CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208630Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 110655

MEETING MINUTES

NX Development Corporation
Attention: Alan M. Ezrin, Ph.D.
President and Chief Executive Officer
1827 South Bayshore Lane
Miami, FL 33133

Dear Dr. Ezrin:

Please refer to your Pre-Investigational New Drug Application (PIND) file 5-Aminolevulinic Acid (5-ALA); Gliolan, 30 mg/mL powder for oral solution.

We also refer to the meeting between representatives of your firm and the FDA on September 22, 2014. The purpose of the meeting was to discuss your plans for the submission of an NDA for Gliolan.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Modupe Fagbami, Regulatory Project Manager at (301) 796-1348.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging and Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type C
Meeting Category:	Pre-IND
Meeting Date and Time:	September 22, 2014, at 3:00 pm
Meeting Location:	WO, Building 22, Room 1315.
Application Number:	IND 110655
Product Name:	5-Aminolevulinic Acid (5-ALA); Gliolan, 30 mg/mL powder for oral solution.
Indication:	As an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery
Sponsor Name:	NX Development Corporation
Meeting Chair:	Alex Gorovets, M.D., Deputy Director, DMIP
Meeting Recorder:	Modupe Fagbami, Regulatory Project Manager, DMIP

FDA ATTENDEES

Charles Ganley, M.D., Office Director, ODEIV (Phone)
Louis Marzella, M.D., Division Director, DMIP
Alex Gorovets, M.D., Deputy Director, DMIP
Ira Krefting, M.D., Medical Officer, Team Leader, DMIP
Yanli Ouyang, Ph.D., Acting Pharmacology/Toxicology Supervisor, DMIP
Ron Honchel, Ph.D., Pharmacology/Toxicology Reviewer, DMIP
Gene Williams, Ph.D., Clinical Pharmacology Team Leader, DCPV
Christy John, Ph.D., Clinical Pharmacology Reviewer, DCPV
Eldon Leutzinger, Ph.D., CMC Team Leader, ONDQA
Joyce Weaver, Pharm.D., Drug Risk Management Analyst, OSE
Neil Ogden,M.S., B.M.E.,Chief, General Surgery Devices Branch 1, DSD/CDRH (Phone)
Betsy Ballard, M.D., General Surgery Devices Branch 1, DSD/CDRH
Kejing Chen, Ph.D., Lead Reviewer, General Surgery Devices Branch 1, DSD/CDRH
Satish Misra, Ph.D., Mathematical Statistician, OB/DBV (Phone)
Kyong Kang, Chief Project Management, Staff, DMIP
Alberta Davis-Warren, Regulatory Project Manager, DMIP
Modupe Fagbami, Regulatory Project Manager, DMIP

SPONSOR ATTENDEES

Dr. Alan Ezrin, CEO, Photonamic GmbH & Co. KG (Inventor Organization)
Dr. Anne Moor, Project manager, Preclinical and Clinical Development
Dr. Ulrich Kosciessa, CEO, Principal Investigator of North America 5-ALA (Gliolan) Consortium
(b) (4)
Independent Experts
(b) (4)
(b) (4)
Consultants
(b) (4) Consultant

BACKGROUND

The product is Gliolan 30 mg/mL powder for oral solution. Gliolan contains the active substance 5-aminolevulinic acid hydrochloride (5-ALA HCl), presented in the form of a powder for the subsequent preparation of an oral solution by dissolving in 50 mL tap water. The product is a lyophilized preparation in colorless glass vials, containing 1.5 g 5-ALA HCl (corresponding to 1.17 g of 5-ALA), sealed with a rubber stopper. No other ingredients are used.
Gliolan is an imaging agent to facilitate the real time detection and visualization of malignant tissue during glioma surgery. The sponsor requested the meeting on July 23, 2014, to finalize plans for the submission of an NDA for Gliolan.

The Sponsor meeting was held on September 22, 2014; at 3:00 pm to enable Sponsor discuss the briefing package questions.

DISCUSSION

Nonclinical

In addition to providing in the NDA information on the pharmacokinetics and pharmacology of Gliolan in animal studies, data from good laboratory practice (GLP)-compliant, nonclinical studies will be provided in the NDA to support the safety of Gliolan (Table 1).

