CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-059

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics NDA Review

Brand name: TYKERB™

Generic name: lapatinib ditosylate

Type of dosage form and strength(s): immediate release tablet, 250 mg

Indication(s): the Applicant's proposed indication is, "TYKERB, in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2)

NDA number, type: NDA 22-059, 1P

Applicant name: GlaxoSmithKline

Submission date (letter date):	13-SEP-2006	N	000	
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OCP Division name: Division of Pharmaceutical Evaluation V

OND: Division name: Division of Drug Oncology Products

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OCP Primary QT Reviewer: Roshni Ramchandani, Ph.D.

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1. Executive Summary

1.1. Recommendations

Assuming that our recommendations for the package insert are negotiated to satisfaction, this NDA is acceptable from the clinical pharmacology and biopharmaceutics perspective.

We request that the Sponsor submit the ECGs related to study EGF10003 to the CDER ECG warehouse.

1.2. Identify recommended Phase 4 study commitments if the NDA is judged approvable

Based upon the ability of laptinib to act as a CYP 3A4 inhibitor *in vitro*, the Applicant agrees to perform an *in vivo* drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of midazolam. A positive finding in this study may initiate a need for further studies.

Based upon the ability of laptinib to act as a CYP 2C8 inhibitor *in vitro*, the Applicant agrees to perform an *in vivo* drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of paclitaxel or rosiglitazone. A positive finding in this study may initiate a need for further studies.

Based upon the ability of laptinib to act as a Pgp inhibitor *in vitro*, the Applicant agrees to perform an *in vivo* drug interaction study of the ability of steady-state lapatinib dosing to alter the pharmacokinetics of a single dose of digoxin. A positive finding in this study may initiate a need for further studies.

1.3 Recommendations to the Applicant

The results of the *in vitro* CYP experiments (Study Report RD2000/01947/00 00AVT0021) do not include an accounting of the percentage of parent drug metabolized, nor identification (and quantitation using reference standards) of the metabolites produced. For these reasons, it is possible that unidentified CYP metabolites are being formed. The human mass balance study results, on average, failed to identify the moieity(ies) in which more than 37% of the administered ^{14}C resides. Taken together, these data leave open the possibility that a major metabolite is formed by CYP P450s. We recommend that beginning with *in vitro* studies that account for the disappearance of parent and identification and quantitation of metabolites, you perform studies that will determine if major heretofore undiscovered CYP-formed metabolites occur.

The results of the *in vitro* CYP experiments indicate that lapainib is a P-glycoprotein transport (Pgp) substrate. We recommend that you consider performing an *in vivo* drug interaction study of the effect of concomitant dosing of a strong Pgp inhibitor on the pharmacokinetics of lapatinib.

1.4 Summary of Clinical Pharmacology and Biopharmaceutics Finding

Oral absorption of lapatinib in humans is incomplete and variable. Plasma concentrations of lapatinib peak at approximately 4 hours and decline with measured half-lives of up to 14 hours. However, accumulation with daily dosing achieves steady-state in 6-7 days, suggesting an effective half-life of 24 hours.

Lapatinib is a P-glycoprotein (P-gp) substrate with an efflux ratio of 15.6 at a concentration that approximates steady-state Cmax.

The extent of absorption of lapaitinib is increased 4-fold by a high-fat meal.

Lapatinib undergoes extensive metabolism to numerous oxidated and N- and O dealkylated products, with negligible urinary excretion of parent or metabolites (<2% of the dose). The most prominent metabolites identified are the carboxylic acid GSK342393 and the O-dealkylated phenol GW690006, which demonstrate pharmacological activity *in vitro*.

In vitro studies in human hepatocytes and hepatic microsomes indicate that lapatinib is primarily metabolized by CYP3A4 and CYP3A5 with smaller contributions from CYP2C8, and CYP2C19.

Systemic exposure to lapatinib was increased 14% in moderate and 63% in severe hepatic impairment.

Clinically relevant concentrations of lapatinib inhibit all of the CYP enzymes tested with an I/Ki ratio > 0.1. The strongest CYP inhibition was observed for CYPs 2C8 ($I/K_i = 9.2$) and 3A4 ($I/K_i = 5.0$). Lapatinib also inhibits Pgp with an I/IC50 of 1.4.

Lapatinib exposure were reduced by 72% after CYP3A4 induction by carbamazepine, and increased to 3.6 times control after CYP3A4 inhibition by ketoconazole.

Mixed-effects modeling of the Fridericia corrected QT interval (QTcF) indicated a significant relationship between lapatinib concentration and the QTcF interval. Based on the model parameters, the predicted change in QTcF was estimated at peak concentrations following the recommended dose of lapatinib (1250 mg/day in combination with capecitabine).

- At the mean peak concentration (Cmax) of 3203 ng/ml following the 1250 mg daily dose, the predicted change in QTcF was estimated to be 13.5 msec.
- Using the upper 95% confidence limit of the slope estimate, the predicted QTcF prolongation at the mean Cmax was estimated to be 23.4 msec.

Additionally, factors that could increase lapatinib concentrations, such as co-administration of CYP3A4 inhibitors, administration of drug with food, or administration to patients with hepatic impairment, would be expected to further prolong the QTc interval.

2. *Question-Based Review*

2.1. General attributes of the drug

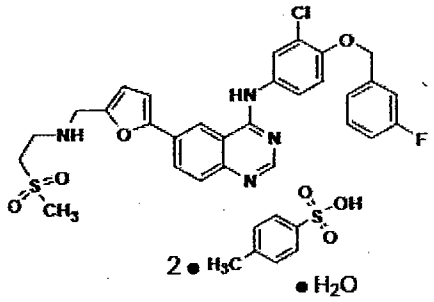
What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

The NDA contains a single Phase 3 study. The protocol for this study was the topic of a Special Protocol Assessment by the FDA. The NDA was submitted based upon a protocol-specified interim analysis for time-to-tumor-progression.

2.1.1. 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?

The active ingredient in the drug product is lapatinib (GW572016F). Its International Union of Pure and Applied Chemistry (IUPAC) name is N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furyl]quinazolin-4-amine bis(4-methylbenzenesulfonate) monohydrate. A structural representation is shown below as **FDA Figure 1.**

FDA Figure 1. Lapatinib ditosylate monohydrate, Applicant's Section m3.2.S.1.2., p. 1



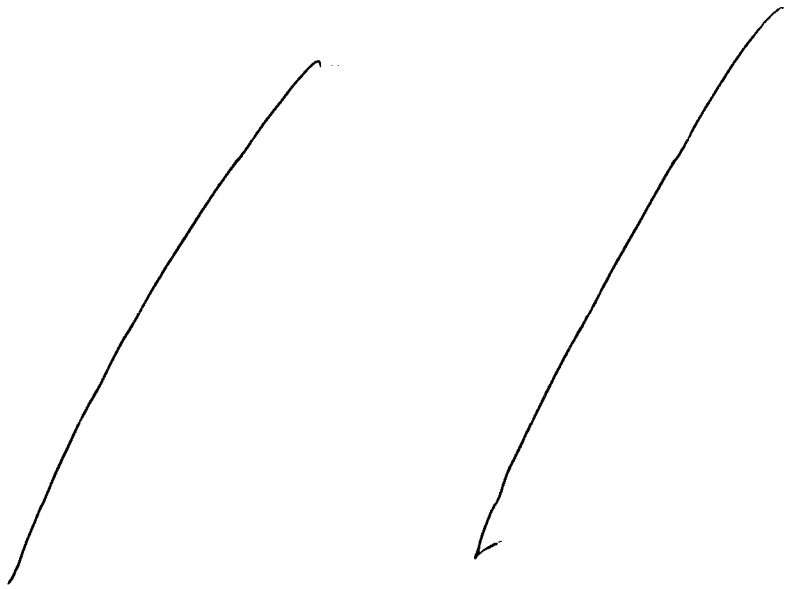
$C_{29}H_{26}ClFN_4O_4S(C_7H_8O_3S)_2H_2O$

The molecular formula for the ditoyslate monohydrate is C29H26ClFN4O4S(C7H8O3S)2H2O and the molecular weight is 943.48 grams per mole. Lapatinib ditosylate possesses no chiral centers or external olefinic bonds which precludes the existence of stereoisomers or geometric isomers.

Lapatinib Ditosylate Tablets, 250 mg are biconvex, oval, orange, film-coated tablets which contain 405 mg lapatinib ditosylate (salt) which is equivalent to 250 mg lapatinib (free base) for oral administration.

