CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-790

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-790
[Resubmission]

Drug name:	DACOGEN™
Generic name:	Decitabine
Formulation:	Lyophilized powder (50 mg/vial) for reconstitution and intravenous administration
Indication:	Myelodysplastic syndrome
Current Submission:	NDA-NME
Applicant:	MGIPHARMA Inc. (MGI) 6611 Tributary Street Baltimore MD, 21224-6515
OCP Division:	Division of Clinical Pharmacology V (HFD-860)
OND Division:	Division of Drug Oncology Products (HFD-150)
Submission Date:	Nov-14-2005
Primary Reviewer:	Roshni Ramchandani, Ph.D.
Acting Team Leader:	Brian Booth, Ph.D.

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I. Executive Summary

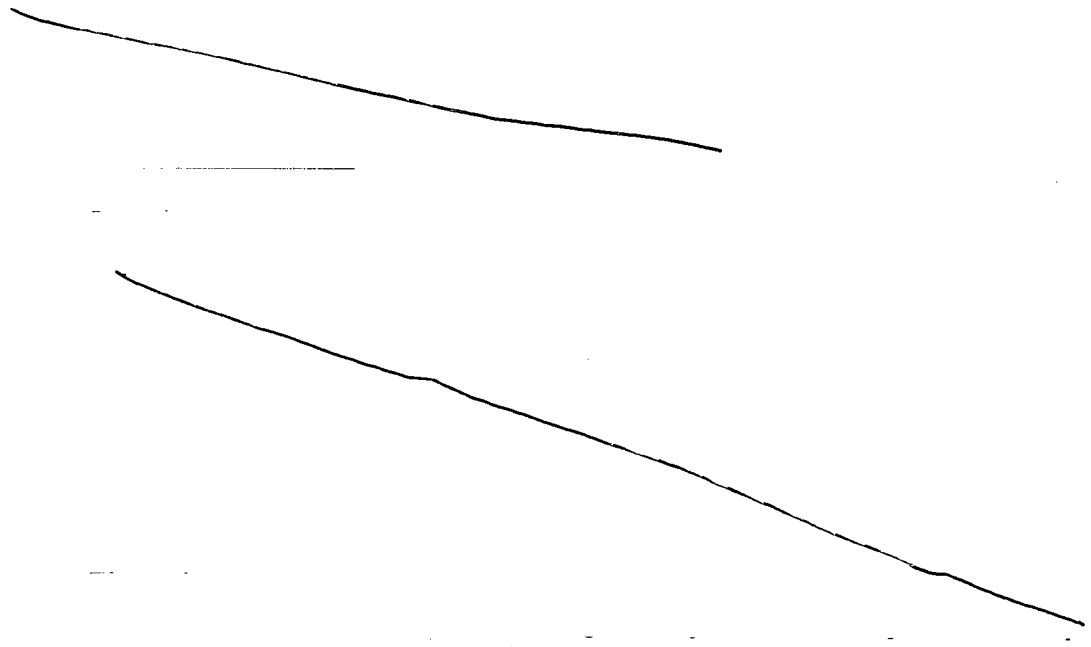
Dacogen (decitabine) is an analog of the naturally occurring nucleoside 2-deoxycytidine. Decitabine has been previously evaluated for its anti-leukemic activity in adults and children, although it was associated with significant myelotoxicity. More recent studies had evaluated lower doses of decitabine for the treatment of myelodysplastic syndrome (MDS). This product was previously owned by Supergen Inc. There was a transfer of ownership to MGIPHARMA Inc., on December 23, 2005, and this was acknowledged by the Agency on January 11, 2006. Supergen Inc. had previously submitted two phase 2 studies and one phase 3 study of decitabine in support of their proposed indication for the treatment of advanced MDS. The proposed regimen is 15 mg/m^2 as a 3-hr infusion given every 8 hours for 3 days, with cycles repeated every 35 days. No pharmacokinetic data was collected in the clinical studies. The Agency had sent the applicant an "approvable letter" with several recommendations, including several clinical pharmacology recommendations. The applicant has either addressed or has submitted plans to address these recommendations. These plans are acceptable to the Agency.

A. Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the Clinical Pharmacology section of NDA 21-790 and finds it to be acceptable, with the following recommendations:

- We recommend that you conduct *in vitro* studies in human hepatic microsomes to evaluate if decitabine inhibits CYP2C8.

Revisions to Label:



2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Clin Pharm/Bio- 1

B. Phase IV Commitments

None.

C. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

No pharmacokinetic or pharmacodynamic studies were conducted by the applicant as part of this NDA, which included two phase 2 studies and one phase 3 study of decitabine in patients with advanced MDS. The proposed regimen is 15 mg/m^2 as a 3-hr infusion q8h for 3 days, with cycles repeated every 35 days.

The current submission included reports of *in vitro* studies evaluating the CYP inhibition and induction potential of decitabine.
In vitro studies indicate that Decitabine does not inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. The applicant did not conduct experiments to evaluate the inhibitory potential on CYP2C8. Decitabine does not have any *in vitro* induction potential for CYP3A4/5, CYP1A2, CYP2C9 or CYP2B6. However, the results for CYP1A2 showed that two of the liver donors were not induced by the prototypical inducer, isoniazid (100 μM). Hepatocytes from the third liver donor showed an increase in the CYP2E1 activity after treatment with isoniazid as well as with decitabine. Given that two of the three hepatocyte cultures in your CYP2E1 induction study did not appear to be viable, we recommend that the applicant repeat the *in vitro* experiments to confirm whether decitabine induces CYP2E1 in human hepatocytes.

OCPB Briefing for this re-submission was held on 15-Mar-2006. The briefing for the original submission was held on 12-Jul-2005.

Attendees: Drs. A. Rahman, B. Booth, S. Nallani, M. Orr, R. Ramchandani

II. Question Based Review

The current submission is a re-submission of the NDA for decitabine, following the Agency's decision to issue an approvable letter for the applicant's initial NDA.
At the time of the initial review, there were several recommendations made from the clinical pharmacology perspective. The applicant has addressed the recommendations, and included reports of studies evaluating the in vitro inhibition and induction potential of decitabine.
This review will focus on the applicant's responses and the submitted study reports. All other sections of the Question Based Review remain unchanged from the previous submission.

Recommendations to Applicant following original submission and Applicant's Responses:

1. We recommend that you conduct a mass balance study to assess renal and non-renal pathways of elimination of decitabine and we recommend that you screen any major metabolites in vitro for pharmacological activity to determine if there any need for any organ impairment studies.
   Rationale: Very limited data are available on the pharmacokinetics of decitabine. The exact metabolic fate and pathways of elimination of decitabine are unknown. This information is critical in determining if decitabine can be used in patients with renal and/or hepatic impairment and if dosing adjustments would be needed for the safe use of decitabine in these patients.

   Applicant's Response:

   The applicant plans to conduct a human mass balance study using 14C-labeled decitabine. They are currently developing the radio-labeled drug for use in the study, and intend to submit the study protocol to the Agency for review.

   Reviewer's Comment:

   This is acceptable.

2. We recommend that you conduct exposure-response analyses for measures of toxicity and effectiveness in ongoing and future clinical studies. You should consider assessing intracellular levels of drug and active metabolites as measures of exposure in the exposure-response analysis. These analyses may help enable the determination of optimal dosing regimens for MDS as well as for other indications.
   Rationale: The optimal dosing regimen for decitabine in MDS is not known. Only one dosing regimen of decitabine was evaluated in the current submission. The exposure-response relationship for decitabine has not been elaborated. Characterization of the exposure-response relationship for decitabine can help in optimization of dosing regimens for MDS as well as for other future indications.

   Applicant's Response:

   The pharmacokinetics of decitabine will be examined in an ongoing study using the proposed dosing regimen (DACO-018), as well as for an alternate dosing regimen (20

mg/m2 IV over 1 hr daily x5 days q4wks, DACO-020 and DACO-017) and a new route of administration (subcutaneous, DACO-019). The PK data from these studies will enable the examination of exposure-response relationships for toxicity and effectiveness. Regarding the intracellular levels of drug and metabolites, the applicant plans to measure these as part of the human mass balance study. Based on the results of the mass balance study and the feasibility of assaying for the metabolites, the applicant intends to discuss future potential studies with the Agency.

Reviewer's Comment:

This is acceptable.

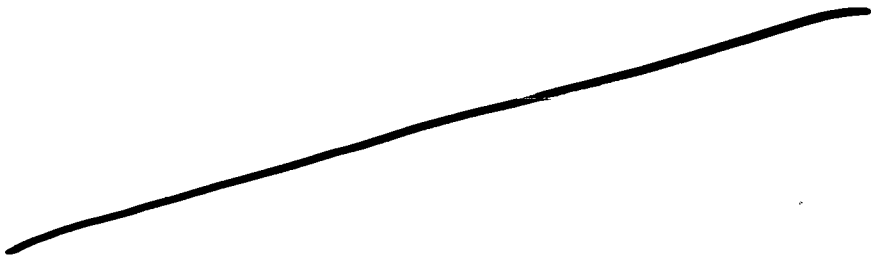
3. We suggest that you plan to evaluate the *ex vivo* DNA methyl transferase (DNMT) inhibition following decitabine, as a measure of its pharmacological activity, and if DNMT inhibition is correlated with exposure and with response rates in ongoing and future studies.
Rationale: In vitro data indicates that decitabine inhibits DNMT, and studies have shown that hypomethylation of DNA restores expression of tumor suppressor genes and induces cell differentiation. Examination of the ex vivo DNMT inhibition in ongoing and future clinical studies of decitabine would be important in improving the understanding of the PK-PD relationship for decitabine. Further, understanding the correlation of exposure of decitabine and/or its active metabolites to DNMT inhibition and how that links to clinical response rates would be important in predicting exposures associated with optimal clinical response rates and might help to identify responders and non-responders to treatment.

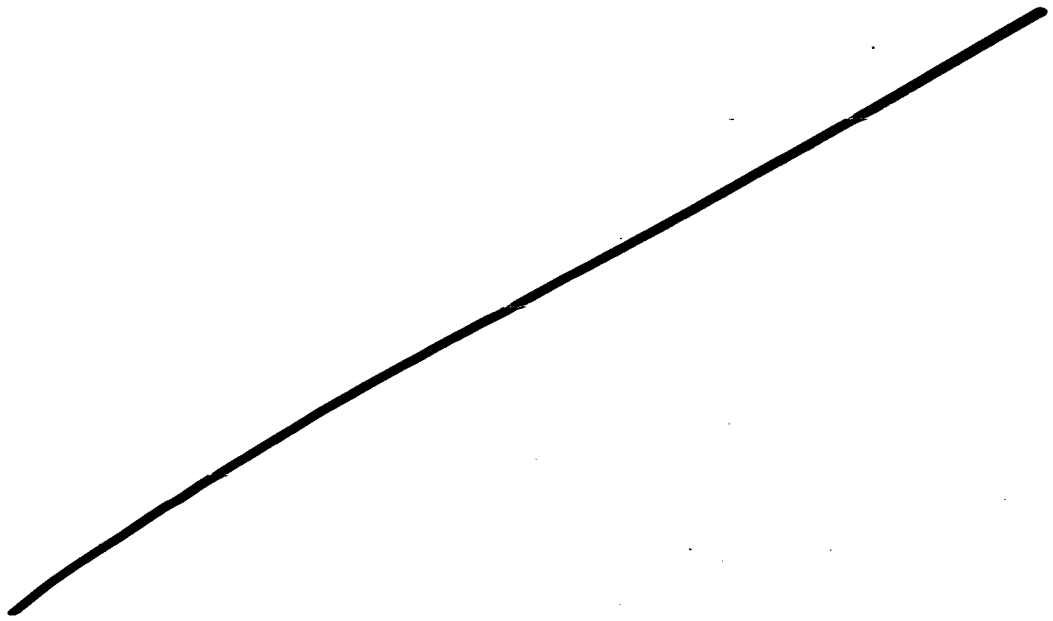
Applicant's Response:

The applicant states that the measurement of ex vivo DNMT enzymatic activity and/or protein levels is technically very difficult, and is currently being attempted in several NCI-sponsored clinical studies of decitabine. The possibility of measuring ex vivo DNMT inhibition in the applicant's future studies would depend on the outcome of the NCI-sponsored investigations. If ex vivo measurement of DNMT inhibition is not achievable due to technical limitations, the applicant proposes to measure treatment-induced changes in DNA methylation in ongoing and future studies. DNA demethylation is the downstream effect of decitabine's effect on DNMT and could represent an appropriate measure to correlate with decitabine exposure.