Table 1: Nonclinical Studies Supporting the Safety of Gliolan

Type of Study	Study Design	Study Report No.	Species/Strain
Safety Pharmacology	Gastrointestinal	(b) (4) 10117/1/96	Guinea pig
	Central nervous system	10118/1/96 10119/1/96	Mouse
	Renal	10116/1/96	Rat
	Cardiovascular	10115/1/96	Dog

Type of Study	Study Design	Study Report No.	Species/Strain
Pharmacokinetics	Method of analysis	(b) (4) 9721/1/96 13105/00 (b) (4) 47/97-055.P9	
	PK, single, i.v. and oral administration	(b) (4) 13105/00	Dog
	Excretion, 14-day oral administration	11651/98	Rat
	Excretion, 14-day i.v. administration	11664/98	Dog
Single-dose Toxicity	Acute, i.v. administration	11654/98	Mouse
	Acute, i.p. administration	10122/1/96	Mouse
	Acute, oral administration	11653/98	Rat
	Acute, i.v. administration	10123/1/96	Rat
Repeat-dose Toxicity	14-day, oral administration	11651/98	Rat
	7-day, i.v. administration	10827/97	Rat
	7-day, i.v. administration	11652/98	Dog
	14-day, i.v. administration	10828/97	Rat
	14-day, i.v. administration	11664/98	Dog
	4-week, oral administration	DM 10262	Dog
Genotoxicity	*S. typhimurium* reverse mutation	(b) (4) 10112/96	
	Gene mutation	10113/96	Mammalian V79 cells
	Chromosome aberration	10114/96	Human peripheral lymphocytes
	Micronuclei	17551/03	Mouse
Reproductive and Developmental Toxicity	Embryo-fetal development	DM 10264	Rabbit
Local Tolerance	Single i.v., i.a., s.c., i.m., paravenous administration	(b) (4) 11655/98	Rabbit
Phototoxicity	i.v. administration	10121/1/96	Mouse
Skin Sensitization	i.v. and topical administration	153/1/02	Guinea pig

NX Development Corp believes that adequate nonclinical safety data exist to support the clinical use of Gliolan. No additional toxicology studies are proposed to demonstrate the safety of the clinical dose. Gliolan is intended as adjunctive tool for the visualization of malignant tissue during glioma surgery. In addition, postmarketing data have not revealed any concerns in the affected population.

According to FDA guidance on assessing the safety of medical imaging drugs, long-term rodent carcinogenicity studies are not needed to support the safety of such drugs in the NDA

submission. Based on its acute use in patients with cancer, NX Development Corp does not intend to conduct a long-term rat carcinogenicity study on Gliolan.

1. Does the Agency agree that no additional carcinogenicity studies are needed to support the safety of Gliolan for the proposed indication?

FDA Response:

We agree.

***Meeting Discussion:* There was no meeting discussion.**

NX Development Corporation will include in the NDA for Gliolan a study report (DM 10264) that provides the results of an embryo-fetal toxicity study of the drug in rabbits. NX Development Corp does not intend to conduct additional reproductive/developmental toxicology studies, including any studies of to evaluate effects on reproductive organs and will seek a waiver based on the use of the drug as a single administration in patients with this fatal disease.

2. Does the Agency agree that no further reproductive/development toxicology studies are needed to support the safety of Gliolan for the proposed indication and that a waiver for these studies is appropriate for this drug product
3.
4. **FDA Response:**

We have no recommendations for further reproductive toxicology studies at this time. We previously informed you that a definitive determination on the need for additional nonclinical safety studies cannot be made until all nonclinical study reports have been submitted and reviewed. We agree that you should request a waiver as outlined in "Guidance to Industry: Developing Medical Imaging Drug and Biological Products – Part 1: Conducting Safety Assessments" if you think that standard nonclinical Reproductive Toxicology studies are not needed.

5. Does the Agency agree that no additional nonclinical testing is needed to address the interactions between Gliolan and other drugs?

FDA Response:

We agree.

***Meeting Discussion:* There was no meeting discussion.**

Clinical

In addition to data from bioavailability studies in healthy volunteers (MC-ALS20/BV), data from clinical studies conducted to support the EU marketing authorization for Gliolan will be provided in the NDA to support the safety of Gliolan (Table 2).