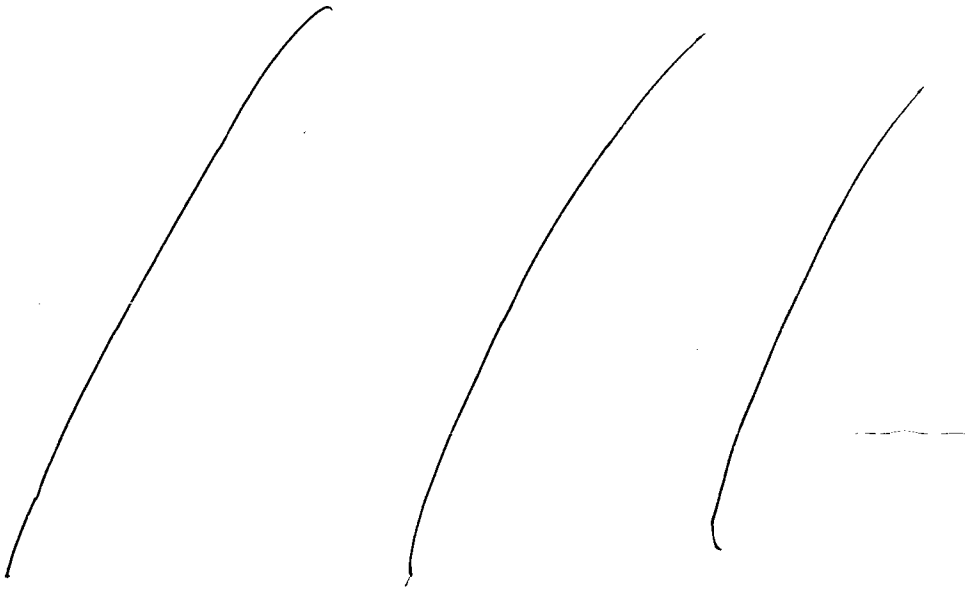
2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

The below (indent, font change) **Mechanism of Action** and **INDICATIONS AND USAGE** are reproduced from the Applicant's proposed package insert.



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

The below (indent, font change) **DOSAGE AND ADMINISTRATION** and **Dose Modification Guidelines** are reproduced from the Applicant's proposed package insert.



2.2. General clinical pharmacology

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

The proposed starting regimen (lapatinib 1250 mg/day continuously in combination with capecitabine 2000 mg/m^2/day on Days 1-14 of a 21-day treatment cycle) is the regimen used in the pivotal study EGF100151.

The recommended dose for the combination arm for the Phase III study was based on data from Study EGF1005, a Phase I safety and tolerability study in which lapatinib was administered with capecitabine. The 1250/2000 regimen was identified as the "optimum treatment regimen (OTR)" based upon empirical consideration of tolerability. The OTR was defined as the dose of lapatinib and capecitabine at which no more than 1 of 6 subjects experienced a dose-limiting toxicity (DLT). The DLTs that determined the OTR were grade 3 diarrhea and grade 3 rash. Although the approved capecitabine dose is 2500mg/m^2/day, the clinical trial data submitted for the regulatory approval of capecitabine included dose modification, either a dose reduction or interruption, in 55% of the subjects. Thus the data used for capecitabine approval included a substantial number of subjects who received 2000mg/m2/day.

2.2.2 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?

The primary efficacy endpoint in Study EGF100151 was time to disease progression (TTP). An analysis of progression free survival (PFS) was also performed as a sensitivity analysis. PFS differs slightly from TTP in that non-cancer deaths are included as events in the former and are censored in the latter analysis. These surrogate endpoints are selected based upon the belief that they are likely to correlate with clinical benefit.

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

The performance of the bioanalytical methods will be reviewed in Section 2.6.

In human studies other than the mass balance study, metabolites were not measured.
Two metabolites have been shown to possess pharmacological activity. The potency with which GSK342393A inhibits EGFR and ErbB2 *in vitro* relative to parent is 329% and 152%, respectively. The potency with which GW690006 inhibits EGFR and ErbB2 *in vitro* relative to parent is 86% and 3%, respectively. In cell cultures derived from HN5 and BT474 tissue lines, which over-express EGFR and ErbB2, respectively, these relative potencies are lower (2% and 3%, 17% and 1%, respectively).

Following oral dosing of ^{14}C-lapatinib, a pooled plasma sample collected over the first 4 hours post-dose showed no radioactive peaks other than lapatinib. The lower limit of quantitation for

this analysis is estimated to be 10% of the parent peak. No additional plasma sampling timepoints were analyzed for metabolite concentrations.

The absolute bioavailabilty of laptinib, and the absolute bioavailability of each metabolite (i.e., the amount of each metabolite seen by the body) are unknown. Also, as very little drug-derived material is excreted in urine (> 2% of administered ^{14}C), urine data is of little aid in discerning bioavailabilities. For these reasons, the relative contribution of metabolites to efficacy and safety, and thus, whether the decision to not measure metabolites was appropriate, can not be determined.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *efficacy*? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Clinical studies assessing the relationship between exposure and efficacy were not performed. The basis of the proposed package insert dosing recommendations is presented in Section 2.2.1. Pharmacokinetics data were not collected in Study EGF100151.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for *safety*? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

Clinical studies assessing the relationship between exposure and safety were not performed. The basis of the proposed package insert dosing recommendations is presented in Section 2.2.1. Pharmacokinetics data were not collected in Study EGF100151.

2.2.4.3 Does this drug prolong the QT or QTc interval? *(You must answer this question, unless this is addressed in the question above.)*

A thorough QTc study was not performed.

Review of the QT data for this submission was performed by the *CDER Interdisciplinary Review Team* (IDRT) for QT Studies. The entirety of the IDRT's review is Appendix 3 of this document. Sections 1.0 and 2.0 from this review are reproduced, below.

1.0 RECOMMENDATION

The Agency's analysis indicates a significant relationship between lapatinib concentration and the QTcF interval. Based on the pharmacokinetics, factors that could increase lapatinib concentrations, such as co-administration of CYP3A4 inhibitors, administration of drug with food, or administration to patients with hepatic impairment, would be expected to further prolong the QTc interval.

Based on these findings, the IRT recommends that the product label should be revised to include: (1) information on the risk of QT prolongation at the expected clinical concentrations of lapatinib, and (2) the potential for an increased risk of QTc prolongation as a result of factors that could increase lapatinib concentrations such as co-administration of CYP3A4 inhibitors, administration of drug with food, or administration to patients with hepatic impairment.

Please ask the Sponsor to submit ECGs related to study EGF10003 to the ECG warehouse.

2.0 SUMMARY OF FINDINGS

The QT prolongation potential of lapatinib was assessed as part of a phase 1 dose escalation study of lapatinib in advanced cancer patients. Eighty-one (81) patients received daily doses of lapatinib ranging from 175 mg/day to 1800 mg/day. Serial ECGs were collected on day 1 and day 14 to evaluate the effect of lapatinib on QT intervals. Review of the QT data indicated that 13 (of the 81) subjects were found to have either a QTcF duration > 480 msec or a QTcF prolongation of > 60 msec. According to the Sponsor, "independent review indicated that none of these abnormalities were clinically significant."

Mixed-effects modeling of the Fridericia corrected QT interval (QTcF) indicated a significant relationship between lapatinib concentration and the QTcF interval (p=0.04). Based on the model parameters, the predicted change in QTcF was estimated at peak concentrations following the recommended dose of lapatinib (1250 mg/day in combination with capecitabine).

- At the mean peak concentration (Cmax) of 3203 ng/ml following the 1250 mg daily dose, the predicted mean change in QTcF was estimated to be 13.5 msec.
- Using the upper 95% confidence limit of the slope estimate, the predicted QTcF prolongation at the mean Cmax was estimated to be 23.4 msec.

Additionally, factors that could increase lapatinib concentrations, such as co-administration of CYP3A4 inhibitors, administration of drug with food, or administration to patients with hepatic impairment, would be expected to further prolong the QTc interval.

The Sponsor did not submit related ECGs to the ECG warehouse; consequently, we are unable to verify that the QT measurements were made appropriately.

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

The relationship between dose-concentration and response is largely unknown. The currently recommended regimen was based on a maximum tolerated dose determined in small numbers of

patients. The dose limiting toxicities were grade 3 diarrhea and grade 3 rash. The efficacy of lower doses is unknown. Determination of an optimal dose is an unresolved dosing issue.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters? *(Provide tables to refer to in subsequent questions in this section.)*

The mass balance study, Study EGF10019, was the study with the most extended single dose sampling (168 h). This study was the only single dose study where sampling was "complete" – all subjects had one or more samples below the lower limit of quantitation by the end of the sampling period. Because of the extended sampling this study is potentially the best data to use in determining single dose pharmacokinetic parameters. However, the study was performed at a non-clinical dose (250 mg, the clinical dose is 1250 mg), with a suspension formulation, in only six subjects. For these reasons, the reviewer selects Study 10032, the only study performed at the approximate clinical dose in more than six patients and with 48 hour sampling, to determine pharmacokinetic parameters. The pharmacokinetic results of Study 10032 are presented below in **FDA Table 1.** The estimate of terminal half-life from Study 10032 (14.2 h) is consistent with that from Study EGF10019 (15.3 h).