Reviewer's Comment:

This is acceptable.

4. 



5. We recommend that you conduct *in vitro* studies to determine the CYP450 inhibition and induction potential of decitabine. Depending on the results, drug-drug interaction studies may be necessary. We also recommend that you conduct *in vitro* studies to evaluate if decitabine is a substrate of p-glycoproteins (P-gp) and its inhibition potential for p-glycoproteins.

   Applicant's Response:

   The applicant has completed and submitted reports for in vitro studies of CYP450 inhibition and induction potential of decitabine. The applicant is planning to conduct a study to evaluate if decitabine is a substrate of P-gp and its P-gp inhibitory potential.

   Reviewer's Comment

   The sponsor has submitted a protocol to evaluate whether decitabine is a P-gp substrate and/ or a P-gp inhibitor. The proposed protocol is acceptable.

A. General Attributes of the Drug

A1. What pertinent background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Background (summarized from previous submission):

Decitabine was synthesized in Czechoslovakia in 1964 and was first demonstrated to possess anti-leukemic activity in mice in 1968, and in humans (children with chemotherapy-resistant acute leukemia) in 1981. Early trials with decitabine were conducted in many tumor types, but

few responses were noted in solid tumors (doses: 75-100 mg/kg as 1-hr infusion). Studies in hematological malignancies showed more responses, but myelotoxicity was notable with the dose schedules used (300-500 mg/m^2 as 72-hr infusion).

Decitabine was granted Orphan Drug Status for use in patients with MDS in the US in November 2000 and in the EU in February 2003.

The applicant assumed responsibility for the IND 33,929 on October 8, 1999 from Pharmachemie, B.V. Based on the results of two phase 2 studies of decitabine in MDS and some published studies (Wijermans et al., 1997; Wijermans et al., 2000), the applicant developed a phase 3 study, the protocol for which was reviewed by the Agency in January 2001.

Three clinical trials are provided in support of the use of Dacogen in the treatment of all subtypes of MDS:

- D-007: A randomized, open-label, Phase III trial of decitabine (n = 89) versus supportive care (n= 81) in adults with advanced-stage myelodysplastic syndrome (n = 170)
- PCH 95-11: A Phase II open-label study of decitabine in patients with advanced MDS (n = 66)
- PCH 97-19: A Phase II compassionate-use study of decitabine in patients with advanced MDS (n = 98).

For questions A2-A4, please refer to the clinical pharmacology review under NDA 21790 submission date Oct 29, 2004.

A2. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

A3. What are the proposed mechanism(s) of action and therapeutic indication(s)?

A4. What are the proposed dosage(s) and route(s) of administration?

B. Clinical Pharmacology

For questions B1-B7, please refer to the clinical pharmacology review under NDA 21790 submission date Oct 29, 2004.

General attributes

B1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

B2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

B3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Exposure-response

B4. Is there a relationship between decitabine exposure and effectiveness (response rates) in MDS patients?

No PK data was collected in any of the phase 2 or phase 3 studies submitted with this application. For details refer to NDA 21790 (submission date Oct 29, 2004)
The following table shows the response rates obtained in the phase 3 study and the phase 2 studies of decitabine.

Table 1: Summary of clinical results of phase 3 and phase 2 studies of decitabine in MDS.[updated from re-submitted clinical data]

PHASE 3 STUDY **Parameter**	**Decitabine**	**Supportive Care**
INTENT TO TREAT ANALYSIS	**N=89**	**N=81**
Overall Response Rate (CR+PR) †	**15 (17%)**	**0 (0%)**
Complete Response (CR)	8 (9%)	0 (0%)
Partial Response (PR)	7 (8%)	0 (0%)
Median time to (CR+PR) response (days)	93 (55-272)	0
Median Duration of (CR+PR) response (days)	288 (116-388)	0
EVALUABLE PATIENT ANALYSIS	**N=56**	**N=78**

Overall Response Rate (CR+PR) †	**12 (21%)**	**0 (0%)**
Complete Response (CR)	6 (11%)	0 (0%)
Partial Response (PR)	6 (11%)	0 (0%)
Median time to (CR+PR) response (days)	91 (55-272)	0
Median Duration of (CR+PR) response (days)	288 (116-337)	0
PHASE 2 STUDIES	**Decitabine**	
Parameter	**Study A N = 66**	**Study B N=98**
Overall Response Rate (CR+PR)	17 (26%)	24 (24%)
Complete Response (CR)	14 (21%)	19 (19%)
Partial Response (PR)	3 (5%)	5 (5%)
Median time to (CR+PR) Response (days)	98 (42-184)	92 (83-269)
Median Duration of (CR+PR) Response (days)	250 (78-456)	146 (1-535)

B5. Is there a relationship between decitabine exposure and incidence of adverse events in MDS patients?

B6. Does this drug prolong the QT or QTc interval?

B7. Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Pharmacokinetics

B8. What are the PK characteristics of decitabine?

(Summarized from original NDA submission 21790, submission date Oct 29, 2004).

The PK of decitabine has not been evaluated in MDS patients in the submitted studies or in previous studies. Limited PK data is available from studies of decitabine conducted in patients with other hematologic and non-hematologic cancers.

Table 2 lists the studies in which PK data on decitabine was collected. The first 6 studies listed below provide information about the steady-state plasma levels of decitabine reached following continuous IV infusions for durations ranging from 24 to 96 hours.

There are only 2 studies in which PK parameters for decitabine were estimated; one was a study of 100 mg/m2/day as a 1-hr infusion given every 8 hours in 5 patients, and the other is a study of 20, 25 and 30 mg/m2/day given as a 72-hour infusion in 17 patients.

Table 2: Summary of decitabine studies in which PK data was collected.

No. Patients	Age (Years)	Route of Administration	Dose	T½ (min.)	Steady State (SS) Level (µg/mL)	Other Notables	Reference
8 (ALL, AML)	2–15	CIV 24–40 Hours	24–80 mg/kg (1–2 mg/kg/h)	12 (11–14)	0.5 (0.3–0.9)	–	Rivard et al., 1981.
27 (ALL, AML)	< 10–20	CIV 36–60 Hours	37–81 mg/kg (1 mg/kg/h)	15–20	0.2–0.4*t	CSF levels ~20% of steady state plasma levels	Momparler et al., 1985.
2 (ALL, AML)	NA	CIV 96 Hours	300 mg/m2/d (~0.3 mg/kg/h)	NA	0–0.17* (not SS)	–	Debusscher et al., 1990.
5 (Various Solid Tumors)	> 18	CIV 72 Hrs.	30–40 mg/m2/d (~0.04 mg/kg/h)	NA	0.12–0.16 µM (0.027– 0.037 µg/mL)	–	Aparicio et al., 2003.
6 (Various Solid Tumors)	NA	CIV 72 Hrs.	40 mg/m2/d (~0.04 mg/kg/h)	NA	0.029 ± 0.014t	–	Zhao M, 2002.
8 (metastatic lung)	NA	IV over 8 Hours	600 mg/m2 (~2 mg/kg/h)	NA	0.58-0.83* 0.59-1.16t	–	Momparler R et al., 1997.
5 (Various Solid Tumors)	NA	IV (over 1 hour every 8 hours)	100 mg/m2/d (33.3 mg/m2 per dose)	T½α=7* T½ β=35*	NA	Cmax=2µM (0.46µg/mL) AUC=408±88 µg•h/L CL=126±21 mL/min/kg VD=4.59±1.42 L/kg <0.01 to 0.9% found in urine	Van Groeningen et al., 1986.
6 cycle 1, 11 cycle 2 (Various Solid Tumors)	NA	IV 72 hours	20, 25, and 30 mg/m2/day	0.51 h (C1); 0.53 h (C2)	7.6, 10.3, and 10.3 ng/mL at 3 doses, respectively ŧ	124 ±10 L/h/m2 in C1 and 108 ± 26 L/h/m2 in C2	Zamboni WC, 2004

*: Pk measured by bioassay
t: PK measured by HPLC
ŧ: PK measured by LC-MS/MS

The following overview of the PK characteristics of decitabine was derived from these studies.

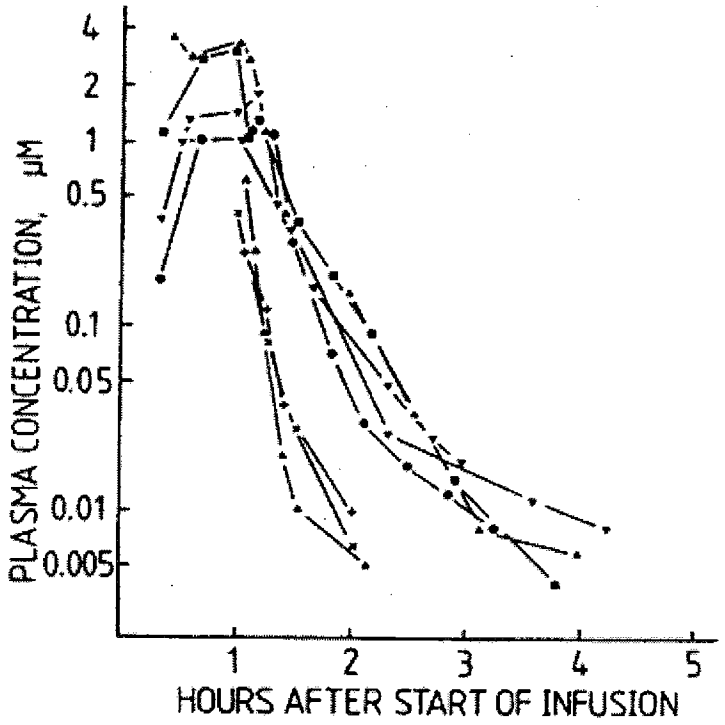
Decitabine is rapidly cleared in a biphasic manner in humans. The half-life ($t_{1/2}$) is short, probably due to extensive metabolism by cytidine deaminase. The half-life is slightly prolonged after long-duration infusion compared with IV bolus infusion. The drug penetrates the cerebrospinal fluid (CSF), reaching 14–21% of plasma concentrations seen in humans. Given the low solubility of decitabine, CSF penetration is likely due to an active transport mechanism for nucleosides. Human plasma protein binding is < 1%.

B9. What are the single dose and multiple dose PK parameters?

Please refer to original NDA submission 21790 (date October 24, 2004).