Table 2: Clinical Studies Supporting the EU Marketing Authorization for Gliolan

Study ID	Study Title	Number of Subjects
MC-ALS.8-I/GLI	Clinical Phase I/II study on 5-aminolevulinic acid hydrochloride (5-ALA) for the fluorescence-guided resection of malignant glioma	21 GBM patients
MC-ALS.28/GLI	Clinical Phase II trial of 5-aminolevulinic acid hydrochloride (5-ALA, 5-ALS) for fluorescence-guided resection of malignant gliomas	39 GBM patients
MC-ALS.3/GLI	Fluorescence-guided resection of malignant glioma with 5-aminolevulinic acid (5-ALA) versus conventional resection	415 GBM patients (207 in 5-ALA arm, 208 in control arm)
MS-ALS.30/GLI	Clinical Phase II trial of MC 506/1 (5-aminolevulinic acid hydrochloride, 5-ALA, 5-ALS) for fluorescence-guided resection of malignant gliomas in progression therapy	40 patients with relapsed GBM
MC-ALS.32/GLI	Clinical investigation of fluorescence-guided resection of malignant gliomas with 5-aminolevulinic acid	243 GBM patients

GBM = glioblastoma multiforme

Data from the safety database from the clinical development program of a total of 550 patients who received Gliolan revealed that Gliolan does not cause clinically meaningful side effects after a single oral dose of 20 mg/kg. The only remarkable observed adverse events are nausea, hypotension, and phototoxicity. NX Development Corp believes that sufficient data exist on the safety of Gliolan for its intended use from five clinical studies that were conducted on the drug to support the European regulatory approval of the drug. These data will be provided in the NDA. In addition, NX Development Corp will provide postmarketing safety data based on exposure of approximately 26,000 patients available following the approval of the drug in the EU and other countries to support the safety of the drug.

6. Does the Agency agree that the safety database is of sufficient size to support the safety of Gliolan?

FDA Response:

The size of the safety database of Gliolan seems reasonable. We anticipate you will provide a thorough analysis of the post-marketing safety experience.

Meeting Discussion: ***There was no meeting discussion.***

Electrocardiogram (ECG) data are available from studies MC-ALS.28/GLI and MC-ALS.8-I/GLI. ECGs were taken 30, 60, and 120 minutes following administration of Gliolan. In addition, Study MC-ALS.8 includes data regarding QT time for all patients. Data from these studies indicate no changes in ECG parameters that were suggestive of a cardiovascular safety concern. NX Development Corp does not intend to conduct further QT prolongation studies to support the NDA for Gliolan.

7. Does the Agency agree that further QT studies are not necessary to address the drug's potential for QT prolongation?

FDA Response:

The submitted material does not allow us to estimate the degree of QT change that can be ruled out using the available data. Thus, we cannot comment on the adequacy of the current database. Alternative proposals to the 'thorough QT' study including ECG collection with time matched PK sampling may be appropriate. Submit QT data for QT-IRT review. Refer to the Guidance for Industry entitled "*E14 Clinical Evaluation of QT/QTc Interval Prolongation*" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf.

Meeting Discussion: ***There was no meeting discussion.***

Data from the following clinical studies will be provided in the NDA to support the efficacy of Gliolan with regard to the positive predictive value of the drug to differentiate between normal and tumor tissue in the brain (Table 3).

Table 3: Clinical Studies Providing Data on the Positive and Negative Predictive Values, Sensitivity and Specificity of Gliolan

Study ID	Study Title	Number of Patients
MC-ALS.28/GLI	Clinical Phase II trial of 5-aminolevulinic acid hydrochloride (5-ALA, 5-ALS) for fluorescence-guided resection of malignant gliomas	39 GBM patients
MC-ALS.30/GLI	Clinical phase II trial of MC 506/1 (5-amino-levulinic acid hydrochloride, 5-ALA, 5-ALS) for fluorescence-guided resection of malignant gliomas in progression therapy	40 patients with relapsed GBM

Study MC-ALS.28/GLI was designed to determine the positive predictive value of Gliolan-induced tissue fluorescence for tumor cell detection in patients with newly diagnosed malignant glioma. For this purpose, the percentage of patients showing positive tumor cell identification in all biopsies taken from areas of weak and strong fluorescence was registered (positive predictive

value on patient level). Additionally, positive predictive value on biopsy level defined as the number of tumor- positive biopsies among all biopsies taken from areas of weak and strong fluorescence was determined. Study MC-ALS.30/GLI was a similar study involving patients with a diagnosis of a recurrent malignant glioma (WHO grades III-IV), for which repeat-surgery was indicated. The NDA will provide data from these clinical studies with regard to Gliolan's positive predictive value with regard to intraoperatively visualizing potentially malignant glioma tissue in the brain.