FDA Table 1. Single Dose Pharmacokinetics, Study 10032

Parameter	Mean	StDev	%CV	Median	Range
Tmax (h)	NA	NA	NA	3.98	2 - 16
Vz/F_obs (L)	2279	1262	55	2007	415 - 5093
Cl/F_obs (L/h)	114	54	48	110	23 - 283
Terminal_phase_half-life (h)	14.2	5.5	38.5	12.5	8.6 - 33.4
Cmax (ng/mL)	1046	516	49	982	—
C_48h (ng/mL)	85	93	109	55	—

Subjects are cancer patients; n = 27 for all values
Dose was 1500.mg (clinical dose is 1250 mg)
Sampling was for 48 hours

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Studies in healthy subjects were limited to single doses of 250 mg or less; the sole exception being an ascending multiple dose study that used doses up to 175 mg QD (Study 10002). Doses less than or equal to 250 mg were used in only one study in cancer patients: Study 10003 included three patients that received a dose of 175 mg. Without performing analyses, the Applicant concluded that, "The pharmacokinetics of lapatinib in subjects with cancer at higher doses are consistent with its pharmacokinetics at lower doses in healthy subjects." The FDA

reviewer performed an analysis comparing the dose-normalized AUC of the three patients in Study 10003 to those receiving 175 – 250 mg in studies using tablet formulations with medium – high dissolution (Studies 10012, 10018 and 10024) and concludes that clearance in healthy subjects is 21- 39% greater than in patients. It should be emphasized that these calculations were made using data from only three patients.

2.2.5.3 What are the characteristics of drug absorption?

As food increased the AUC of a 1500 mg dose approximately 4-fold, it appears that the average absolute bioavailaiblity of lapatinib is 25% or less. Consistent with the low absorption and poor aquesous solubility of lapatinib, peak plasma concentrations do not occur until approximately 4h post-dose.

2.2.5.4 What are the characteristics of drug distribution? *(Include protein binding.)*

Distribution of lapatinib is influenced by very extensive binding to albumin and α1-acid glycoprotein. Plasma protein binding exceeded the limit of the radiochemical purity of the tracer to make distinctions; at concentration at and above 1 μM lapatinib was greater than 98.9% bound to human plasma proteins.

In spite of the high plasma protein binding, volume of distribution of the terminal phase was > 2200 L (see **FDA Table 1.**) -- much greater than body water.

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

> 2% of administered ^{14}C was recovered in urine, suggesting that the hepatic route is the primary route of elimination.

2.2.5.6 What are the characteristics of drug metabolism? *(This may include data on extraction ratio; metabolic scheme; enzymes responsible for metabolism; fractional clearance of drug.)*

Lapatinib undergoes extensive metabolism in humans to numerous oxidated and N- and O-dealkylated products. No single metabolite constitutes 15% or more of the total drug-derived excreted mass (see **FDA Table 2.**). The most prominent metabolites are the carboxylic acid GSK342393, and the O-dealkylated phenol GW690006. GW690006 undergoes sulfation as well as glucuronidation by UGTs 1A1, 1A3, 1A4, 1A8, 1A9 and 1A10. Relative to parent drug, GW690006 produced approximately equipotent inhibition of ErbB1-dependent tumor cell growth *in vitro*, but was approximately 100-fold less potent in ErbB2-dependent tumor cells. GSK342393 was found to be approximately 40-fold less potent than parent drug in both ErbB1- and ErbB2-dependent tumor cells. N-oxidation of the secondary aliphatic amine produced a cascade of about 8 metabolites present as less than 5% of drug-related material.

In experiments to determine the role of cytochromes P450 (CYPs) subtypes in metabolism, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5 recombinant enzymes were incubated separately at 150 pmol/mL with 2 µg/mL ^{14}C-GW572016 for 1 hour at 37° C and the incubations analyzed by HPLC with UV and radiochemical detection. Samples containing no NADP were included as negative controls for each of the enzyme systems. Metabolic viability for all of the enzymes was confirmed with CYP450 probe substrates with either fluorescence or HPLC/UV detection.

GW572016 metabolites were observed in CYP3A4, CYP3A5, CYP2C8 and CYP2C19 expressed microsomes, with metabolite peaks with areas of approximately 69%, 30%, 15% and 5% relative to that of parent, respectively (**FDA Table 2.**).

FDA Table 2. Applicant's Table 6 from Page 19 of RD2000/01947/00 00AVT0021

Table 6 **Percentage of GW572016 Metabolism in Recombinant Human CYP450 Enzymes**

Recombinant Human CYP450 Enzymes	Total % Peak Areas of GW572016 Metabolites [1]
CYP1A2	-[2]
CYP2C9	-
CYP2C19	5%
CYP2D6	-
CYP3A4	69%
CYP3A5	30%
CYP2B6	-
CYP2A6	-
CYP2E1	-
CYP2C8	15%

1. The percentage of metabolism was calculated by summing the % peak areas of the metabolites (NADP-dependent peaks) of GW572016 formed in each incubation.
2. No NADP-dependent peaks were observed.

These percentages are based upon based upon the relative areas of non-parent peaks in the radiochromatographs. The major NADP-dependent peak was at — minutes, a minor NADP-dependent peak at — minutes was observed in the CYP3A4 and CYP2C19 incubations. In the absence of NADP, no GW572016 metabolite peaks were observed in any of these enzyme systems.

In follow-up experiments, pooled human liver microsomes (0.4 mg/mL) were incubated with 0.31 µg/mL and 3.1 µg/mL GW572016 with and without the CYP3A4/5 probe substrate inhibitor, ketoconazole, for 1 hour at 37° C and the incubations were analyzed by HPLC with UV detection. Ketoconazole completely inhibited the formation of metabolite peaks at a concentration of 0.31 µg/mL, and 89% inhibition was observed at a GW572016 concentration of 3.1 µg/mL (**FDA Table 3.**; GW572016X is lapatinib (GW572016F) free base.). For reference, the observed average steady state Cmax in clinical studies was 3.2 µg/mL.

FDA Table 3. Applicant's Table 7 from Page 20 of RD2000/01947/00 00AVT0021

Table 7 Percentage of Inhibition of GW572016 Metabolism by Ketoconazole in Pooled Human Liver Microsomes

Sample	% Inhibition by Ketoconazole [1]
GW572016X (0.31 µg/mL)	100%
GW572016X (3.1 µg/mL)	89%
Midazolam (positive control)	96%

1. The percentage of inhibition of GW572016 metabolism, based on the reduction of GW572016X metabolite formation, is calculated as follows:

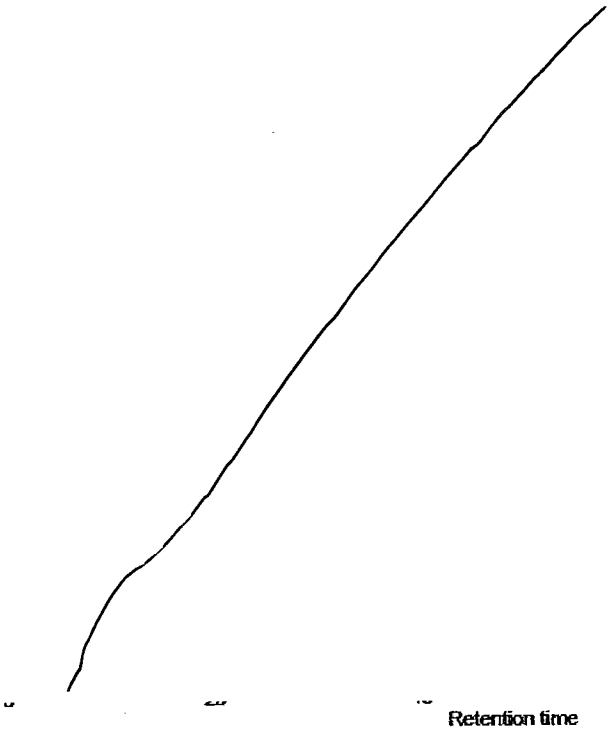
$$1 - \frac{\text{area of GW572016 metabolite peak in the presence of ketoconazole}}{\text{area of GW572016 metabolite peak in the absence of ketoconazole}} \times 100$$

Based on these data, the Applicant concludes that the major route of CYP450-mediated metabolism in humans is predicted to be CYP3A4 and CYP3A5 with minor contributions from CYPs 2C8 and 2C19.

The Reviewer finds these data incomplete because the % disappearance of parent drug is not reported. From a visual inspection of the chromatogram presented (**FDA Figure 2.**), it appears that the sum of the areas of the parent and metabolite peaks in the absence of ketoconazole (part A of the figure) approximates the area of the parent peak in the presence of ketoconazole (part B of the figure) (**FDA Figure 2.**). However, this interpretation does not allow a conclusion that ketoconazole inhibits all significant hepatic metabolism because, first, it relies on the assumption that the sensitivity of the analytical method for the metabolite is similar to that of the parent, and second, it relies on a crude visual analysis of the chromatogram.