Figure 1 shows the concentration-time profiles for 8 patients receiving 1-hr infusions of decitabine in the van Groeningen study. The three lowest curves are for patients receiving 60 mg/m^2 (n=2) and 75 mg/m^2 (n=1). The five upper curves are for the patients who received 100 mg/m^2.

Figure1: Concentration vs. time profiles for 8 patients receiving 1-hr infusions of decitabine (from van Groeningen et al., 1986).



The following table lists the PK parameters for decitabine following a single 100 mg/m^2 dose given as a 1-hr infusion (Van Groeningen et al., 1986).

Table 3: Mean ± SE pharmacokinetic parameter estimates for decitabine following a 100 mg/m^2 dose given to 5 patients.

	Mean ± SE (n=5)
T1/2α (min)	7 ± 1
T1/2β (min)	35 ± 5
Cl (mL/min/kg)	126 ± 21
Vd (L/kg)	4.6 ± 1.4
Urine (%)	< 1

There are no data submitted on multiple dose PK of decitabine in cancer patients.

For questions B10-B12, please refer to the clinical pharmacology review under NDA 21790 submission date Oct 29, 2004.

B10. How does the PK of decitabine in healthy volunteers compare to that in patients?

B11. What are the characteristics of drug absorption?

B12. What are the characteristics of drug distribution?

B13. Does the mass balance study suggest renal or hepatic as the major route of elimination?

Please refer to original NDA submission 21790 (date Oct 29, 2004).

No specific mass-balance studies have been conducted. Urinary excretion of decitabine was assessed in the study by van Groeningen, who found <0.01 to 0.9% of the dose in urine across subjects. However, this was done in a small number of patients (11 total, of which only 4 were receiving the highest dose of 100 mg/m^2), and individual results were not provided in the publication for interpretation. The CL in the study was estimated as 126 ml/min/kg, and this high value suggests hepatic and extra-hepatic metabolism as the major routes of elimination.

In this re-submission the applicant has indicated that a mass balance study is planned.

B14. What are the characteristics of drug metabolism?

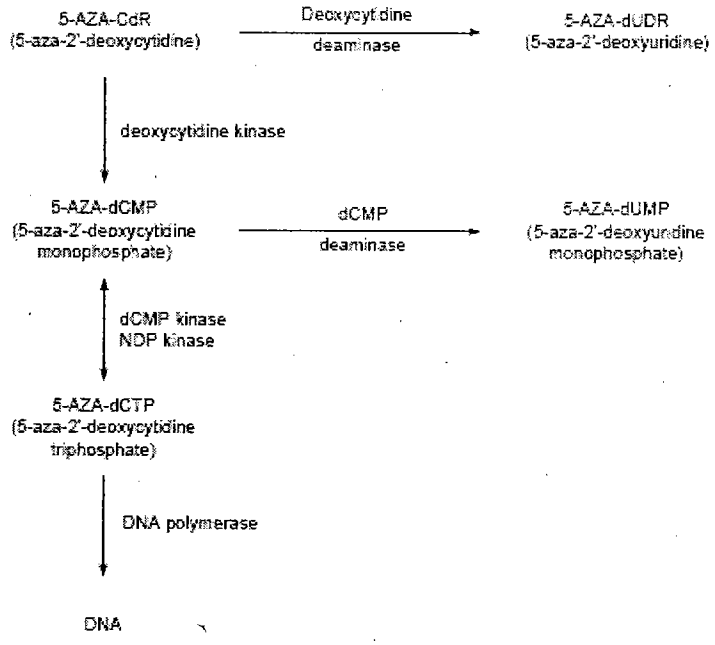
Please refer to original NDA submission 21790 (date Oct 29, 2004).

Decitabine appears to be extensively metabolized by cytidine deaminase present in the liver as well as in granulocytes, intestinal epithelium and plasma. The metabolite, 5-aza-2'-deoxyuridine, is not cytotoxic. Decitabine also undergoes anabolism, i.e., phosphorylation to the triphosphate form which is cytotoxic.

The fraction of drug metabolized through each pathway is not known.

The following figure gives the scheme for the metabolism of decitabine.

Figure 3: Metabolic scheme for decitabine.



The sponsor has conducted a study to evaluate the in vitro metabolism of decitabine in pooled human liver microsomes. The following table summarizes the results.

Table 4: Summary of results of in vitro metabolism studies with decitabine.

Test Article Identification	Percent Recovery	% Test Article Remaining at				$T_{1/2}$ (min)
		0 min	15 min	30 min	60 min	
DAC	93	100	90	98	75	>100
DAC with THU	97	100	94	103	89	>100
Heat-Inactivated Microsomes	96	100			86	
No Microsomes	78	100			81	

DAC: Decitabine; THU: tetrahydrouridine

Decitabine was found to undergo approximately 25% degradation over a period of 60 min in the presence of human liver microsomes. However, the loss was only 11% when the cytidine deaminase inhibitor, tetrahydrouridine (THU), was present in the incubation. The degradation of decitabine was about 14% in the presence of heat-inactivated microsomes and 19% in the absence of microsomes. This implies that decitabine undergoes chemical degradation as well as enzyme-mediated metabolism, possibly by a non-cytochrome P450 mechanism. Testosterone and propranolol were used as positive controls to verify the activity of the microsomes in the preparation. The half-lives of testosterone and propranolol were 5.8 min and 72 min respectively (within acceptable limits) confirming that the microsomal preparation was active.

B15. What are the characteristics of drug excretion?

Please refer to original NDA submission 21790 (date Oct 29, 2004).

According to the limited data in the study by van Groeningen et al. (1986), decitabine is not excreted unchanged in urine. The drug predominantly undergoes metabolism to an inactive metabolite, 5-aza-2'-deoxyuridine. Since no mass balance study was done, the possibility of renal excretion of the metabolites cannot be ruled out.

B16. Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Please refer to original NDA submission 21790 (date Oct 29, 2004).

B17. How do the PK parameters change with time following chronic dosing?

Please refer to original NDA submission 21790 (date October 24, 2004).

A study by Zamboni et al. (2004) examined the PK of decitabine following 72-hr infusions at 3 different rates, 20, 25 and 30 mg/m^2/day in patients with esophageal or lung cancers. Six patients were evaluated during the first cycle of treatment, and 11 patients were evaluated during their second cycle of treatment. The interval between cycles of treatment was not specified in the study report. The following table shows the mean clearance and terminal half-life of decitabine for the 2 cycles:

Table 5: Decitabine clearance and half-life for cycle 1 and cycle 2 of decitabine 72-hr infusions.

	Cycle 1 (n=6)	Cycle 2 (n=11)
Mean ± SD CL (L/hr/m^2)	123.8 ± 19.0	107.8 ± 25.7
Mean ± SD t1/2 β (hr)	0.51 ± 0.31	0.53 ± 0.28

These results suggest that decitabine PK parameters do not change for at least 2 cycles of dosing.

B18. What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Based on the limited data from the study of van Groeningen et al. (1986), the inter-subject variability in the PK parameters appears to be moderate to high, with CV% (estimated from the SE) of 37% for CL and 68% for Vd. The CV% for AUC following the 100 mg/m^2 dose was 53% (Mean ± SE = 408 ± 88 mg·hr/ml).
Results of the study by Zamboni et al. (2004) indicated somewhat lower inter-subject variability for CL (CV%: 15%), but higher variability for volume of distribution (CV% for Vc ~ 100%).

C. Intrinsic Factors

C1. What is the influence of intrinsic factors on the PK of decitabine?

The effects of age, gender or race on the PK of decitabine have not been studied.

C2. What is the influence of hepatic or renal impairment on the PK of decitabine?

The effects of renal or hepatic impairment on the PK of decitabine have not been studied.

D. Extrinsic Factors

D2. Is there a significant pharmacokinetic interaction of decitabine with other drugs administered concomitantly in this patient population?

Please refer to original NDA submission 21790 (date Oct 29, 2004).

No drug interaction studies have been conducted with decitabine.

In vitro metabolism studies suggest that decitabine is not a substrate for the human liver cytochrome P450 enzymes. Decitabine appears to be metabolized by cytidine deaminase, however the applicant reports that there is a low potential for interaction with substrates of this enzyme (including other nucleoside analogs such as Ara-C), as the Km for decitabine is relatively high (250 μM).

D3. What is the CYP inhibition potential of decitabine?

The potential for decitabine to inhibit CYP450 enzymes was examined in vitro using liver microsomal preparations. Assays were performed in the presence and absence of Decitabine (0, 0.5, 1, 5, 10, and 25 μM) and a single substrate concentration, approximating the K_m for human hepatic microsomes. The five CYP isoenzymes examined in the study were CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. The following table shows the substrates for each isozyme:

Table 6: Isozymes and substrates used in the in vitro CYP inhibition study.

Isozymes	Substrate and activity measured
CYP1A2	Phenacetin O-deethylase
CYP2C9	Diclophenac 4'-hyroxylase
CYP2C19	S-mephenytoin 4-hydroxylase
CYP2D6	Bufarolol 1'-hydroxylase
CYP3A4	Testosterone 6β-hydroxylase Midazolam 1'-hyrdoxylase

Results indicated that there were no significant decreases in enzyme activity for any of the CYP450 isozymes at any of the decitabine concentrations evaluated. This indicates that the IC50 for decitabine is > 25 μM for each of the CYP450 isozymes.

In order to completely characterize the potential for CYP450 inhibition, the IC50 should be compared to the Cmax (Css) of the drug. Since the PK of decitabine has not been evaluated for the proposed regimen, there are no observed data on Cmax or Css following decitabine infusions. However, the expected concentrations of decitabine following the proposed dosing regimen (15 mg/m^2 over 3 hrs or 5 mg/m^2/hr) can be estimated as follows:

- Based on the estimates of CL of 124 L/hr/m^2 from the Zamboni study, the expected Css following the proposed infusion of 15 mg/m^2 over 3 hrs (Ko=5 mg/m^2/hr) can be estimated as:

  Css = Ko/CL = 5 mg/m2/hr / 124 L/hr/m2 = 0.042 mg/L = 42 μg/L, which corresponds to 0.2 μM [42 μg/L / 228, where 228 is the MW].

Comparison of the expected Css following the proposed dosing regimen (0.18 μM) and the IC50 for inhibition of CYP450 isozymes (>25 μM) indicates that decitabine is not likely to inhibit the CYP450 isozymes.

It is recommended that the applicant examine the potential of decitabine to inhibit CYP2C8 in vitro.

D4. What is the CYP induction potential of decitabine?

The induction potential of decitabine on five drug-metabolizing enzymes (CYP1A2, CYP2B6, CYP2C9, CYP3A4, and CYP2E1) was investigated using cultures of primary human hepatocytes from three individual human liver donors.

After a 72-hour treatment period with decitabine or vehicle (0.1% dimethylsulfoxide (DMSO) for CYP1A2, 2C9, 3A4, and 2E1, 0.2% DMSO for CYP2B6) in the hepatocyte cultures, activities of various P450 isozymes were quantified by the formation of marker metabolites from CYP450 isoform-specific probe substrates. The marker metabolites of the probe substrates were:

acetaminophen for CYP1A2
2-hydroxybupropion for CYP2B6
4-hydroxytolbutamide for CYP2C9
6ß-hydroxytestosterone for CYP3A4/5
6-hydroxychlorzoxazone for CYP2E1.

LC/MS/MS was used for detection of analytes. Induction potential was evaluated by comparing CYP450 activities in the hepatocytes treated with decitabine to those treated with the vehicle controls.

