to Accutane® treatment, but no excess *psychiatric* morbidity, including depression, in comparison with normative prevalence figures. Prospectively defined analysis showed a statistically significant lessening in *anxiety* after treatment with Accutane®, but not in depression. Niemeier et al. (Dermatology 1998,196:108-15) investigated depression and social anxiety in acne vulgaris patients in the course of evaluating a chronic skin disorders questionnaire. Comparison was made between the 50 acne patients and a control group of 33 persons without skin disorders (the two groups were *not* matched for age or gender). The two groups did not differ significantly on the Beck Depression Inventory (mean score non-depressed for both), but the acne patient group did show significant differences on other scales seen as indicative of psychosocial distress (e.g., social anxiety and avoidance) compared to the control group.

[3] Dr. Nelson led the "Accutane Monitoring Group" in the Epidemiology Division during prior employment at FDA.

The approval of Accutane in 1982 was followed by reports of severe congenital malformations[4], leading to changes in labeling, advisory committee hearings (1988-1991), and implementation of the Roche Pregnancy Prevention Program and registry. Risk management strategies to address persistent problems with fetal exposures are on the agenda for panel discussion.

In the NF arm of the trial, one patient became pregnant while taking isotretinoin. The stated facts of the case do not suggest patient non-compliance with contraceptive measures. A pregnancy among 244 female patients in the controlled setting of a trial for a known teratogen is of great concern. The issue of a possible drug interaction that would decrease the effectiveness of hormonal contraceptives is not unique to the new formulation and is on the agenda for panel discussion.

Because available data for isotretinoin are inadequate to rule out an interaction that might decrease the effectiveness of currently marketed hormonal contraceptives, the Sponsor and the Agency developed a formal study plan to address this critically important question for both AC and NF[5]. As an interim safety measure, the labeling for Accutane® has been revised to further emphasize the need for two effective forms of contraception.

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[4] Accutane causes abnormal development of craniofacial bones, eyes, ears, thymus, heart, and brain. Congenital malformations range from severe physical and developmental defects to significant neurodevelopmental dysfunction in long-term survivors of in-utero exposure who appeared to be without major congenital malformation at birth. It is also associated with spontaneous abortion.

[5] Biopharmaceutics Overview: Oral Contraceptive-Accutane

Because of the known teratogentic potential of isotretinoin at the time of the original approval of Accutane, Roche conducted a pharmacokinetic drug interaction trial between Accutane and Ortho-Novum 1/35. At the time of the original approval the results of this study were used to support the generalized recommendation that hormonal contraceptives did not interact with isotretinion and vice versa. The accuracy of this conclusion is now open to question as the hormonal contraceptive marketplace has changed greatly in the last 15 years. With the development of “low dose”, “tri-cyclic”, and implantable contraceptive options, we believe that the level of assurance provided by the original in vivo biostudy has been superceded by market options.

In light of this, a program to re-evaluate the contraceptive efficacy of these agents using current methods has been developed. Since it is not feasible to test all hormonal contraceptives in clinical trials, a program of in vitro metabolism studies combined with selective in vivo studies has been developed to cover the current options available in the marketplace. A description of this program and its development will be presented at the advisory committee meeting.

“Sharing” of isotretinoin is of significant public health importance because the drug can cause serious adverse events, including birth defects, and the drug is highly efficacious for a common disease of young people. Of the approximately 600 subjects enrolled in this trial, one subject was discontinued because her daughter consumed her study medication. The current labeling and patient brochure for Accutane® warn against sharing. While the trial event was not “sharing” in the intentional sense, it underscores the need for robust risk management strategies to ensure the interests of both the public health and the patients who need this uniquely efficacious drug.

Laboratory Abnormalities

Hypertriglyceridemia due to isotretinoin is reportedly reversible and appears to be only rarely associated with serious acute outcomes (the long-term effects, if any, are unknown). Of the nine patients who withdrew prematurely from the study because of elevated triglycerides, three were in the NF group and six in the AC group. These early terminations for hypertriglyceridemia would likely have been manageable by dose adjustment in a practice setting (dose adjustment was not allowed in the trial). According to the Sponsor’s analysis of laboratory findings, the relative increase in levels was 49% and 88% over baseline for NF and AC, respectively. Neither triglyceride nor cholesterol values had returned to baseline by Week 20. According to the Sponsor, all abnormal liver function tests in both arms returned to baseline by Week 20 except GGT, which was greater in the AC group than in the NF group. These findings are consistent with lower serum levels of isotretinoin in the NF arm.

Risk-Benefit Analysis

As stated by the Sponsor, the rationale for evaluating Accutane NF is to provide a new formulation of isotretinoin that can be administered once daily and without food. The Sponsor expects this dosing regimen to enhance convenience and patient compliance, and reduce intra- and inter-patient variability while at the same time retaining the efficacy and safety profiles of currently marketed Accutane. This hypothesized benefit would seem completely dependent on equivalent (or better) safety and efficacy, since the impact of the convenience factor is likely to be small (taking medication without food is *more* difficult than with food, not less).