FDA Figure 2. Applicant's Figure 5. from Page 25 of RD2000/01947/00 00AVT0021

Figure 5 **Representative HPLC-UV chromatograms of Pooled Human Liver Microsomes with 3.1 µg/mL GW572016X in the Absence (a) and presence (b) of Ketoconazole**



FDA Table 4. summarizes the results of the mass balance study. Sampling was performed for 168 hours and recovery of ^{14}C averaged 86%. Excretion was primarily via feces (all subjects excreted less than 2% of the administered ^{14}C in urine). The total amount of administered ^{14}C that was not accounted for as an identified moiety in excreta averaged 38%.

FDA Table 4. Recovery of lapatinib and metabolites following a single oral ^{14}C dose of 250 mg									
Subj	**Recovery of ^{14}C Total (% dose)**	**Recovery of ^{14}C in Feces (% dose)**	**Recovery of ^{14}C in Urine (% dose)**	**Recovery of Parent (GW572016) in Feces (% dose)**	**Recovery of GSK342393A in Feces (% dose)**	**Recovery of GW690006 in Feces (% dose)**	**Recovery of M2 in Feces (% dose)**	**Recovery of M3 in Feces (%dose)**	**Total unidentified (100% – sum of identified moieties) (% dose)**
Mean	86.34	85.22	1.12	30.11	14.61	5.34	6.65	5.74	37.56
1606									
1607									
1608									
1609									
1610									
1611									

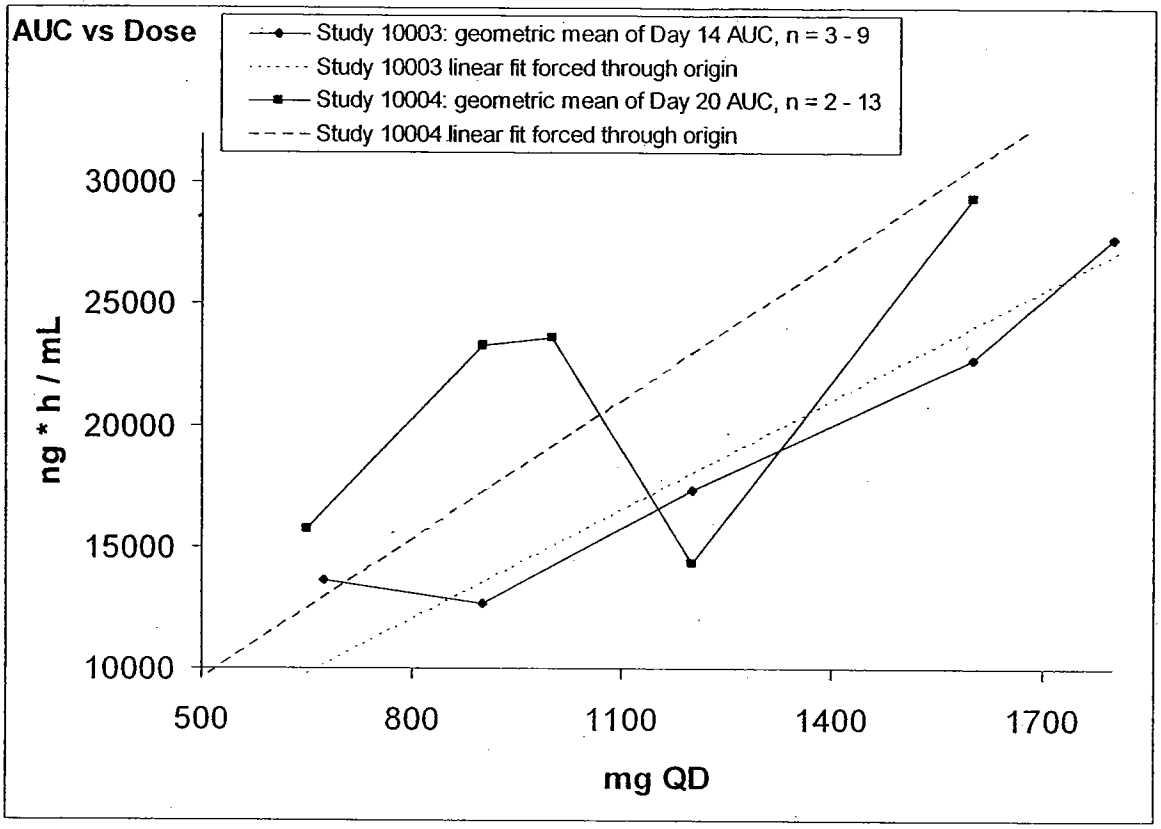
In the mass balance study, an average of 37% of the radioactive dose could not be attributed to the moieties identified (7th column of **FDA Table 4.**).

2.2.5.7 What are the characteristics of drug excretion?

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

Studies 10003 and 10004 were multiple dose studies that utilized clinical doses and included sampling for pharmacokinetics. The steady-state AUC data from these studies is presented in **FDA Figure 3.** While the data are variable (particularly in Study 1004), both studies support that pharmacokinetics are does-proportional.

FDA Figure 3. AUC versus Dose



The proposed package insert does not include dose frequencies other than QD, and the primary study supporting efficacy and safety were performed using only QD dosing. However, it is noteworthy that administration of the same total daily dose on a twice-daily schedule results in approximately 2-fold greater systemic exposure than a once daily schedule. The reason for increased bioavailability with more frequent dosing is uncertain, but may relate to overcoming the limits on absorption imposed by poor aqueous solubility, increasing luminal pH, and small intestinal residence time.

2.2.5.9 How do the PK parameters change with time following chronic dosing? *(This may include time to steady-state; single dose prediction of multiple dose PK; accumulation ratio.)*

The data in **FDA Figure 3.** appear to support that prolonged dosing results in an increase in AUC (compare Study 10003 with Day 14 AUC and Study 10004 with Day 20 AUC). The Applicant speculates that increases with exposure upon chronic dosing may be due to auto-inhibition of CYP3A4-mediated metabolism. The *in vitro* data supporting lapainib as a CYP inhibitor are presented in Section 2.4.2.3 of this review.

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

FDA Table 1. includes data on inter-individual variability. The sources of this variability are unknown, but, for those parameters that are a function of bioavailability, may relate to variability in absorption imposed by poor aqueous solubility.

2.3. Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

With the exception of hepatic impairment, no formal analyses of the effects of intrinsic factors on pharmacokinetics were performed. Pharmacokinetic data were not included in the primary efficacy and safety study (EGF100151).

In Study EGF100151 response rates were analyzed by age group (<65 years old, ≥65 years old). As the majority of subjects in both treatment groups were below 65 years of age (89%) no statistical comparison could be made but the data do not appear to indicate a difference between the age groups (**FDA Table 5.**)

FDA Table 5. Summary of Independent Review Panel-evaluated Time to Progression by Age

	< 65	≥ 65
n (capecitabine + lapainib / capecitabine)	44 / 64	5 / 8
Hazard Ratio (capecitabine + lapainib vs. capecitabine)	0.51	0.44
95% Confidence Interval of Hazard Ratio	0.35 - 0.74	0.15 - 1.33

Source: pages 369 - 370 of UM2004/00001/00 EGF100151

In Study EGF100151 response rates were analyzed by race. As the majority of subjects in both treatment groups were white (88%) there were too few subjects in other racial groups to draw any conclusions (**FDA Table 6.**).

FDA Table 6. Summary of Independent Review Panel-evaluated Time to Progression by Race

	White	Black	Asian	American Hispanic	Other
n (capecitabine + lapainib / capecitabine)	45 / 61	2 / 2	2 / 3	0 / 3	0 / 3
Hazard Ratio (capecitabine + lapainib vs. capecitabine)	0.51	0.59	0.8		
95% Confidence Interval of Hazard Ratio	0.34 - 0.74	0.08 - 4.48	0.14 - 4.65		

Source: pages 375 - 379 of UM2004/00001/00 EGF100151

The Applicant's examination of the combined data from all of the studies summarized in this document, which includes more than 300 females and 450 males suggests no obvious difference. Males were not studied in the primary efficacy and safety study.

An effect of renal impairment on pharmacokinetics is unlikely, given that less than 2% of an administered dose is eliminated by this route. Hemodialysis is unlikely to alter lapatinib concentrations as lapatinib has very high plasma protein binding.

The effect of hepatic impairment on the pharmacokinetics of lapatinib was assessed in Study EGF10014. Data were obtained from eight healthy controls, eight moderately impaired subjects, and 4 severely impaired subjects. Hepatic impairment was defined as

1. a known medical history of liver disease with or without a known history of alcohol abuse; and
2. previous confirmation of liver cirrhosis or chronic hepatitis transforming to cirrhosis by liver biopsy, or macroscopic evaluation by laparoscopy or CT scan or, at least, ultrasonography associated with an unambiguous medicalhistory; and,
3. Child-Pugh score of either 7-9 for classification as moderately impaired OR >9 for classification as severely impaired.