The following table summarizes the results which indicated that CYP1A2, 2B6, 2C9, and 3A4/5 activities were not induced by the treatment of decitabine at 1, 3 and 10 μM, whereas, prototypical inducers, β-naphthoflavone (50 μM) for CYP1A2, phenobarbital (750 μM) for

CYP2B6, and rifampin (50 μM) for CYP2C9 and CYP3A4/5 increased CYP1A2, 2B6, 2C9, and 3A4 activity by 15.9, 10.5, 2.32, and 4.83-fold, respectively, compared to the vehicle controls.

Table 7: Summary of results of CYP induction study in hepatocytes.

Treatment	CYP1A2	CYP2B6	CYP2C9	CYP3A4/5	CYP2E1[b]
	Fold Over Control				
Vehicle Control[a]	1.00	1.00	1.00	1.00	1.00
Positive Control	15.9 ± 11.29	10.5 ± 5.16	2.32 ± 0.38	4.83 ± 1.76	3.88
Decitabine 1 μM	0.76 ± 0.14	0.88 ± 0.28	0.70 ± 0.13	0.86 ± 0.11	3.78
Decitabine 3 μM	0.85 ± 0.10	0.86 ± 0.49	0.72 ± 0.11	0.76 ± 0.14	2.71
Decitabine 10 μM	0.80 ± 0.13	0.79 ± 0.30	0.63 ± 0.09	0.80 ± 0.18	23.20
Positive Control (μM)	β-naphthoflavone (50)	Phenobarbital (750)	Rifampin (50)	Rifampin (50)	Isoniazid (100)
Probe Substrate (μM)	Phenacetin (100)	Bupropion (500)	Tolbutamide (50)	Testosterone (125)	Chlorzoxazone (500)

[a] Vehicle controls for CYP1A2, 2C9, 3A4/5, and CYP2E1 incubations were 0.1% DMSO. For CYP2B6 incubations were 0.2% DMSO.

[b] Data represent the mean of triplicate determination of only one liver donor, since the other two liver donors were not induced by isoniazid.

CYP2E1 activities in the first and the second donor livers were not induced by the prototypical inducer, isoniazid. Therefore, the data acquired from these two liver donors could not be evaluated. Hepatocytes from the third liver donor showed a 3.88-fold increase in the CYP2E1 activity after the treatment of isoniazid (100 μM). After treatment with decitabine, CYP2E1 activity in this liver showed a 3.78-fold increase at 1 μM, 2.71-fold at 3 μM, and 23.2-fold at 10 μM.

In conclusion, decitabine was not a CYP1A2, CYP2B6, CYP2C9, or CYP3A4/5 inducer at concentrations up to 10 μM. Given that two of the three hepatocyte cultures in your CYP2E1 induction study were not viable, the effect of decitabine on CYP2E1 induction is unclear. CYP2E1 is involved in the metabolism of several anesthetic drugs, and this may be clinically relevant in MDS patients if they require surgery. Thus, it is recommended that the in vitro evaluation of CYP2E1 induction potential should be repeated.

D5. Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

The interaction of decitabine with p-glycoprotein (P-gp) is not known. The applicant has submitted a proposal to evaluate where decitabine is a substrate and/or inhibitor of P-gp in vitro. Please see Appendix B for applicant's proposal.

D6. Based on the above (intrinsic and extrinsic factors), are there any recommendations for dosing adjustments for this population?

There are no recommendations for dosage adjustments at this time.

Other

D7. Are there any additional unresolved issues or omissions with regard to the evaluation of the PK and PD of decitabine?

Based on the information provided by the sponsor, the PK of decitabine does not appear to be completely characterized. In vitro studies to determine non-microsomal metabolism of decitabine would need to be done. The in vivo disposition of the drug, and the fraction eliminated by the various pathways would need to be determined from a human mass balance study that includes the characterization of the metabolites of decitabine. Based on this study, the need for renal or hepatic impairment studies will be determined.

E. Analytical Section

E1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

An LC/MS/MS method was used in the *in vitro* CYP450 inhibition and induction studies

E2. Which metabolites have been selected for analysis and why?

No metabolites of decitabine were selected for analysis.

E3. For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

In both in vitro studies, total drug concentrations were measured.

E4. What is the bioanalytical method that is used to assess concentrations of decitabine and its metabolites?

Please refer to original NDA submission 21790 (date October 24, 2004).

23 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Clin Pharm/Bio- 1

C. CPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	21-790	**Brand Name**	DACOGEN
OCPB Division (I, II, III)	DPE-I	**Generic Name**	Decitabine
Medical Division	HFD-150	**Drug Class**	Anti-cancer – anti-metabolite
OCPB Reviewer	Roshni Ramchandani	**Indication(s)**	Myelodysplastic Syndrome
OCPB Team Leader	Brian Booth	**Dosage Form**	Lyophilized powder (50 mg/vial)
		Dosing Regimen	15 mg/m^2 over 3 hrs q8h for 3 days
Date of Submission	11/14/05	**Route of Administration**	Intravenous
Estimated Due Date of OCPB Review	3/31/06	**Sponsor**	SuperGen Inc.
PDUFA Due Date	5/14/06	**Priority Classification**	S
Division Due Date	3/31/06		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	X	2		
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				

Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments

	"X" if yes	*Comments*
Application filable?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	In vitro CYP inhibition and CYP induction studies.	
Other comments or information not included above	Sponsor has provided responses to the CPB recommendations made during the initial NDA review.	
Primary reviewer Signature and Date	Roshni Ramchandani	
Secondary reviewer Signature and Date	Brian Booth	

CC: NDA 21-790, HFD-850 (Electronic Entry), HFD-150 (Atkins),
HFD-860 (Huang, Rahman, Booth, Ramchandani), CDR (Biopharm).

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

/s/

Roshni Ramchandani
3/27/2006 02:02:42 PM
BIOPHARMACEUTICS

Brian Booth
3/27/2006 02:05:41 PM
BIOPHARMACEUTICS

Shiew-Mei Huang
3/27/2006 02:09:27 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-790
AMENDMENT

Drug name:	DACOGEN™
Generic name:	Decitabine
Formulation:	Lyophilized powder (50 mg/vial) for reconstitution and intravenous administration
Indication:	Myelodysplastic syndrome
Current Submission:	NDA-NME
Applicant:	SuperGen Inc. 4140 Dublin Blvd, Suite 200 Dublin, CA 94568
OCPB Division:	Division of Pharmaceutical Evaluation I (HFD-860)
OND Division:	Division of Oncology Drug Products (HFD-150)
Submission Dates:	29-Oct-2004
Primary Reviewer:	Roshni Ramchandani, Ph.D.
Acting Team Leader:	Brian Booth, Ph.D.

TABLE OF CONTENTS

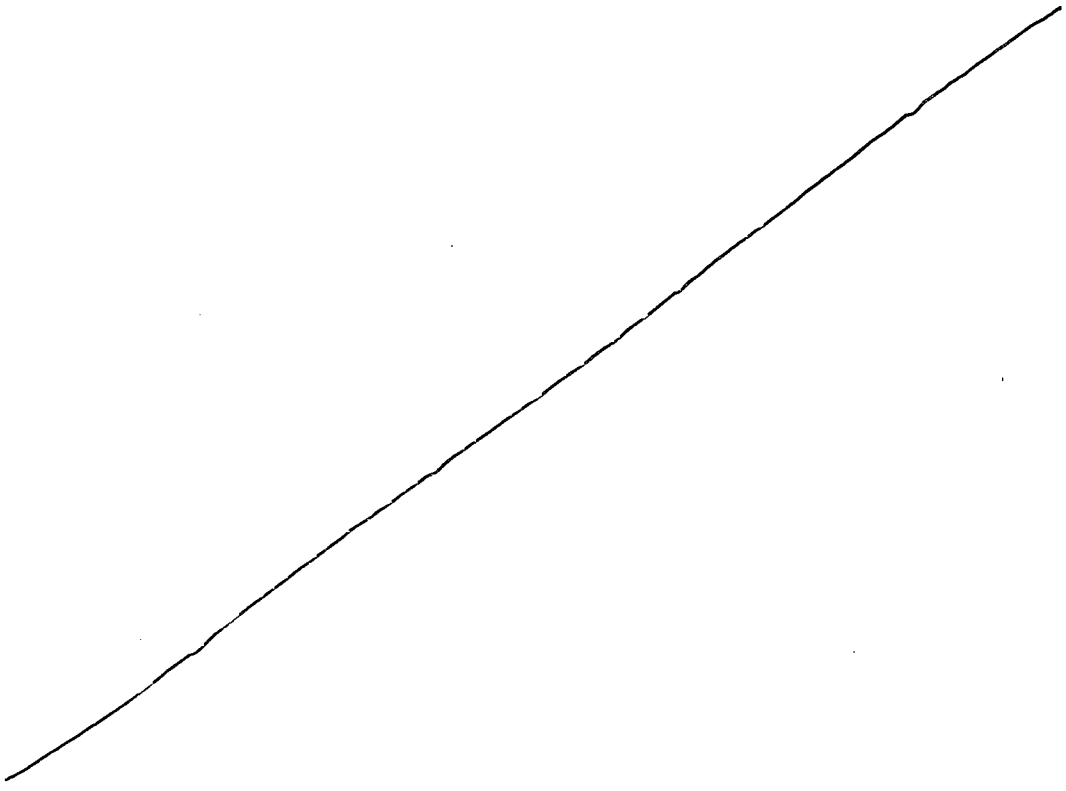
I. Executive Summary

Dacogen (decitabine) is an analog of the naturally occurring nucleoside 2-deoxycytidine. Decitabine has been previously evaluated for its anti-leukemic activity in adults and children, although it was associated with significant myelotoxicity. More recent studies had evaluated lower doses of decitabine for the treatment of myelodysplastic syndrome (MDS). The applicant has submitted two phase 2 studies and one phase 3 study of decitabine in support of their proposed indication for the treatment of advanced MDS. The proposed regimen is 15 mg/m^2 as a 3-hr infusion q8h for 3 days, with cycles repeated every 35 days. No pharmacokinetic data was collected in the clinical studies.

A. Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed the Clinical Pharmacology section of NDA 21-673 and finds it to be incomplete with some revisions to the label.

The applicant's label should be revised as follows:



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2 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Clin Pharm/Bio- 2

B. Phase IV Commitments

1. We recommend that you conduct a mass balance study to assess renal and non-renal pathways of elimination of decitabine and we recommend that you screen any major metabolites in vitro for pharmacological activity to determine if there any need for any organ impairment studies.

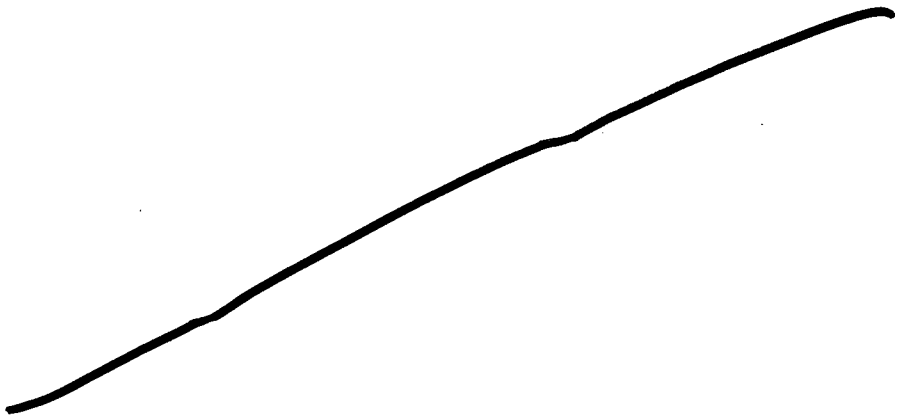
Rationale: Very limited data is available on the pharmacokinetics of decitabine. The exact metabolic fate and pathways of elimination of decitabine are unknown. This information is critical in determining if decitabine can be used in patients with renal and/or hepatic impairment and if dosing adjustments would be needed for the safe use of decitabine in these patients.