The data from the clinical studies are supplemented with histological data from published studies with regard to Gliolan's positive and negative predictive values, sensitivity, and specificity (Table 4).

Table 4: Published Literature with Data on the Positive and Negative Predictive Values, Sensitivity and Specificity of Gliolan

Reference	Study Description	Number of Patients
Coburger et al. 2014	Comparison of 5-ALA fluorescence to MRI to detect invasive tumor	34 high grade gliomas
Diez Valle et al. 2011	Efficacy and applicability of surgery guided by 5-ALA fluorescence; data available on positive and negative predictive value	28 newly diagnosed GBM patients, 8 patients with recurrent GBM
Hefti et al. 2008	Feasibility study of 5-ALA in daily clinical practice	47 newly diagnosed GBM patients
Iodate et al. 2011	Examination of predictive value of 5-ALA in patients with glioma; data available on positive and negative predictive value	21 newly diagnosed GBM patients, 9 patients with recurrent GBM
Panciani et al. 2012	Multicenter study to compare the accuracy of fluorescence and image guided resection; data available on sensitivity, specificity	23 newly diagnosed GBM patients
Roberts et al. 2011	Compared contrast enhancement on preoperative MR imaging and observable intraoperative 5-ALA fluorescence	11 newly diagnosed GBM patients
Stummer et al. 1998	Examined the effect of tumor fluorescence on tumor visualization	8 newly diagnosed GBM patients
Stummer et al. 2000	Examined the effect of tumor fluorescence on tumor visualization	52 new diagnosed GBM patients
Utsuki et al. 2007	Examined 5-ALA induced fluorescence by histological examination of the resected fluorescent tissue	40 patients with GBM or anaplastic astrocytoma

In addition, two recent publications (Ewelt et al. 2011 and Widhalm et al. 2013), examined the use of 5-ALA for the intraoperative identification of anaplastic foci. These studies provide further information with regard to the ability of 5-ALA to detect malignant tissue.

NX Development Corp believes that sufficient data exist from Studies MC-ALS.28/GLI and MC-ALS.30/GLI with regard to positive predictive value of Gliolan, as supplemented by published studies, to demonstrate that the drug can reliably differentiate between normal tissue and malignant glioma. As such, NX Development Corp does not intend to conduct additional clinical studies to demonstrate the efficacy of the drug.

8. Does the Agency agree that no additional clinical data are necessary to demonstrate the efficacy of the drug to support the intended indication?

FDA Response:

The information in your meeting package is insufficient for us to make a meaningful assessment of the adequacy of the clinical data to support the proposed use of Gliolan. We recommend that you schedule a Pre-NDA meeting after you have acted upon the following information requests.

1. **We agree with your plan to provide data on the performance of Gliolan for distinguishing between normal and malignant tissue by using as truth standard the histopathology of brain biopsies. The reliability of this performance estimate will depend on factors such as:**

    a. **control of bias in the selection of patients for study and selection of tissues for biopsy**
    b. **use of reproducible methods and standards for the evaluation of fluorescence**
    c. **evaluation of histopathology blinded to fluorescence imaging data.**

    We therefore recommend that you provide detailed summaries of studies MC-ALS.28/GLI and MC-ALS.30/GLI and a full discussion of strengths and weaknesses of the study designs and methods.

2. **In addition you will need to provide data demonstrating that the information Gliolan provides is clinically useful.**

As previously discussed, the assessment of extent of tumor resection based on postoperative imaging is not an adequate efficacy endpoint; moreover an effect of Gliolan-aided tumor resection on progression free survival is difficult to interpret in the absence of effect on overall survival.