Moderate and severe impairment were associated with 14% and 63% increases in systemic exposure (AUC), respectively (**FDA Table 7.**).

FDA Table 7. Effect of Hepatic Impairment on PK Parameters			
	Non-impaired	Moderately Impaired	Severely Impaired
mean AUC (% of non-impaired)	100	114	163
%CV AUC	55	48	60
n	8	8	4
mean Cmax (% of non-impaired)	100	105	59
%CV Cmax	51	35	76
n	8	8	4
mean half-life (% of non-impaired)	100	114	297
%CV half-life	34	40	63
n	8	8	4

The Applicant modeled the changes in exposure due to hepatic impairment. In the model estimates are adjusted for age, sex, body mass index, AAG, and albumin (**FDA Table 8.**).

FDA Table 8. Applicant's Table 11.3 from page 117 of RM2006/00068/00 EGF10014

Table 11.3
Summary of the Ratios of AUCINF, Cmax, and Thalf for the Severely Hepatically Impaired vs. the Healthy Group and the Moderately Hepatically Impaired vs. the Healthy Group

Transformation: Log, 90% Confidence Interval

PK Parameter	Comparison	LS Mean Num.	LS Mean Denom.	Ratio	Confidence Interval
AUCinf (ng*h/mL)	Severe/Healthy	2754.72	1492.80	1.85	(0.47, 7.21)
	Moderate/Healthy	2328.34	1492.80	1.56	(0.73, 3.34)
Cmax (ng/mL)	Severe/Healthy	108.64	100.61	1.08	(0.27, 4.24)
	Moderate/Healthy	170.70	100.61	1.70	(0.79, 3.64)
T1/2 (h)	Severe/Healthy	21.21	13.65	1.55	(0.83, 2.91)
	Moderate/Healthy	13.10	13.65	0.96	(0.68, 1.36)

Estimates are adjusted for age, sex, body mass index, AAG, and albumin.

The changes in AUC due to hepatic impairment for the Applicant's model are greater than those in the Reviewer's unadjusted analysis. If dose adjustment is recommended using the model, dose would be a function of age, sex, body mass index, AAG and albumin. Given the paucity of data available, and a lack of information on how these factors may have contributed to pharmacokinetic changes in the efficacy and safety study, the Reviewer does not recommend this approach. Rather, adjustment based upon hepatic impairment without adjustment for the other factors in recommended (see section 2.3.2.6).

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Elderly

No dosage regimen adjustments are recommended.

2.3.2.2 Pediatric patients. Also, what is the status of pediatric studies and/or any pediatric plan for study?

We are unsure of the Applicant's plans for studying pediatric patients.

2.3.2.2 Gender

No dosage regimen adjustments are recommended.

2.3.2.4 Race

No dosage regimen adjustments are recommended.

2.3.2.5 Renal impairment

No dosage regimen adjustments are recommended.

2.3.2.6 Hepatic impairment

Based upon the 63% increase in AUC observed in subjects with hepatic impairment, we recommend that dose be reduced 40% in patients with severe hepatic impairment. As the package insert regimen is five 250 mg tablets given once daily and the pharmacokinetics are linear (Section 2.2.5.8) a 40% dose reduction is readily accomplished: three tablets can be given.

2.3.2.7 What pharmacogenetics information is there in the application and is it important or not?

Erb2 over-expression was an inclusion criteria for Study EGF100151.

In study EGF100151, archived tumor tissues were collected at screening for the detection of 4 ErbB/EGFR family members (ErbB1, ErbB2, ErbB3, and ErbB4), AKT and MAPK. Blood samples were collected for determination of levels of serum ErbB1 and ErbB2 at baseline, at the beginning of every 6-week cycle for the first 24 weeks, followed by every 12-weeks, and at discontinuation of study treatment. No assessment of the biomarker data from Study EGF100151

was conducted at the interim analysis which is the basis of the current NDA. Data are to be reported separately at a later date.

In both Study EGF20002 and Study EGF20008, paraffin sections from tumors were collected and analyzed by a central laboratory. In Study EGF20002, five of the six responders by investigator assessment had an ErbB2 expression level of 3+ by IHC, and one had an ErbB2 expression level of 1+ by IHC. Tumors from three of the responders were ErbB2 FISH positive. Three of the responders did not have an ErbB2 FISH assay performed. In Study EGF20008, all six responders by investigator assessment had an ErbB2 expression level of 3+ by IHC, and five responders were ErbB2 FISH positive. One of the responders did not have a FISH assay performed.

2.3.2.8 What pregnancy and lactation use information is there in the application?

There is no pregnancy and lactation use information in the application. There were no pregnancies reported during Study EGF100151.

2.3.2.9 Are there other human factors that are important to understanding the drug's efficacy and safety?

Though the assumption of proportional hazards was not met, a number of covariates which may be associated with the aggressiveness of individual subjects tumors were evaluated in a proportional hazards model. **FDA Table 9.** shows the only covariate tested that had a significant effect on the independently-assessed time to progression was the subjects' treatment group. No other baseline variables had significant effect on time to progression.

FDA Table 9. Applicant's Table 47 from page 62 of UM2004/00001/00 EGF100151

Table 47 Summary of Cox Proportional Hazards Regression Model for Independently Reviewed Time to Progression (ITT Population) Study EGF100151

Covariate	Effect Tested	Hazard ratio [95% CI][1]	P-value
Treatment group	lapatinib+capecitabine / capecitabine	0.47 [0.32, 0.68]	<0.001
Number of metastatic sites	≥ 3 sites / < 3 sites	0.98 [0.66, 1.46]	0.931
Stage of disease at screening	Stage IIIb or IIIc with T4 lesion / stage IV	0.86 [0.25, 2.91]	0.806
Stage of disease at screening	Visceral/ non-visceral	1.08 [0.68, 1.70]	0.744
ER/PR status	ER- Pr- / ER+ or Pr+	0.60 [0.21, 1.72]	0.345
ER/PR status	Unknown / ER+ or Pr+	1.06 [0.72, 1.56]	0.772
Time from last dose of trastuzumab to randomization	≤ 8 weeks / > 8 weeks	0.85 [0.58, 1.25]	0.418
Age	Trend per one year increase in age	1.01 [0.99, 1.02]	0.561
ECOG Performance status	0 / ≥1	0.79 [0.53, 1.16]	0.230
Number of previous chemotherapy regimens	≥3 or <3 regimens	0.84 [0.51, 1.39]	0.502

Data Source: Study EGF100151 Table 7.34

1. A hazard ratio of <1 indicates a lower risk.

FDA Table 10. shows the response rate by independent review by stratification factors.

FDA Table 10. Applicant's Table 48 from page 63 of UM2004/00001/00 EGF100151

Table 48 Summary of Best Response Evaluated by Independent Review Committee and by Stratification Factor (ITT Population) Study EGF100151

	Lapatinib+ Capecitabine N=163	Capecitabine N=161
Response rate (CR+PR)	36/163 (22)	23/161 (14)
Stage of disease at screening		
Stage IIIb or IIIc with T4 lesion	1/7 (14)	0/7
Stage IV	35/156 (22)	23/154 (15)
Site of disease at screening		
Visceral	26/116 (22)	19/118 (16)
Non-visceral	9/40 (23)	4/36 (11)
NA	1/7 (14)	0/7
Stage/site of disease		
Stage IIIb or IIIc with T4 lesion	1/7 (14)	0/7
Stage IV – visceral	26/116 (22)	19/118 (16)
Stage IV – non-visceral	9/40 (23)	4/36 (22)

Data Source: Study EGF100151 Table 7.17

2.4. Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

With the exception of food and drugs, no studies were conducted to assess correlations between extrinsic factors and the PK profiles or derived parameters for lapatinib.

2.4.1.1 Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

With the exception of food and drugs, which appear in other sections of this review, no dosage regimen changes are recommended.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an *in vitro* basis to suspect in vivo drug-drug interactions?

Yes. Section 2.2.5.6. discusses the ability of CYP P450 enzymes to metabolize lapatinib and Section 2.4.2.3 discusses the ability of lapatinib to inhibit CYP P450 enzymes.

2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

As discussed in section 2.2.5.6, lapatinib is primarily metabolized by CYP3A4 and CYP3A5, with smaller contributions from CYP2C8 and CYP2C19. There are no data indicating that metabolism is influenced by genetics.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

FDA Table 11. summarizes the *in vitro* data describing lapatinib as an inhibitor of CYP enzymes. *In vivo* experiments have not been performed.