2. We recommend that you conduct exposure-response analyses for measures of toxicity and effectiveness in ongoing and future clinical studies. You should consider assessing intracellular levels of drug and active metabolites as measures of exposure in the exposure-response analysis. These analyses may help enable the determination of optimal dosing regimens for MDS as well as for other indications.

Rationale: The optimal dosing regimen for decitabine in MDS is not known. Only one dosing regimen of decitabine was evaluated in the current submission. The exposure-response relationship for decitabine has not been elaborated. Characterization of the exposure-response relationship for decitabine can help in optimization of dosing regimens for MDS as well as for other future indications.

3. We suggest that you plan to evaluate the *ex vivo* DNA methyl transferase (DNMT) inhibition following decitabine, as a measure of its pharmacological activity, and if DNMT inhibition is correlated with exposure and with response rates in ongoing and future studies.

Rationale: In vitro data indicates that decitabine inhibits DNMT, and studies have shown that hypomethylation of DNA restores expression of tumor suppressor genes and induces cell differentiation. Examination of the ex vivo DNMT inhibition in ongoing and future clinical studies of decitabine would be important in improving the understanding of the PK-PD relationship for decitabine. Further, understanding the correlation of exposure of decitabine and/or its active metabolites to DNMT inhibition and how that links to clinical response rates would be important in predicting exposures associated with optimal clinical response rates and might help to identify responders and non-responders to treatment.



Additional Recommendations for the Applicant:

1. We recommend that you conduct *in vitro* studies to determine the CYP450 inhibition and induction potential of decitabine. Depending on the results, drug-drug interaction studies may be necessary. We also recommend that you conduct *in vitro* studies to evaluate if decitabine is a substrate of p-glycoproteins and its inhibition potential for p-glycoproteins.

C. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

No pharmacokinetic or pharmacodynamic studies were conducted by the applicant as part of this NDA, which included two phase 2 studies and one phase 3 study of decitabine in patients with advanced MDS. The proposed regimen is 15 mg/m^2 as a 3-hr infusion q8h for 3 days, with cycles repeated every 35 days.

The applicant has included limited pharmacokinetic (PK) information in the form of a published report in solid tumor patients receiving 25-100 mg/m^2 decitabine as a 1-hr infusion. The doses administered in the reported pharmacokinetic studies were higher than that used in the clinical studies. PK data in 5 patients at the 100 mg/m^2 dose was reported in this study. The applicant has also included a report of an NCI study of a 72-hr infusion study of decitabine (20-30 mg/m^2/day) in esophageal and lung cancer patients. Based on pre-NDA discussions with the Agency, the applicant is currently conducting a PK study using the proposed regimen in MDS patients.

In patients with advanced solid tumors (n=5), after 1-hour intravenous (IV) infusion of 100 mg/m^2, the mean (± SD) maximum plasma concentration (Cmax) was 459 ± 100 ng/mL and mean area under the concentration-time curve ($AUC_{0\text{-}inf}$) was estimated to be 408 ± 88 ng·h/mL. In the 72-hour infusion study, following doses of 20 (n=7), 25 (n=6), or 30 (n=4) mg/m2/day, the ($AUC_{0\text{-}inf}$) of decitabine was 543 ± 158, 743 ± 95.0, and 743 ± 124 ng•h/mL, respectively.

Decitabine has a volume of distribution at steady state (Vdss) of approximately 4.59 ± 1.42 L/kg. Plasma protein binding of decitabine is negligible (<1%).

The exact route of elimination and metabolic fate of decitabine is not known. One of the pathways of elimination of decitabine appears to be via deamination by cytidine deaminase found principally in the liver but also in granulocytes, intestinal epithelium and plasma. In vitro metabolism studies have suggested that decitabine is not a substrate for the human liver cytochrome P450 enzymes. In patients with advanced solid tumors receiving the 72-hour IV infusion of 20-30 mg/m^2/day of decitabine, the (mean ± SE) total body clearance was 124 ± 19 L/hr/m^2 and the terminal phase elimination half-life was 0.51 ± 0.31 hr.

The effects of renal or hepatic impairment, gender, age or race on the pharmacokinetics of decitabine have not been studied. The CYP450 inhibition and induction potential of decitabine has not been evaluated.

OCPB Briefing was held on 12-Jul-2005:

Attendees: Drs. Shiew-Mei Huang, John Hunt, Jerry Collins, Felix Frueh, Edward Kaminskas, Atik Rahman, Brian Booth, John Lazor, June Komura.

II. Question Based Review

A. General Attributes of the Drug

A1. What pertinent background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Decitabine was synthesized in Czechoslovakia in 1964 and was first demonstrated to possess anti-leukemic activity in mice in 1968, and in humans (children with chemotherapy-resistant acute leukemia) in 1981. Early trials with decitabine were conducted in many tumor types, but few responses were noted in solid tumors (doses: 75-100 mg/kg as 1-hr infusion). Studies in hematological malignancies showed more responses, but myelotoxicity was notable with the dose schedules used (300-500 mg/m^2 as 72-hr infusion).

The applicant assumed responsibility for the IND 33,929 on October 8, 1999 from Pharmachemie, B.V. Based on the results of two phase 2 studies of decitabine in MDS and some published studies (Wijermans et al., 1997; Wijermans et al., 2000), the applicant developed a phase 3 study, the protocol for which was reviewed by the Agency in January 2001.

At the time this protocol was designed, there was no approved treatment for MDS in either the EU or US. In both the US and EU, supportive medical care was generally considered the standard of care for most of these patients. Vidaza (5-azacytidine) was approved in the US in May 2004 for treatment of advanced MDS, based on a retrospective analysis of a CALGB Phase III protocol and supportive Phase II studies. No agent is currently approved in the EU for the treatment of MDS. Decitabine was granted Orphan Drug Status for use in patients with MDS in the US in November 2000 and in the EU in February 2003.

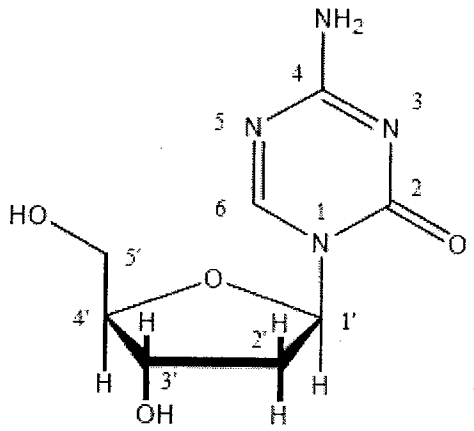
Three clinical trials are provided in support of the use of Dacogen in the treatment of all subtypes of MDS:

- D-007: A randomized, open-label, Phase III trial of decitabine (n = 89) versus supportive care (n= 81) in adults with advanced-stage myelodysplastic syndrome (n = 170)
- PCH 95-11: A Phase II open-label study of decitabine in patients with advanced MDS (n = 66)
- PCH 97-19: A Phase II compassionate-use study of decitabine in patients with advanced MDS (n = 98).

A2. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Dacogen (decitabine) for Injection contains decitabine, an analogue of the natural nucleoside 2'-deoxycytidine. Decitabine is a fine, white, crystalline powder with the molecular formula of $C_8H_{12}N_4O_4$ and molecular weight of 228.21. Its chemical name is 4-amino-1-(2-deoxy-β-D-erythro-pentofuranosyl)-1,3,5-triazin-2(1*H*)-one and it has the following structural formula.

Figure 1: Structural formula of decitabine.



Decitabine is slightly soluble in ethanol/water (50/50), methanol/water (50/50) and methanol; sparingly soluble in water; and soluble in dimethylsulfoxide (DMSO).
Dacogen (decitabine) for Injection is a white to almost white sterile lyophilized powder supplied in a clear colorless glass vial. Each 20 mL, single dose, glass vial contains 50 mg decitabine, 68 mg Monobasic Potassium Phosphate (Potassium Dihydrogen Phosphate) and 11.6 mg Sodium Hydroxide.

A3. What are the proposed mechanism(s) of action and therapeutic indication(s)?

Decitabine is a specific and potent inhibitor of the DNA methyltransferase (DNMT) enzymes. DNA methylation and demethylation has been associated with the control of gene expression. Specifically, methylation in or near promoter regions of a gene has been shown to inhibit expression of tumor suppressor genes, genes inhibiting angiogenesis and metastasis, and genes involved in DNA repair. This can result in unregulated growth and proliferation of cells and carcinogenesis. Two main genes shown to be hypermethylated in cancer are p15 and p16, which are inhibitors of cyclin-dependent kinases. The p15 (INK4B) gene is frequently and selectively hypermethylated in myelodysplastic syndrome (MDS).

Decitabine induces hypomethylation of genes, following incorporation into DNA. This DNA demethylation restores gene expression. Trapped enzyme complexes of DNA methyltransferase and decitabine may cause apoptosis when cells emerge from DNA synthesis and induce cell cycle arrest and mitotic catastrophe. Gene activation with inhibitors of DNA methylation, such as decitabine, can result in induction of differentiation, a desired effect in MDS and other hematological malignancies, and activation of tumor suppressor and other genes with implications for many tumor types.

Alternative mechanisms such as overcoming drug resistance, facilitating immune responses, as well as inducing apoptotic cell death could also contribute to the activity of decitabine.

Decitabine is an S-phase specific agent. Cells have to spontaneously reach S-phase before decitabine exerts its maximum effect.

The therapeutic indication being sought by the applicant is the treatment of myelodysplastic syndrome, including previously treated and untreated, *de novo* and secondary MDS.

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hemopathies characterized by maturation defects that result in ineffective hematopoiesis and dysplastic changes in myeloid, erythroid, and megakaryocytic progenitors. Patients experience cytopenias affecting one or more of the three hematopoietic lineages and their clinical manifestations include various combinations of anemia (fatigue), leukopenia (infections) and thrombocytopenia (bleeding). In addition, variable blast expansion and, less commonly, leukocytosis are observed. Bone marrow cellularity is increased in most cases, but may also be decreased or normal. MDS evolves into acute myeloid leukemia (AML) in 10% to 70% of patients. MDS occurs most frequently in elderly patients with the age of diagnosis ranging from 60-75 years. In a minority of cases, MDS is secondary and/or related to long-term bone marrow damage after radiation or chemotherapy. While MDS affects both genders, it is more common in men than women (reports vary from 1.88:1 to 1.19:1).

A4. What are the proposed dosage(s) and route(s) of administration?

First Treatment Cycle: The recommended decitabine dose is 15 mg/m^2 administered by continuous intravenous infusion over three hours repeated every eight hours (q8h) for three days. Patients should be pre-medicated with standard anti-emetic therapy.

Subsequent Treatment Cycles: This cycle should be repeated every six weeks. It is recommended that patients be treated for a minimum of 4 cycles; however, a complete or partial response may take longer than 4 cycles. Treatment may be continued as long as the patient continues to benefit.