The maximum dose of Accutane used in this trial was approximately 1 mg/kg/day with food. The new formulation was reportedly "dose-adjusted" to compensate for increased bioavailability (0.32 to 0.44 mg/kg/day). However, patients who received Accutane 1.0 mg/kg/day with food in the therapeutic study likely had approximately 240% higher exposure to isotretinoin than the subjects who received the new formulation. Thus, the trial is essentially a 2-arm isotretinoin dose-ranging study. At the dosage tested, the new formulation is essentially therapeutically equivalent to Accutane. Viewed within the context of the relative serum levels of isotretinoin, the results suggest that the *currently recommended dosing range for Accutane® is too high*[6]*.*

The safety database for a new drug at the time of approval is almost always "inconclusive" in the sense that the database is too small to detect all relevant signals. This NDA has *inconclusive signals*. Specifically, it can not be definitively determined whether the new formulation is associated with a higher incidence of psychiatric adverse events, nor whether the new formulation reduces the effectiveness of hormonal contraceptives.

The possibility of an interaction between currently prescribed hormonal contraceptives has not been adequately studied for either formulation. This is a very serious deficiency in the safety database for a potent teratogen widely prescribed for healthy women of reproductive potential. *If* there is an interaction that decreases the effectiveness of hormonal contraceptives, the information is critical to improving compliance with the labeled advice about using two methods simultaneously. In addition, if there is an interaction, many prescribers and female patients may choose other acne management strategies.

If there is an interaction between hormonal contraceptives and isotretinoin, there is no pharmacokinetic basis to suspect that the lower dose new formulation would be less safe than currently marketed Accutane®. Interim measures for risk management pending completion of the formal studies now underway are on the agenda for panel discussion.

The trial data are also inconclusive regarding psychiatric adverse events, suggesting the possibility that the lower dose new formulation is less safe than Accutane. Although the *reported* incidence in the trial was significantly higher in the lower dose new formulation arm, the disproportion appears to be more apparent than real if all cases with symptoms from any source in the database are included. In addition, the incidence reported by the Sponsor in the new formulation arm does not exceed the range suggested in the published literature

[6] The currently recommended dosage range for Accutane® is 0.5 mg/kg to 2.0 mg/kg/day with food.

for psychiatric adverse events with currently marketed Accutane. This supports the notion that the results reflect *under*-accounting in the Accutane arm, instead of increased incidence in the lower dose new formulation arm. The disproportion in *reporting* is, however, unexplained. Disproportion in discontinuations for psychiatric adverse events is also unexplained because problems with protocol interpretation should have been balanced. However, all four discontinuations for psychiatric adverse events were confined to 2 of 17 sites.

A chance finding for the disproportion is consistent with the lower serum levels of isotretinoin in the new formulation arm, assuming there is no greater central nervous system accumulation of the new formulation relative to Accutane. It is also consistent with the finding that the more common adverse events were not significantly increased in the lower dose new formulation arm (although the one patient with possible pseudotumor cerebri was in this arm, and headache duration was longer). It is, however, an *assumption* that the incidence of psychiatric events should track with the incidence of well-established dose-related effects, such as hypertriglyceridemia or mucocutaneous drying. The dose-threshold, in any, for isotretinoin-associated psychiatric events is unknown.

Causality between psychiatric disease and isotretinoin use has not been established. If there is no causal relationship, then a lower dose new formulation cannot be less safe than Accutane in this regard. The uncertainty about the new formulation might be resolved if an adequately powered, well-designed trial showed no evidence for causality. If the data *did* support a causal relationship, there would be doubts about the relative safety of the two formulations based on the observations in the NDA 21-177 trial. However, if the lower dose new formulation is safer than Accutane in other *significant* respects, it is unlikely that a small increase in risk of reversible psychiatric symptoms would override the advantages of the new formulation.

Since it would seem that the safety of isotretinoin treatment might be improved by simply lowering the recommended dosage of current Accutane® given with food, is there reason to replace Accutane with the new formulation if there is *any* possibility that the new formulation is less safe[7]?

The food effect is so large with Accutane®, that even adequate dose-ranging would not eliminate "over-dosage" and 'under-dosage" due to the realities of compliance with food instructions. The clinical significance of over-dosage has already been addressed. Under-dosing, which would likely result if patients took a minimum effective dose of current Accutane *without* food, has significant public health importance because many years of experience support the observation that cumulative dosage is positively correlated with "cure" rates. Re-treatment with Accutane exposes patients to many more weeks of potentially serious adverse effects, increases the risk of fetal exposure, and delays resolution of nodulocystic lesions that can lead to permanent disfiguring scars.

We believe that the relative food independence of the new formulation is an important advantage over the currently marketed formulation because of reduced pharmacokinetic variability, independent of "convenience". There does not appear, however, to be any apparent public health advantage to marketing both formulations.

8/21AC

[7] The term "less safe" encompasses both the adverse event profile already discussed, and the potential switch-over problems delineated in the NDA:

- Inappropriate dosing of Accutane® and Accutane NF
- Concurrent administration of Accutane® and Accutane NF
- Confusion about capsule strengths on the prescription
- Uncertainty about bioavailability and actual drug exposure
- Misunderstanding about once daily administration without food for Accutane NF and twice daily with food for Accutane
- Potential for inappropriate substitution at the pharmacy