FDA Table 11. Ability of lapatinib to inhibit CYP enzymes

	I/Ki, I/IC50 or I/(highest concentration tested)	Ki, uM	IC50 (if Ki not determined), uM	Highest concentration tested (if Ki & IC50 not determined), uM
CYP3A4	5.00	1.1	NA[1]	NA
CYP2C8	9.17	0.6	NA	NA
CYP1A2	0.47	ND[2]	ND	11.8
CYP2C9	0.47	ND	ND	11.8
CYP2C19	0.47	ND	ND	11.8
CYP2D6	0.47	ND	ND	11.8
UGT	0.47	ND	ND	11.8

[1]NA -- not applicable (a more complete characterization was performed)

[2]ND -- not determined

Lapatinib modestly inhibits its own *in vitro* metabolism by CYP3A4 (K_{INACT}= 0.031 min^{-1}, K_I = 29.2 μM). This is consistent with the increase in AUC seen with chronic dosing (see Section 2.2.5.9).

The PXR (pregnane X receptor) reporter gene assay for CYP3A induction was used to assess the ability of lapatinib ditosylate to induce CYP3A An EC50 value for lapatinib was calculated as 52.5 μM; this compares to EC50 values of 14.6 - 21.5 μM for the positive control rifampicin. This extent of activity in inducing CYP3A4 was not reflected in experiments conducted with primary cultures of human hepatocytes exposed to lapatinib (**FDA Table 12.**)

FDA Table 12. Induction of CYP enzymes by lapatinib *in vitro*						
	CYP3A4		CYP1A2		CYP2C9	
Agent	Rifampicin	Lapatinib (3 - 50 uM)	3-Methylchol - anthrene (3-MC)	Lapatinib (3 - 50 uM)	Rifampicin	Lapatinib (3 - 50 uM)
Catalytic activity	3.3-fold increase	30% decrease - 0.9 -fold increase	10-fold increase	(0.5 - 2.0) -fold increase	2.1-fold increase	40% decrease – 0.2-fold increase
mRNA expression	15-fold increase	(0.6 - 2.2) -fold increase	29-fold increase	20% decrease - 0.3-fold increase	2.9-fold increase	45% decrease – 0.1-fold increase

Based on the data in **FDA Table 12.**, the Reviewer agrees with the Applicant's assessment that lapatinib is unlikely to cause CYP induction to an extent that would result in significant drug interactions *in vivo*.

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

2.4.2.5 Are there other metabolic/transporter pathways that may be important?

Lapatinib is a substrate of the efflux transporters P-glycoprotein (Pgp, ABCB1), and breast cancer resistance protein (BCRP, ABCG2).

The efflux ratio for 3 μM lapatinib (human steady-state $C_{MAX} \approx 5.5$ μM) was 15.6 (i.e. >2, the acceptance criteria for Pgp substrate classification) and decreased to 0.33 in the presence of the Pgp inhibitor GF120918, consistent with lapatinib being a substrate for Pgp. The passive membrane permeability for 3 μM lapatinib was estimated to be 11.3 ± 0.2 nm/s ($P_{7.4}$ B→A + GF120918), supporting that lapatinib had low passive membrane permeability (criteria: low <50 nm/s, moderate 50 to 250 nm/s; high >250 nm/s) under the assay conditions.

FDA Table 13. summarizes the *in vitro* data describing lapatinib as an inhibitor of transport processes. *In vivo* experiments have not been performed.

FDA Table 13. Ability of lapatinib to inhibit transport processes			
Transporter	**Type of transporter**	**I/IC50**	**IC50 (Ki not determined), uM**
pGP/ABCB1	human P-glycoprotein	1.41	3.91
BCRP/ABCG2	murine breast cancer resistance protein	2.96	1.86
OATP 1B1	human organic anion transporting polypeptide	1.37	4.02
hOAT3	human organic anion transporter	0.18	30 µm inhibited 59.8%, for I/IC50 let IC50 = 30

As I/IC50 for pGP/ABCB1 is greater than 0.1, an *in vivo* drug interaction study with a P-gp substrate such as digoxin is recommended as a Phase 4 commitment.

2.4.2.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Lapatinib is administered with capecitabine. The potential for an interaction in subjects with cancer receiving capecitabine 1000mg/m2 twice daily and lapatinib 1250mg once daily was examined. However, the study was not powered to show equivalence between arms because the Applicant concluded that the high intrinsic variability of the regimen would require too many patients to determine equivalence.

Subjects enrolled into the PK portion of the study received lapatinib and capecitabine according to one of three randomly assigned sequences which are described in the Applicant's Tables 8 through 10, which are reproduced below as **FDA Table 14**.

FDA Table 14. Applicant's Tables 8 – 10 from pages of 35 – 36 of ZM2004/00055/00 EGF10005

Table 8 Dosing Sequence 1 and PK Sampling

Sequence 1								
	Cycle 1 Days 1-21				Cycle 2 Days 22-42			Day 43
Days	1-13	14	15-20	21	22-34	35	36-42	43+
Capecitabine	X	X	Off	Off	X	X	Off	Continue Treatment with Cycle 3
Lapatinib			X[c]	X	X	X[d]	X	Continue Daily Dosing
PK Sampling		X[b]		X[a]		X[ab]		

a Blood samples for lapatinib analysis (2 mL) obtained at: pre-dose, and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 hours post-dose.

b Blood samples for capecitabine and 5-FU analysis (2 mL) obtained at: pre-dose, and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, and 10 hours post-dose.

c Daily dosing of lapatinib to begin the morning of day 15 and continue until subject was discontinued from study.

d On PK sampling days when lapatinib was administered with chemotherapy, lapatinib administered just prior to the capecitabine

Table 9 Dosing Sequence 2 and PK Sampling

Sequence 2									
			Cycle 1 Days 8-28			Cycle 2 Days 29-49			Day 50
Days	1-6	7	8-20	21	22-28	29-41	42	43-49	50+
Capecitabine			X	X	Off	X	X	Off	Continue Treatment with Cycle 3
Lapatinib	X	X	X	X[c]	X			X	Continue Daily Dosing
PK Sampling		X[a]		X[a,b]			X[b]		

a Blood samples for lapatinib analysis (2 mL) obtained at: pre-dose, and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 hours post-dose.

b Blood samples for capecitabine and 5-FU analysis (2 mL) obtained at: pre-dose, and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, and 10 hours post-dose.

c On PK sampling days when lapatinib was administered with chemotherapy, lapatinib administered just prior to the capecitabine.

Table 10 Dosing Sequence 3 and PK Sampling

Sequence 3								
	Cycle 1 Days 1-21			Cycle 2 Days 22-42				Day 43
Days	1-13	14	15-21	22-34	35	36-41	42	43
Capecitabine	X	X	Off	X	X		Off	Continue Treatment with Cycle 3
Lapatinib	X	X[c]	X			X	X	Continue Daily Dosing
PK Sampling		X[ab]			X[b]		X[a]	

a Blood samples for lapatinib analysis (2 mL) obtained at: pre-dose, and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 hours post-dose.

b Blood samples for capecitabine and 5-FU analysis (2 mL) obtained at: pre-dose, and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, and 10 hours post-dose.

c On PK sampling days when lapatinib was administered with chemotherapy, lapatinib administered just prior to the capecitabine.

Following dosing with capecitabine, the AUCtau and Cmax of lapatinib increased 20% and 34%, respectively (**FDA Table 15.**). Following dosing with lapatinib, the Cmax for capecitabine was decreased 28%. The active capecitabine metabolite, 5-FU, reflected this behavior, with a 30% lower Cmax. However, the downstream metabolite FBAL showed no impact of lapatinib co-administration. As dose finding for the combination regimen was empirical, and clinical experience with alternative regimens is limited, the data do not support an alteration in dosing of the combination.

FDA Table 15. Applicant's Pharmacokinetic Synopsis Table from page 7 of ZM2004/00055/00 EGF10005

Title: A Phase I, Open-Label Pharmacokinetic Study of the Safety and Tolerability of GW572016 Daily in Combination with Capecitabine on a Three Week Schedule in Patients with Solid Tumors

Pharmacokinetics

Parameter	AUCtau[1], (h•µg/mL)	Cmax[1] (µg/mL)	tmax[2] (h)	tlag[2] (h)
Lapatinib				
Lapatinib	36.2 (23.4-56.0)	2.43 (1.57-3.77)	3.5 (2.0-10)	0.25 (0.0-0.75)
Laptatinib + Capecitabine	45.5 (32.7-63.2)	3.20 (2.40-4.28)	4.0 (0.5-10.17)	0.27 (0.0-1.5)
L+C versus L	1.20 (0.80-1.79)	1.34 (0.90-1.99)	-0.5 (-1.24-0.25)	0.13 (0.0-0.38)
Capecitabine				
Capecitabine	6.64 (5.56-7.93)	7.17 (5.16-9.96)	0.75 (0.25-3.0)	NA
Laptatinib + Capecitabine	6.71 (5.64-7.98)	5.87 (4.31-7.98)	1.0 (0.48-2.5)	NA
C+L versus C	0.96 (0.78-1.17)	0.72 (0.49-1.07)	0.13 (-0.13-0.5)	NA
5- Fluorouracil				
Capecitabine	0.697 (0.525-0.924)	0.472 (0.343-0.650)	0.75 (0.50-4.0)	NA
Laptatinib + Capecitabine	0.633 (0.520-0.772)	0.375 (0.274-0.512)	1.5 (0.48-3.0)	NA
C+L versus C	0.86 (0.71-1.05)	0.70 (0.51-0.95)	0.14 (-0.26-0.75)	NA
FBAL				
Capecitabine	20.4 (17.0-24.4)	4.17 (3.73-4.66)	2.0 (1.0-5.0)	NA
Laptatinib + Capecitabine	20.4 (16.3-25.5)	3.96 (3.38-4.65)	3.0 (1.5-5.0)	NA
C+L versus C	1.01 (0.91-1.12)	0.95 (0.86-1.04)	0.24 (-0.26-0.75)	NA

1. Geometric mean (95% confidence interval) for each treatment, geometric LS mean ratio (90% confidence interval) for treatment comparisons
2. Median (range) for each treatment, median difference (90% confidence interval) for treatment comparisons NA = not applicable

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

Because of the toxicities associated with the regimen, anti-diarrheals, therapy for rash, and anti-emetics are likely to be co-administered.