Dose Adjustment or Delay Based on Hematology Laboratory Values:
If hematologic recovery (ANC $\geq$ 1,000/μL and platelets $\geq$ 50,000/μL) from a previous decitabine treatment cycle requires more than six weeks, then the next cycle of decitabine therapy should be delayed and dosing temporarily reduced by following this algorithm:

- Recovery requiring more than six, but less than eight weeks – decitabine dosing to be delayed for up to two weeks and the dose temporarily reduced to 11 mg/m2 q8h (33 mg/m2/day, 99 mg/m2/cycle) upon restarting therapy.
- Recovery requiring more than eight, but less than 10 weeks - Patient should be assessed for disease progression (by bone marrow aspirates); in the absence of progression, the decitabine dose should be delayed up to two more weeks and the dose reduced to 11 mg/m2 q8h (33 mg/m2/day, 99 mg/m2/cycle) upon restarting therapy, then maintained or increased in subsequent cycles as clinically indicated.

If any of the following non-hematologic toxicities are present, decitabine treatment should not be restarted until the toxicity is resolved: 1) serum creatinine ≥2 mg/dL; 2) SGPT, total bilirubin ≥2 times ULN; and 3) active or uncontrolled infection.

B2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

For the Phase 3 study, the applicant originally proposed the response rate (complete response (CR) + partial response (PR)) as the primary endpoint. An additional co-primary endpoint of "Time to AML or death" was recommended by the Agency as a requirement for approval (End of Phase II meeting, January 31, 2001). This change was implemented prior to accrual of any patients into the study. In the final statistical analysis plan, response rate and time to AML or death were evaluated as co-primary endpoints in the study. For the Phase 2 studies, the primary study objectives were overall response rate, duration of response and survival. Time to AML or death was not assessed.

The secondary objectives of the phase 3 study included survival, transfusion requirements, rate of febrile neutropenia, the rate and duration of Improvement rate (CR+PR+hematological improvement (HI)), quality of life (QOL), and cytogenetic response.

In addition, the safety of decitabine was monitored by performing medical examinations and clinical laboratory tests, collecting adverse events, and conducting NCI CTC toxicity assessments of laboratory tests and adverse events. Improvement rate (CR+PR+HI), transfusion requirements, cytogenetics, and changes in ECOG performance status were additional secondary endpoints in the Phase II studies.

B3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

No pharmacokinetic data was collected in any of the 3 studies included in this submission. All three studies employed the same dosing regimen, 15 mg/m^2 once every 8 hours for 3 days, repeated every 5-6 weeks. Thus, exposure-response relationships could not be assessed for this drug. There wais no reliable PK data to develop a model whereby the concentrations could be predicted for possible PK-PD analysis of the phase 2/3 studies.

Exposure-response

B4. Is there a relationship between decitabine exposure and effectiveness (response rates) in MDS patients?

No PK data was collected in any of the phase 2 or phase 3 studies submitted with this application. Earlier studies have indicated that high doses of decitabine are cytotoxic, showing anti-leukemic effects, but these high doses were also associated with a high incidence of toxicities (75-100 mg/kg as 1-hr infusion or 300-500 mg/m^2 as 72-hr infusion).

Studies, such as those by Wijermans et al., which used continuous infusions of low doses of decitabine, showed effectiveness against MDS in elderly patients. This effect is thought to be a result of hypomethylation (or inhibition of hypermethylation) of CpG islands in the promoter regions of the tumor suppressor genes such as p15 and p16. The two phase 2 studies used doses of 15 mg/m^2 every 8 hours and showed response rates of 24 and 26%, and the hematological improvement rates of 38% and 41%.

However, the submitted studies have not directly evaluated the relationship between decitabine dose and response rates (or any other endpoint) in MDS patients.

The following tables shows the response rates obtained in the phase 3 study and the phase 2 studies of decitabine.

Table 2:Summary of clinical results of phase 3 and phase 2 studies of decitabine in MDS.

PHASE 3 STUDY **Parameter**	**Decitabine** **N=89**	**Supportive Care** **N=81**
Overall Response Rate (CR+PR) †	**15 (17%)**	**0 (0%)**
Complete Response (CR)	8 (9%)	0 (0%)
Partial Response (PR)	7 (8%)	0 (0%)
Duration of Response		
Median time to (CR+PR) response: Days (range)	89 (55-153)	NA
Median Duration of (CR+PR) response : Days (range)	266 (131-346)	NA
Overall Improvement Rate (CR+PR+HI)	**26 (29%) ****	**5 (6%)**
Overall Response Rate (CR+PR)	15 (17%)	0 (0%)
Hematologic Improvement (HI)	11 (12%)	5 (6%)
Duration of Overall Improvement		
Median time to (CR+PR+HI) response: Days (range)	44 (11-215)	95 (7-191)
Median Duration of (CR+PR+HI) response: Days (range)	253 (50-449)	212 (71-260)
Response by IPSS Classification (CR + PR)		
Int-1	4/28 (14%)	0/24 (0%)
Int-2	8/38 (21%)	0/36 (0%)
High Risk	3/23 (13%)	0/21 (0%)

PHASE 2 STUDIES	**Decitabine**	
Parameter	**Study A N = 66**	**Study B N=98**
Overall Response Rate (CR+PR)	17 (26%)	24 (24%)
Complete Response (CR)	14 (21%)	19 (19%)
Partial Response (PR)	3 (5%)	5 (5%)
Duration Of Response		
Median Duration of (CR+PR) Response (days)	250	146

Overall Improvement Rate (CR+PR+HI) Overall Response Rate (CR+PR) Hematologic Improvement (HI)	25 (38%) 17 (26%) 8 (12%)	40 (41%) 24 (24%) 16 (16%)
Duration of Overall Improvement Median Duration of (CR+PR+HI) Improvement (Days)	289	159

B5. Is there a relationship between decitabine exposure and incidence of adverse events in MDS patients?

As indicated previously, no PK data was collected in any of the phase 2 or phase 3 studies submitted with this application. Therefore no dose-response relationship could be developed for measures of toxicity.

The following table shows the grade 3 and grade 4 adverse events seen in the patients in the phase 2 and phase 3 studies.

Table 3: Summary of adverse events (grade 3 and grade 4) in patients in phase 2 and phase 3 studies.

MedDRA System Organ Class MedDRA PT for Adverse Event	D-0007				PCH 95-11		PCH 97-19	
	Dacogen N = 83 (%)		Supportive Care N = 81 (%)		Dacogen N = 66 (%)		Dacogen N = 98 (%)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Blood and Lymphatic								
Febrile Neutropenia	14 (17)	5 (6)	3 (4)	0	5 (8)	0	4 (4)	1 (1)
Neutropenia	8 (10)	64 (77)	20 (25)	20 (25)	3 (5)	0	6 (6)	2 (2)
Thrombocytopenia	18 (22)	52 (63)	22 (27)	13 (16)	0	0	5 (5)	2 (2)
Leukopenia (NOS)	7 (8)	12 (14)	4 (5)	2 (2)	0	0	1 (1)	0
Anaemia	9 (11)	1 (1)	11 (14)	1 (1)	0	0	1 (1)	1 (1)
Gastrointestinal Disorders								
Nausea	1 (1)	0	3 (4)	0	0	0	1 (1)	0
Diarrhoea	0	0	1 (1)	1 (1)	3 (5)	0	2 (2)	0
Abdominal pain NOS	2 (2)	0	3 (4)	0	0	0	1 (1)	0
General Disorders								
Pyrexia	4 (5)	1 (1)	0	1 (1)	7 (11)	0	8 (8)	0
Pain NOS	3 (4)	0	0	0	1 (2)	0	2 (2)	0
Fatigue	5 (6)	2 (2)	9 (11)	1 (1)	1 (2)	0	0	0
Lethargy	2 (2)	1 (1)	0	0	0	0	0	0
General physical deterioration	0	0	0	0	1 (2)	0	3 (3)	1 (1)
Peripheral oedema	3 (4)	0 (0)	0	0	0	0	0	0
Hepatobiliary Disorders								
Hyperbilirubinaemia	4 (5)	1 (1)	0	0	0	0	0	0
Infection and Infestations								
Pneumonia	11 (13)	2 (2)	6 (7)	2 (2)	3 (5)	3 (5)	8 (8)	2 (2)
Sepsis NOS	0	0	0	0	1 (2)	0	3 (3)	3 (3)
Cellulitis	2 (2)	1 (1)	0	0	2 (4)	0	0	0
Staphylococcal infection	2 (2)	1 (1)	0	0	0	0	0	0
Metabolism and Nutritional Disorders								
Hyperglycaemia	7 (8)	0 (0)	1 (1)	0	0	0	0	0
Hypokalaemia	2 (2)	0	4 (5)	0	0	0	0	0
Musculoskeletal								
Arthralgia	3 (4)	0	0	0	0	0	0	0
Renal and Urinary Disorders								
Renal failure NOS	0	1 (1)	1 (1)	1 (1)	0	0	0	3 (3)
Respiratory, Thoracic, Mediastinal Disorders								
Dyspnoea NOS	3 (4)	3 (4)	5 (6)	5 (6)	3 (5)	0	2 (2)	0

B6. Does this drug prolong the QT or QTc interval?

QT/QTc prolongations were not seen in any of the MDS patients in the phase 2 or phase 3 studies.

B7. Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Exposure, i.e. dose or concentration, vs. response relationships have not been developed for this drug, therefore it cannot be determined if the dose and dosing regimen selected by the applicant are optimal.

Pharmacokinetics

B8. What are the PK characteristics of decitabine?

The PK of decitabine has not been evaluated in MDS patients in the submitted studies or in previous studies. Limited PK data is available from studies of decitabine conducted in patients with other hematologic and non-hematologic cancers.

Table 4 lists the stdies in which Pk data on decitabine was collected. The first 6 studies listed below provide information about the steady-state plasma levels of decitabine reached following continuous IV infusions for durations ranging from 24 to 96 hours.
There are only 2 studies in which PK parameters for decitabine were estimated; one was a study of 100 mg/m2/day as a 1-hr infusion given every 8 hours in 5 patients, and the other is a study of 20, 25 and 30 mg/m2/day given as a 72-hour infusion in 17 patients.

The following overview of the PK characteristics of decitabine was derived from these studies.

Decitabine is rapidly cleared in a biphasic manner in humans. The half-life ($t_{1/2}$) is short, probably due to extensive metabolism by cytidine deaminase. The half-life is slightly prolonged after long-duration infusion compared with IV bolus infusion. The drug penetrates the cerebrospinal fluid (CSF), reaching 14–21% of plasma concentrations seen in humans. Given the low solubility of decitabine, CSF penetration is likely due to an active transport mechanism for nucleosides. Human plasma protein binding is < 1%.

Table 4:Summary of decitabine studies in which PK data was collected.