We recommend that you consider providing data that demonstrates the use of Gliolan for enhancing delineation of tumor resection margins. In an adequately controlled study, patients with WHO grade 3 and 4 gliomas would undergo maximal tumor resection using the optimal surgical procedures performed under white light only. The patients (except for a small randomly selected sample) would then undergo additional Gliolan-aided resection using the microscope modified to visualize fluorescence. Documentation of fluorescence in the resection margin

before and after would be performed and biopsies would then be obtained for verification of tumor status.

The analysis of the data would plan to demonstrate superiority of tumor detection rates in the resection margin with fluorescence. At the same time, there should be control on "overcalling" through false positive rates.

Sponsor Clarification questions:

What is the rationale for the inclusion of the small randomly selected sample?

***Meeting Discussion**:*

The Agency posed questions regarding the study designs and whether resections undertaken under white light were compared to those undertaken under blue light. The Sponsor indicated that this was not the objective of the study designs and also indicated that there are more extensive clinical data available for review than have been provided in the presentation and briefing document supporting the PPV > 95% and the observation that if the tissue fluoresces there is a high correlation to malignancy defined by histopathology.

The Agency informed the Sponsor that there are additional medical literature that are pertinent to the clinical usefulness of the drug and also indicated that it may be possible to obtain the necessary evidence of clinical usefulness from existing data from the medac studies and/or from the medical literature. The data would need to support improved delineation of tumor margin as an indication of clinical usefulness. The Sponsor indicated that additional clinical studies are under consideration in view of the guidance received from the Agency.

The Sponsor said that the 505(b)(2) pathway might be utilized.

Does the Agency accept well controlled photo-or video-imaging for documentation of fluorescence?

***Meeting Discussion**:*

We have accepted photos for a variety of indications and procedures. These images should be taken under a well- and pre-defined standardization, for example, specific point of time during the procedure and images including both white light and fluorescence using the same imaging device(s) with the same settings/performance parameters, magnification, distance to target being imaged, etc. It is expected that these images will be submitted as part of the application.

Could the Agency comment/interpret on the meaning of the statement on "overcalling" through false positive rates?

***Meeting Discussion*:**

There were discussions about a clinical study design in which surgeons can resect under white light and then confirm the delineation of the tumor margin under blue light. The remaining fluorescent tissue would then be biopsied for malignant tissue confirmation, but not quantified, as pointed out by the Agency. Although scientifically interesting, it was agreed upon that random biopsies from normal appearing tissue will be difficult to obtain by practicing neurosurgeons and poses an ethical problem.

It was noted that surgeon bias is a recognized concern in that surgeons might not resect completely under white light because they know that the blue light will provide additional information. The Sponsor indicated that the company might utilize video and a peer review centralized process in a clinical investigation to confirm that the initial resection was complete.

NX Development Corp does not intend to collect pharmacokinetic (PK) data from patients with renal or hepatic impairment. (b) (4)

8a. Does the Agency agree (b) (4) ?

FDA Response:

The NDA should provide justification for the idea that the information is non-essential to assure drug efficacy and safety. (b) (4)

As limited data regarding the elimination route of 5-ALA are provided, we are unaware of whether 5-ALA is a substrate for drug metabolizing enzymes (e.g., CYPs) or transporters. Thus, there is potential that inhibitors of CYPs or transporters could increase 5-ALA exposure. Similarly, we are unaware of 5-ALA's activity in inhibiting drug metabolizing enzymes or transporters. Our expectation is that 5-ALA's ability to act as a substrate or inhibitor of drug metabolizing enzymes and transporters be investigated in vitro. If in vitro results are positive, clinical studies may be warranted. We refer you to the FDA Guidance,
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

Meeting Discussion:* *There was no meeting discussion.

Microscopes

NX Development Corp intends to label Gliolan for use with operating microscopes with the appropriate specifications with regard to generating the appropriate wavelength of light and utilizing the necessary filters necessary to differentiate normal tissue from malignant glioma.

There are marketed operating microscopes that currently meet the specifications for use with Gliolan.

8b. Does the Agency agree that Gliolan may be labeled for use with any marketed microscope that meets the appropriate specifications for its use?

FDA Response:

No, we do not agree. The Office of Combination Products will make the final determination on whether Gliolan and the surgical microscope should be developed as a combination product.

In general, surgical microscopes are Class I exempt devices (regulation 878.4700) intended for use during surgery to provide a magnified view of the surgical field. The proposed indication for the drug (or potentially the combination product) is to facilitate the visualization of malignant tissue during glioma surgery. Clearly, when intended for such use, the microscope device exceeds the limitations to the exemption.