2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Yes, two *in vivo* drug interaction studies yielded positive results: co-administration of ketoconazole increased laptinib exposure and co-administration of carbamazepine decreased lapatinib exposure.

The ketoconazole study was an open-label, randomized, two-way crossover study in healthy adult subjects. The treatment sequences were allocated according to the following randomization schedule: AB or BA with Treatment A: lapatinib 100mg x 1 dose (AM dosing) and Treatment B: Ketoconazole 200mg X 2 (AM and PM dosing) for 7 days and 1 dose of lapatinib 100mg (AM dosing) on Day 4. Subjects fasted overnight prior to dosing. Each treatment period was separated by at least a 7-day washout period. On Day 4 of Treatment B, a single oral dose of lapatinib was co-administered with ketoconazole. Pharmacokinetic sampling was obtained over a 72h period in each treatment period.

Twenty healthy subjects completed the study. The results for lapatinib pharmacokinetics are shown below in **FDA Table 16.**

FDA Table 16. Applicant's Table 4 from page 32 of ZM2003/00053/00 EGF10013

Table 4 Pharmacokinetic Parameters for GW572016 when Administered Alone and in Combination with Ketoconazole (n= 20) in EGF10013

Parameter	Geometric Mean (95% CI)[c]		Treatment Comparison
	Alone	With Ketoconazole	
AUC(0-∞)[a] (ng•h/mL)	1429 (1198 – 1704)	5242 (4388 – 6263)	3.57 (3.15, 4.04)[d]
AUClast[a] (ng•h/mL)	1395 (1167 – 1667)	4918 (4164 – 5807)	3.43 (3.02, 3.89)[d]
Cmax[a] (ng/mL)	115 (101 – 130)	252 (210 – 301)	2.14 (1.80, 2.54)[d]
t½[a] (h)	9.55 (8.52 - 10.7)	16.0 (14.0 - 18.3)	1.66 (1.52, 1.81)[d]
tlag[b] (h)	0.25 (0.00 - 0.77)	0.25 (0.00 - 1.00)	0.12 (0.00, 0.13)[e]
tmax[b] (h)	4.0 (2.5 - 8.0)	4.0 (2.5 - 10.0)	0.75 (0.00, 1.50)[e]

Source Data: Table 14.3, 14.4, and 14.5
a Geometric mean (95% CI)
b Median (range)
c CI= confidence interval
d Geometric LS mean ratio (90% CI)
e Median difference (90% CI)

Ketoconazole increased AUC, Cmax, and half-life of lapatinib consistent with CYP3A4 inhibition.

The carbamazepine study was an open-label, fixed sequence, two-period crossover study. Each subject underwent two treatments; a single oral dose of lapatinib (250 mg) administered alone, followed by a 1-week washout period. In Session 2, each subject received carbamazepine 100 mg twice daily (BID) for Days 1 to 3 and carbamazepine 200 mg BID for Days 4 to 20. On the morning of Day 21, a single oral dose of lapatinib (250mg) was co-administered with a single oral dose of carbamazepine 200 mg. Subjects fasted overnight prior to dosing. A pharmacokinetic profile of lapatinib was obtained over 48h on Session 1 and Session 2 beginning on Day 21

Twenty-three healthy subjects completed the study. The results for lapatinib pharmacokinetics are shown below in **FDA Table 17.**

FDA Table 17. Applicant's Table 4 from page 41 of ZM2003/00530/00 EGF10018

Table 4 Pharmacokinetic Parameters for GW572016 when Administered Alone (n=24) and in Combination with Carbamazepine (n=23) in EGF10018

Parameter	Geometric Mean (95%CI)[a]		Treatment Comparison (n=23)
	Alone	With Carbamazepine[b]	
AUC(0-∞)[c] (ng•h/mL)	3526 (2888 – 4306)	984 (826 – 1171)	0.28 (0.24, 0.32)[e]
AUClast[c] (ng•h/mL)	3382 (2754 – 4152)	947 (791 – 1134)	0.28 (0.24, 0.32)[e]
Cmax[c] (ng/mL)	261 (209 – 327)	110 (90.5 – 134)	0.41 (0.35, 0.49)[e]
t½[c] (h)	10.2 (9.24 - 11.3)	9.98 (8.12 - 12.3)	0.98 (0.83, 1.15)[e]
tlag[d] (h)	0.12 (0.00 - 0.50)	0.25 (0.00 - 1.00)	0.00 (0.00, 0.13)[f]
tmax[d] (h)	4.0 (2.5 - 6.0)	3.0 (1.0 - 8.0)	-0.21 (-0.50, 0.52)[f]

Source Data: Table 14.3, Table 14.4, and Table 14.5

a CI= confidence interval

b Carbamazepine administered for 20 days before the Day 21 combination with GW572016

c Geometric mean (95% CI)

d Median (range)

d Geometric Least Square mean ratio (90% CI)

e Median difference (90% CI)

Lapatinib concentrations were decreased by pre-treatment with carbamazepine consistent with induction of CYP3A4. The lack of change in half-life suggests that the primary effect may have been on the bioavailability of lapatinib rather than on post-absorption clearance.

2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

No nonclinical pharmacodynamic studies have been performed to specifically evaluate possible interactions of lapatinib with other drugs that may be co-administered. Various *in vitro* assays have demonstrated lapatinib is a potent inhibitor of substrate phosphorylation catalyzed by both ErbB1 and ErbB2. Secondary pharmacology studies with lapatinib showed "no significant binding activity" at 33 pharmacological receptors and ion channels. However, the norepinephrine and dopamine re-uptake sites, L-type calcium and sodium (II) channel sites, and sigma receptors showed weak binding (with submaximal inhibition). In the case of the sigma receptor and sodium channel, experiments of functional activity in isolated tissue assays were performed and no changes due to lapatinib were observed.

Based on the data available the potential for pharmacodynamic drug interactions appears small.

2.4.2.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

Yes. The issue of potential unidentified metabolites, and the Reviewer's recommendation for a Phase 4 commitment, was described in Section 2.2.5.6. Second, the *in vitro* inhibition data presented in Section 2.4.2.3 demonstrates that the potential for lapatinib to cause metabolic drug interactions is not remote. We recommend a Phase 4 commitment to perform studies examining the ability of lapatinib to alter the metabolism of midazolam (a prototypic CYP3A4 substrate) and paclitaxel (a prototypic CYP2C8 substrate).

2.4.2 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

The clinical activity of lapatinib doses lower than 1250 mg is largely unknown. Thus, it is possible that a lower dose could provide less toxicity while retaining efficacy. However, the dose intensity for capecitabine was nearly identical on both arms of the study, indicating that the average contribution of lapatinib toxicity to the toxicity observed in the combination regimen was not large. The Reviewer concludes that, save the issues addressed in the Phase 4 commitments, there are no unresolved dosing regimen issues that represent a significant omission.

2.5. General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Lapatinib is a BCS Class 4 substance: Low Solubility - Low Permeability.

The highest dose strength of lapatinib is 250 mg. The solubility of lapatinib in 0.1 N HCl is 0.001 mg/L. As the 250 mg dose strength is not soluble in 250 mL, the drug substance is categorized as poorly soluble.