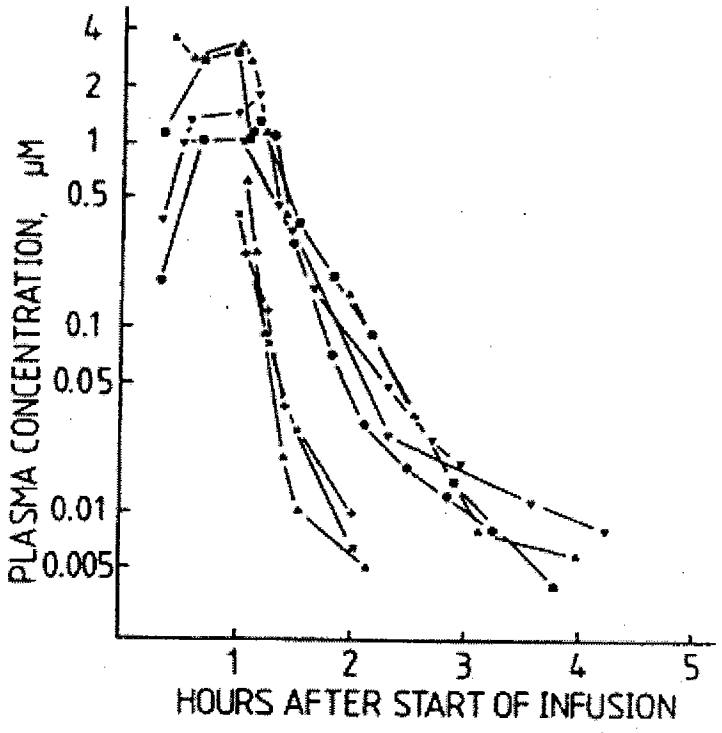
No. Patients	Age (Years)	Route of Administration	Dose	T½ (min.)	Steady State (SS) Level (µg/mL)	Other Notables	Reference
8 (ALL, AML)	2–15	CIV 24–40 Hours	24–80 mg/kg (1–2 mg/kg/h)	12 (11–14)	0.5 (0.3–0.9)	–	Rivard et al., 1981.
27 (ALL, AML)	< 10–20	CIV 36–60 Hours	37–81 mg/kg (1 mg/kg/h)	15–20	0.2–0.4*t	CSF levels ~20% of steady state plasma levels	Momparler et al., 1985.
2 (ALL, AML)	NA	CIV 96 Hours	300 mg/m2/d (~0.3 mg/kg/h)	NA	0–0.17* (not SS)	–	Debusscher et al., 1990.
5 (Various Solid Tumors)	> 18	CIV 72 Hrs.	30–40 mg/m2/d (~0.04 mg/kg/h)	NA	0.12–0.16 µM (0.027– 0.037 µg/mL)	–	Aparicio et al., 2003.
6 (Various Solid Tumors)	NA	CIV 72 Hrs.	40 mg/m2/d (~0.04 mg/kg/h)	NA	0.029 ± 0.014t	–	Zhao M, 2002.
8 (metastatic lung)	NA	IV over 8 Hours	600 mg/m2 (~2 mg/kg/h)	NA	0.58-0.83* 0.59-1.16t	–	Momparler R et al., 1997.
5 (Various Solid Tumors)	NA	IV (over 1 hour every 8 hours)	100 mg/m2/d (33.3 mg/m2 per dose)	T½α=7* T½ β=35*	NA	Cmax=2µM (0.46µg/mL) AUC=408±88 µg•h/L CL=126±21 mL/min/kg VD=4.59±1.42 L/kg <0.01 to 0.9% found in urine	Van Groeningen et al., 1986.
6 cycle 1, 11 cycle 2 (Various Solid Tumors)	NA	IV 72 hours	20, 25, and 30 mg/m2/day	0.51 h (C1); 0.53 h (C2)	7.6, 10.3, and 10.3 ng/mL at 3 doses, respectively t	124 ±10 L/h/m2 in C1 and 108 ± 26 L/h/m2 in C2	Zamboni WC, 2004

*: Pk measured by bioassay
t: PK measured by HPLC
t: PK measured by LC-MS/MS

B9. What are the single dose and multiple dose PK parameters?

Figure 2 shows the concentration-time profiles for 8 patients receiving 1-hr infusions of decitabine in the van Groeningen study. The three lowest curves are for patients receiving 60 mg/m^2 (n=2) and 75 mg/m^2 (n=1). The five upper curves are for the patients who received 100 mg/m^2.

Figure 2: Concentration vs. time profiles for 8 patients receiving 1-hr infusions of decitabine. The



The following table lists the PK parameters for decitabine following a single 100 mg/m^2 dose given as a 1-hr infusion (Van Groeningen et al., 1986).

Table 5: Mean ± SE pharmacokinetic parameter estimates for decitabine following a 100 mg/m^2 dose given to 5 patients.

	Mean ± SE (n=5)
T1/2α (min)	7 ± 1
T1/2β (min)	35 ± 5
Cl (mL/min/kg)	126 ± 21
Vd (L/kg)	4.6 ± 1.4
Urine (%)	< 1

There are no data submitted on multiple dose PK of decitabine in cancer patients.

B10. How does the PK of decitabine in healthy volunteers compare to that in patients?

Decitabine has not been given to healthy volunteers and so the PK of decitabine in that population has not been characterized.

B11. What are the characteristics of drug absorption?

Decitabine is administered intravenously; therefore drug absorption is not an issue.

B12. What are the characteristics of drug distribution?

The volume of distribution of decitabine was estimated as 4.6 L/kg (or 322 L in a 70-kg patient). This large volume suggests extensive distribution of decitabine into tissues.
Decitabine does not bind to plasma proteins (plasma protein binding < 1%).

B13. Does the mass balance study suggest renal or hepatic as the major route of elimination?

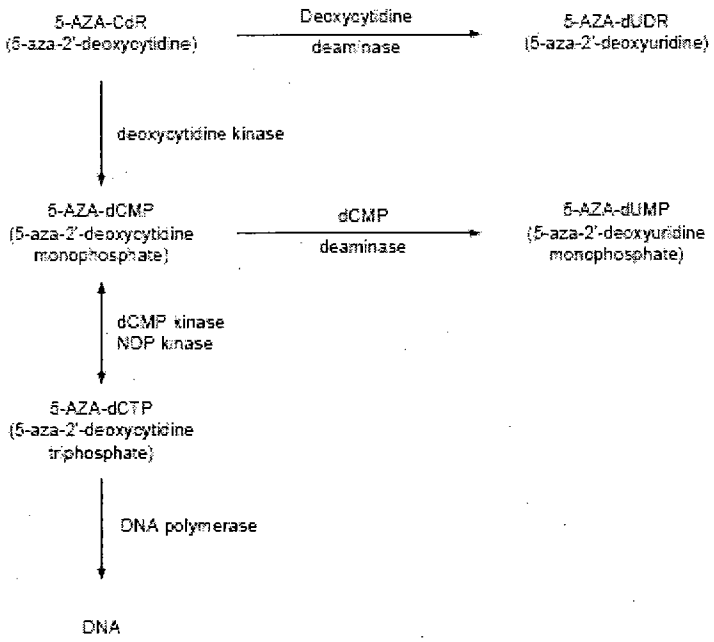
No specific mass-balance studies have been conducted. Urinary excretion of decitabine was assessed in the study by van Groeningen, who found <0.01 to 0.9% of the dose in urine across subjects. However, this was done in a small number of patients (11 total, of which only 4 were receiving the highest dose of 100 mg/m^2), and individual results were not provided in the publication for interpretation. The CL in the study was estimated as 126 ml/min/kg, and this high value suggests hepatic and extra-hepatic metabolism as the major routes of elimination.

B14. What are the characteristics of drug metabolism?

Decitabine appears to be extensively metabolized by cytidine deaminase present in the liver as well as in granulocytes, intestinal epithelium and plasma. The metabolite, 5-aza-2'-deoxyuridine, is not cytotoxic. Decitabine also undergoes anabolism, i.e., phosphorylation to the triphosphate form which is cytotoxic.
The fraction of drug metabolized through each pathway is not known.

The following figure gives the scheme for the metabolism of decitabine.

Figure 3: Metabolic scheme for decitabine.



The sponsor has conducted a study to evaluate the in vitro metabolism of decitabine in pooled human liver microsomes. The following table summarizes the results.

Table 6: Summary of results of in vitro metabolism studies with decitabine.

Test Article Identification	Percent Recovery	% Test Article Remaining at				$T_{1/2}$ (min)
		0 min	15 min	30 min	60 min	
DAC	93	100	90	98	75	>100
DAC with THU	97	100	94	103	89	>100
Heat-Inactivated Microsomes	96	100			86	
No Microsomes	78	100			81	

DAC: Decitabine; THU: tetrahydrouridine

Decitabine was found to undergo approximately 25% degradation over a period of 60 min in the presence of human liver microsomes. However, the loss was only 11% when the cytidine deaminase inhibitor, tetrahydrouridine (THU), was present in the incubation. The degradation of decitabine was about 14% in the presence of heat-inactivated microsomes and 19% in the absence of microsomes. This implies that decitabine undergoes chemical degradation as well as enzyme-mediated metabolism, possibly by a non-cytochrome P450 mechanism. Testosterone and propranolol were used as positive controls to verify the activity of the microsomes in the preparation. The half-lives of testosterone and propranolol were 5.8 min and 72 min respectively (within acceptable limits) confirming that the microsomal preparation was active.

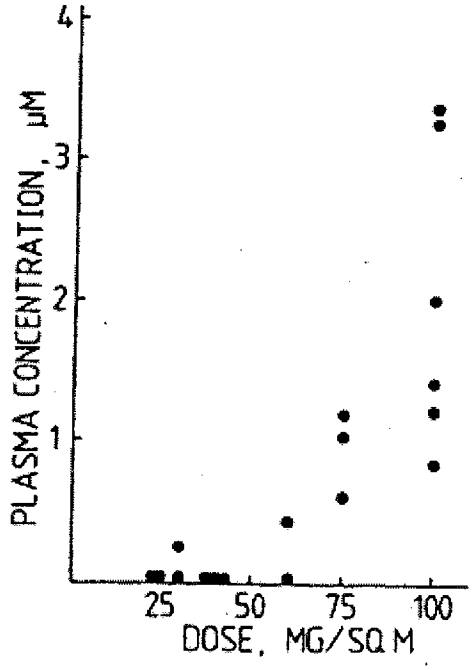
B15. What are the characteristics of drug excretion?

According to the limited data in the study by van Groeningen et al. (1986), decitabine is not excreted unchanged in urine. The drug predominantly undergoes metabolism to an inactive metabolite, 5-aza-2'-deoxyuridine. Since no mass balance study was done, the possibility of renal excretion of the metabolites cannot be ruled out.

B16. Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

In the study by van Groeningen, doses ranging from 25 to 100 mg/m^2 were administered to 15 patients. The following figure shows the peak plasma concentration as a function of dose. PK samples were assayed using a bioassay with a calibration range of 3 to 10 nM (0.003 to 0.01 μM). Seven of the 9 patients who received doses of 25 to 65 mg/m^2 showed peak concentrations (at the end of the infusion) below the limit of quantitation of the assay. Thus the linearity of the dose-concentration relationship is unclear.

Figure 4: Peak plasma decitabine concentration vs. decitabine dose (van Groeningen et al., 1986). [Note: 1 μM=228 ng/ml].



B17. How do the PK parameters change with time following chronic dosing?

A study by Zamboni et al. (2004) examined the PK of decitabine following 72-hr infusions at 3 different rates, 20, 25 and 30 mg/m^2/day in patients with esophageal or lung cancers. Six patients were evaluated during the first cycle of treatment, and 11 patients were evaluated during their second cycle of treatment. The interval between cycles of treatment was not specified in the study report. The following table shows the mean clearance and terminal half-life of decitabine for the 2 cycles:

Table 7: Decitabine clearance and half-life for cycle 1 and cycle 2 of decitabine 72-hr infusions.