We are not aware of an FDA approved microscope with appropriate labeling for use with a drug for the indication proposed. Modifications of a traditional microscope are necessary for the proposed use including a sophisticated combination of excitation and emission filters with slightly overlapping transmission integrated into its optical configuration.

For these reasons, a microscope needs to be identified and concurrently developed for approval for this indication. The overall safety and effectiveness of the microscope will be established in conjunction with its use with the new drug for the proposed indication. .

Sponsor Clarification questions:

How do we proceed to get additional feedback from OCP

Meeting Discussions:

The Division has consulted OCP and the response of the consult will be communicated to the Sponsor as soon as it is received.

Risk Evaluation and Mitigation

Consistent with the approval of Gliolan in the EU and other countries, NX Development Corp intends to implement elements to assure the safe use of Gliolan to facilitate the real time detection and visualization of malignant tissue during glioma surgery. These conditions and restrictions will include mandatory training courses for neurosurgeons to support the safe and effective use of Gliolan, certification of those neurosurgeons who have completed the training course, and restricted access of Gliolan to those neurosurgeons who have been certified as having completed the training course.

9. Does the Agency agree with the applicant's plan to establish a REMS program and the above described elements of the REMS approach?

FDA Response:

We have insufficient information to determine whether the training that healthcare providers will receive should be conducted via a risk evaluation and mitigation strategy (REMS). We ask that you provide a description of the training and the training materials used in other jurisdictions. List all the providers who are required to take training. Is the training provided only to surgeons, or to other personnel involved in the procedure as well? What criteria are used to determine that a provider has the knowledge and skills needed to use the product? Do you certify the healthcare settings as well (i.e., hospitals)? What criteria are used to determine that a hospital can support safe use of the product? Please describe how you determined the appropriateness of your training. For example have you received input from professional societies regarding the adequacy of the training? If so, please provide the comments received from these organizations. Please also provide feedback that you have received from trained healthcare providers on the necessity and adequacy of the training. Additionally, please describe both your trial and marketing experiences, including a description of the adverse events experienced by patients that informed your training requirements. Describe any inadequacies in training that you discovered, and how you responded to the inadequacies in the training.

We ask that you provide this information to the Agency for review prior to submitting a new drug application.

Meeting Discussion: ***There was no meeting discussion.***

10. Are there any special requests the Agency has for this submission?

FDA Response:

Due to the limited information submitted in this meeting package and the complex issues that have arisen during our review, we recommend that you await information from the Office of Combination Products regarding the appropriate regulatory pathway related to microscope question 8 above.

Meeting Discussion: ***There was no meeting discussion.***

NX Development Corp intends to request priority review of the Gliolan NDA.

11. Does the Agency agree that Gliolan meets the criteria for priority review?

FDA Response:

You may request priority review at the time of NDA submission according to the procedures outlined in the following guidance: Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics

(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf). A determination of priority review will be made based upon the information submitted to the NDA supporting the criteria outlined in the guidance:

1. **Serious condition**
2. **Demonstrating the potential to be a significant improvement in safety or effectiveness**

We note that your proposed disease indication "malignant glioma" is a serious condition that fulfills the priority review first criterion. Please note your application will also need to demonstrate that it fulfills the second criterion as well. See our answer to question 6 above.

Meeting Discussion: ***There was no meeting discussion.***

ADDITIONAL COMMENTS

We note that there are Drug Master Files (DMFs) referenced in Section 10.1 for both drug substance and drug product. Please provide letters of Authorization from the DMF holders in the NDA. Also, you should consult the DMF guidance for what CMC information is expected in the DMF. The address of this guidance is as follows: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionrequirements/DrugMasterFilesDMFs/default.htm

PREA REQUIREMENTS

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 product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

ACTION ITEM

The Division of Medical Imaging Products promised to send a list of additional references to NX Development Corporation.

ATTACHMENTS AND HANDOUTS

The presentation below was used by the Sponsor to provide data demonstrating the clinical usefulness of Gliolan and that it meets the appropriate specifications for its use compared to other marketed microscope.

12 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MODUPE O FAGBAMI
10/10/2014

LIBERO L MARZELLA
10/10/2014