	Cycle 1 (n=6)	Cycle 2 (n=11)
Mean ± SD CL (L/hr/m^2)	123.8 ± 19.0	107.8 ± 25.7
Mean ± SD t1/2 β (hr)	0.51 ± 0.31	0.53 ± 0.28

These results suggest that decitabine PK parameters do not change for at least 2 cycles of dosing.

B18. What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Based on the limited data from the study of van Groeningen et al. (1986), the inter-subject variability in the PK parameters appears to be moderate to high, with CV% (estimated from the SE) of 37% for CL and 68% for Vd. The CV% for AUC following the 100 mg/m^2 dose was 53% (Mean ± SE = 408 ± 88 mg·hr/ml).
Results of the study by Zamboni et al. (2004) indicated somewhat lower inter-subject variability for CL (CV%: 15%), but higher variability for volume of dictribution (CV% for Vc ~ 100%).

C. Intrinsic Factors

C1. What is the influence of intrinsic factors on the PK of decitabine?

The effects of age, gender or race on the PK of decitabine have not been studied.

C2. What is the influence of hepatic or renal impairment on the PK of decitabine?

The effects of renal or hepatic impairment on the PK of decitabine have not been studied.

D. Extrinsic Factors

D2. Is there a significant pharmacokinetic interaction of decitabine with other drugs administered concomitantly in this patient population?

No drug interaction studies have been conducted with decitabine. In vitro metabolism studies suggest that decitabine is not a substrate for the human liver cytochrome P450 enzymes. Decitabine appears to be metabolized by cytidine deaminase, however the applicant reports that there is a low potential for interaction with substrates of this enzyme (including other nucleoside analogs such as Ara-C), as the Km for decitabine is relatively high (250 μM).
The potential for decitabine to inhibit or induce the CYP450 enzymes is not known.

D3. Based on the above (intrinsic and extrinsic factors), are there any recommendations for dosing adjustments for this population?

There are no recommendations at this time. Studies will need to be done to evaluate the effects of the various intrinsic and extrinsic factors on decitabine PK. Possible dosage recommendations may be made regarding the concomitant use of CYP substrates after inhibition and induction potential studies with decitabine have been completed.

Other

D4. Are there any additional unresolved issues or omissions with regard to the evaluation of the PK and PD of ·

Based on the information provided by the sponsor, the PK of decitabine does not appear to be completely characterized. In vitro studies to determine non-microsomal metabolism of decitabine would need to be done. The in vivo disposition of the drug, and the fraction eliminated by the various pathways would need to be determined from a human mass balance study that includes the characterization of the metabolites of decitabine. Based on this study, the need for renal or hepatic impairment studies will be determined.

E. Analytical Section

E1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The drug decitabine was measured in plasma in the 2 PK studies. The study by van Groeningen et al. (1986) used a bioassay, while the study by Zamboni et al. (2004) used an LC/MS/MS method.

E2. Which metabolites have been selected for analysis and why?

No metabolites of decitabine were selected for analysis.

E3. For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

In both studies total drug concentrations were measured. This is appropriate since decitabine does not bind to plasma proteins.

E4. What is the bioanalytical method that is used to assess concentrations of decitabine and its metabolites?

The study by van Groeningen et al. (1986) used a bioassay, while the study by Zamboni et al. (2004) used an LC-MS/MS method.
No details or reports of the analytical methods are provided. Only brief summaries of the method and performance characteristics are included in the PK study reports.

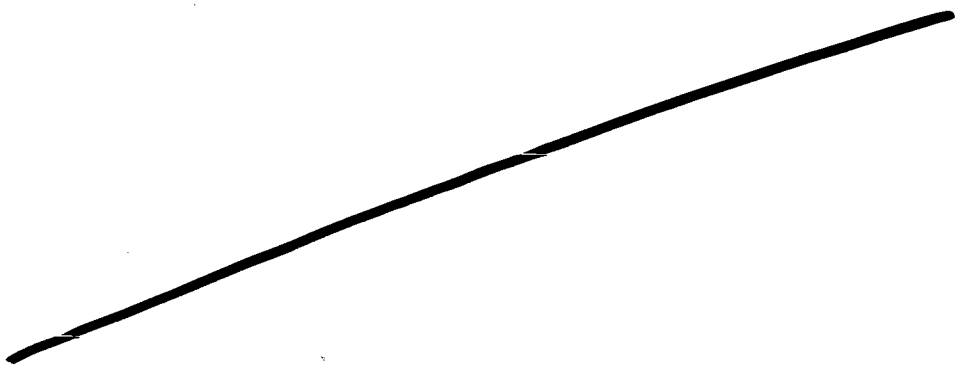
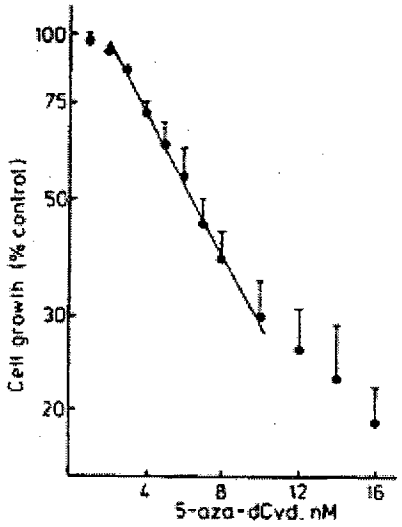


Figure 5: Standard curve for decitabine (5-aza-dCyd). L1210 cells starting at 10,000/ml were grown for 3 days in the presence of decitabine. Cell growth relative to control decreased exponentially with decitabine concentration. Drug concentration shown is that for a standard 500 µl sample added to 1000 µl cell suspension. Mean (SE) values are plotted for 5 curves performed during different weeks. Line drawn for 3-10 nM decitabine was determined by least squares analysis (r^2=0.98). [Note: 1 µM=228 ng/ml. Thus the linear range for the assay is ——



According to the authors, the assay provided high sensitivity and showed good reproducibility with a coefficient of variation of 15% at 8 nM. A narrow working range required that samples be tested over a wide range of dilutions. Plasma samples were serially diluted with Hanks' balanced salt solution. Control samples or pre-dose plasma samples consistently had no effect on cell growth when samples were diluted 10-fold or more. Test sample dilutions of 1:10 or 1:100 usually gave the % of control growth within the log-linear range of the assay, for samples with levels > 30 nM. Samples which showed no detectable levels at 10-fold diluted were re-assayed but after

Summary of LC-MS/MS Method:

21 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Withheld Track Number: Clin Pharm/Bio- 2

B. Individual Study Reviews

I.

van Groeningen CJ, Leyva A, O'Brien AMP, Gall HE, Pinedo HM. Phase I and pharmacokinetic study of 5-aza-2'-deoxycytidine (NSC 127716) in cancer patients. Cancer Research 46:4831-4836, 1986.
(copy of article attached)

6 Page(s) of
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have been Withheld from this
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II.

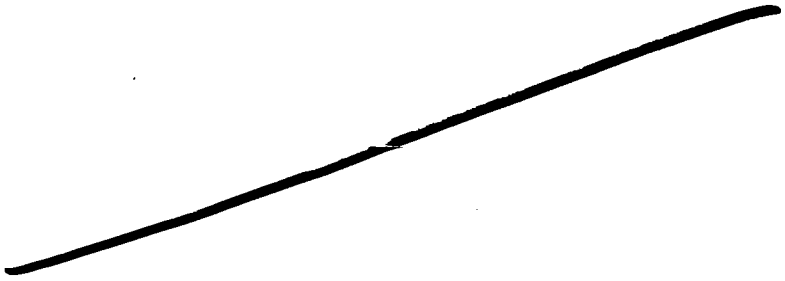
Study #:	99-C-0129 (NCI study)
Title:	Pharmacokinetics of decitabine after administration of a 72-hr continuous infusion, as part of a phase 1 study of decitabine mediated induction of tumor antigen and tumor suppressor gene expression in patients with cancers involving the lung, esophagus or pleura.

Clinical Study Summary:

Objectives: To evaluate the pharmacokinetics of decitabine after administration of a 72-hr continuous infusion, as part of a phase 1 study of decitabine mediated induction of tumor antigen and tumor suppressor gene expression in patients with cancers involving the lung, esophagus or pleura.

Study Design: Three dose levels of decitabine were administered to different groups of patients with lung, esophageal or pleural cancer. Doses of 20 mg/m^2/d, 25 mg/m^2/d or 30 mg/m^2/day were administered as continuous infusions over 72 hours. Due to the limited chemical stability of decitabine, bags were changed every 2 hrs. During cycle 1 or cycle 2, blood samples were collected for decitabine levels prior to administration and at 1, 3, 8, 24, 48, 72, 72,25, 72.5, 72.75, 73, 74 and 75 hrs after the start of the infusion. To each blood sample collected, 8 µl of tetrahydrouridine (THU, a cytidine deaminase inhibitor) was added to the tube and centrifuged to separate the plasma, which was stored at -80oC until analyzed by LC-MS/MS. No analytical report was provided with the study report, however the authors of the PK report included a brief summary of the method.

Summary of Analytical Method:



PK Analysis Methods:

2 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

2

Withheld Track Number: Clin Pharm/Bio- E

D. CPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	21-790	**Brand Name**	DACOGEN
OCPB Division (I, II, III)	DPE-I	**Generic Name**	Decitabine
Medical Division	HFD-150	**Drug Class**	Anti-cancer – anti-metabolite
OCPB Reviewer	Roshni Ramchandani	**Indication(s)**	Myelodysplastic Syndrome
OCPB Team Leader	Brian Booth	**Dosage Form**	Lyophilized powder (50 mg/vial)
		Dosing Regimen	15 mg/m^2 over 3 hrs q8h for 3 days
Date of Submission	10/29/04	**Route of Administration**	Intravenous
Estimated Due Date of OCPB Review		**Sponsor**	SuperGen Inc.
PDUFA Due Date	9/01/05	**Priority Classification**	S
Division Due Date	8/11/05		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods		1		Abstract
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:	X	1		Study report of in vitro metabolism by microsomes
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	X	1		Study report of PK of decitabine in lung cancer patients – part of Phase I study conducted by NCI
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				

Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X	7		Published Phase I and PK studies of decitabine in patients with various cancer
Total Number of Studies				

Filability and QBR comments		
	"X" if yes	*Comments*
Application filable?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	• PK parameters for decitabine in adult patients (have ongoing study in patients and will submit results in 1Q 2005). • less than 1% is eliminated in urine, mass balance study required? • organ impairment studies	
Other comments or information not included above	No clinical pharmacology studies have been conducted to date in myelodysplastic syndrome (MDS) patients at the proposed dose schedule. However, in response to FDA comments, a protocol was developed to examine decitabine pharmacokinetics in adults with MDS or acute myelogenous leukemia (AML). This study has been initiated at the University of Pittsburgh in eight patients per sex administered decitabine by a three-hour infusion at 15 mg/m2 every eight hours for three consecutive days. This is the same dose schedule used in the Phase III study of decitabine in MDS.	
Primary reviewer Signature and Date	Roshni Ramchandani	
Secondary reviewer Signature and Date	Brian Booth	

CC: NDA 21-790, HFD-850 (Electronic Entry), HFD-150 (Atkins),
HFD-860 (Mehta, Rahman, Booth, Ramchandani), CDR (Biopharm).

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/s/

Roshni Ramchandani
10/26/2005 10:09:57 AM
BIOPHARMACEUTICS

Brian Booth
10/26/2005 10:30:25 AM
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