In an exploratory in situ study of permeability in an isolated segment of rat jejunum, using non radiolabeled lapatinib and monitoring only drug disappearance via LC/MS/MS, lapatinib appeared to be highly permeable. Due the low solubility of lapatinib fasted-state simulated intestinal fluid was utilised to evaluate higher concentrations of lapatinib (1, 5, 10, and 30 μM) with the same result, i.e. lapatinib appeared to be highly permeable. Lapatinib was stable in perfusion solution in the gastrointestinal tract and did not adsorb to the tubing during the perfusion. However, this experimental design did not address the mass balance or verify solubility and only measured the disappearance of lapatinib. This is likely the cause of the discrepancy with the in vitro studies in MDCKII-MDR1 cell monolayers that used radiolabel to determine mass balance and found that lapatinib has low membrane permeability. Consistent with the Applicant, the Reviewer concludes that lapatinib has poor permeability.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The to-be-marketed formulation was used in the pivotal clinical trial.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The effect of food was determined in a randomized 3-way crossover study in subjects with cancer receiving a single 1500mg dose of lapatinib ingested on three occasions, fasted, with a low-fat meal, and with a high-fat meal. The washout period between each treatment was at least 7 days. Blood samples were collected for pharmacokinetic analysis from predose to 48 hours post-dose.

The number of subjects who received each dose of investigational product in each period is summarized in **FDA Table 18.**

FDA Table 18. Derived from the Applicant's Table 5 on page 41 of ZM2005/00241/00 EGF10032

	Part 1		
	Treatment A lapatinib 1500mg/ Fasted	Treatment B lapatinib 1500mg/ High-fat Meal	Treatment C lapatinib 1500mg/ Low-fat Meal
No. Subjects Who Received Each Dose	27	27	26

Source Data: Tables 6.2, 6.3, and 6.4

The pharmacokinetics results are shown below in **FDA Table 19.**

FDA Table 19. Applicant's Table 13 from page 64 of ZM2005/00241/00 EGF10032

Table 13 Pharmacokinetic Parameters and AAG Concentration for Each Prandial Condition in EGF10032

Parameter	Fasted state	Low-fat meal	High-fat meal	Low-fat vs fasted	High-fat vs fasted
AUC_∞ (h•µg/mL)[1]	14.5 (11.8-17.8)	38.6 (32.6-45.8)	60.9 (50.2-74.0)	2.67 (2.26-3.16)[3]	4.25 (3.60-5.02)[3]
Cmax (ng/mL)[1]	937 (774-1135)	2377 (1958-2886)	2905 (2443-3454)	2.42 (2.02-2.90)[3]	3.03 (2.53-3.63)[3]
t½ (h)[1]	13.4 (11.7-15.3)	12.0 (10.9-13.3)	11.9 (10.4-13.6)	0.91 (0.82-1.02)[3]	0.92 (0.83-1.02)[3]
tmax (h)[2]	4 (2-16)	4 (2.5-24)	6 (2.5-12)	1.09 (0.50-2.00)[4]	2.53 (1.50-4.00)[4]
tlag (h)[2]	0.25 (0.0-0.5)	0.25 (0.0-0.5)	0.25 (0.0-2.0)	0.13 (0.00-0.13)[4]	0.13 (0.00-0.25)[4]
AAG (g/L)[2]	1.15 (0.56-2.14)	1.16 (0.46-2.54)	1.06 (0.45-2.25)	N/A	N/A

1. geometric mean (95% confidence interval)
2. median (range)
3. geometric LS mean ratio (90% confidence interval)
4. median difference (90% confidence interval)

In the pivotal safety and efficacy trial subjects were instructed to take the combination of the two medications in the morning and to be take the medications at two different times. Lapatinib was to be taken at approximately the same time each day, either 1 hour (or more) before breakfast or 1 hour or more) after breakfast. The capecitabine dose schedule was an intermittent regimen consisting of 2 weeks of daily treatment followed by a 1-week drug-free period. The starting A dose was to be taken twice daily, 12 hours apart, for 14 days, every 21 days. The morning dose was taken with food or within 30 minutes after a breakfast meal with approximately 200 mL of water. The capecitabine evening dose was taken approximately 12 hours after the morning dose and was taken with food or within 30 minutes after food, with approximately 200 mL of water.

These instructions are largely reflected in the proposed package insert. The reviewer recommends edits to assure that the language is clear (Section 3 of this review).

2.5.4 When would a fed BE study be appropriate and was one conducted?

Such a study would not be appropriate and was not conducted.

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

Dissolution specifications for this immediately released product will be determined by the Office of New Drug Quality Assessment.

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?

A single strength is being marketed.

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

The NDA is not for a modified release formulation of an approved immediate release product.

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either *in vitro* or in vivo data to evaluate BE?

Unapproved products or altered approved products were not used as active controls

2.5.9 What other significant, unresolved issues related to *in vitro* dissolution or in vivo BA and BE need to be addressed?

There are no other significant, unresolved issues related to *in vitro* dissolution or in vivo BA and BE.

2.5 Analytical section

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

In all studies save the mass balance study, only lapatinib was measured.

2.6.2 Which metabolites have been selected for analysis and why?

No metabolites were measured.

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

Total lapatinib was measured. Protein binding in humans was greater than could be measured with the radioactive purity of the ^{14}C-compound. If concentration-response were to be assessed, or therapeutic drug monitoring considered, it would be appropriate to measure free drug.

2.6.4 What bioanalytical methods are used to assess concentrations?

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

2.6.4.5 What is the QC sample plan?

Lapatinib concentrations measured in the 14 pharmacokinetic studies using four different methods. Each of these methods is summarized in the following sections, along with reference to the clinical studies they supported.

HPLC-MS/MS Method to Determine Lapatinib in Human Serum (1.02 to 1020 ng/mL)

The method for the determination of lapatinib in human serum was validated . This method was used to support lapatinib studies EGF10001, EGF10002, EGF10003, EGF10004 and EGF10008.

HPLC-MS/MS Method to Determine Lapatinib in Human Plasma (1 to 1000 ng/mL)

The method for the determination of lapatinib in human plasma was validated . This method was used to support lapatinib studies EGF10005, EGF10013, and EGF10018.

HPLC-MS/MS Method for Lapatinib in Human Plasma (1 to 1000 ng/mL)

The method for the determination of lapatinib in human plasma was validated

This method was used to support lapatinib studies EGF10012, EGF10019, and EGF10024.

HPLC-MS/MS Method for Determination of Lapatinib in Human Plasma (5 to 5000 ng/mL)

The method for the determination of lapatinib in human plasma was validated

This method was used to support lapatinib studies EGF10014, EGF10023, and EGF10032.

Summary of Within Study Quality Control Sample Analysis

Quality Control samples were analyzed with each batch of study samples against separately prepared calibration standards. Spiked duplicate standard curve and Quality Control samples were extracted daily to permit the determination of the concentration of lapatinib, and to monitor the day-to-day performance of the method, respectively. For the analysis to be acceptable to the Applicant, no more than one-third of the Quality Control sample results could deviate from the nominal concentration by more than 15%, and at least 50% of the results from each Quality Control concentration should be within 15% of nominal. All reported analytical data resulted from analyses that met these predefined analytical acceptance criteria. Quality Control results from each of the studies are summarised in **FDA Table 20**.

FDA Table 20. Applicant's Appenidx Table 4. from page 32 of 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Appendix Table 4 Between-run Accuracy and Precision of Quality Control (QC) Samples

Study (Protocol)	Total number of QC samples	Average overall precision (≤ %CV)	Accuracy (%bias range)
EGF10001	108	5.5	-1.1 to 6.9
EGF10002	112	11.8	0.4 to 5.3
EGF10003	348	6.1	-8.3 to 7.0
EGF10004	272	5.0	-10.9 to 10.6
EGF10008	97	5.2	-4.3 to 2.2
EGF10024	369	11.3	-4.3 to 0.0
EGF10019	24	7.2	-6.8 to 3.7
EGF10018	120	8.3	1.5 to 9.2
EGF10013	118	12.5	0.8 to 5.7
EGF10012	320	9.3	-1.3 to 6.8
EGF10005	126	10.0	1.4 to 5.7
EGF10032	129	6.9	-0.7 to 1.4
EGF10014	48	8.1	5.0 to 11.0
EGF10023	31	7.3	-3.6 to 1.6

The Applicant's criteria for acceptance of analytical runs is inconsistent with the FDA's May, 2001, Guidance for Industry *Bioanalytical Method Validation* which recommends that that "At least 67% (four out of six) of the QC samples should be within 15% of their respective nominal (theoretical) values; 33% of the QC samples (not all replicates at the same concentration) can be outside the ±15% of the nominal value." The Reviewer finds the data of sufficient quality to allow for interpretation of the studies performed and thus construction of the package insert and recommendation for Phase 4 commitments.

3 *Detailed Labeling Recommendations*

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17 Page(s) Withheld

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___✓___ Draft Labeling

_____ Deliberative Process

4 *Appendices*

4.1 Package insert (proposed)

4.2 Interdisciplinary Review Team for QT Studies (IDRT) Review

4.2 Cover sheet and OCPB filing/review form

Appendix 4.1 Package insert (proposed)

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Appendix 4.2 Interdisciplinary Review Team for QT Studies Review

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Appendix 4.3 Cover sheet and OCPB filing/review form

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Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-059	Brand Name	TYKERB™
OCPB Division (I, II, III, IV, V)	V	Generic Name	lapatinib
Medical Division	Drug Oncology	Drug Class	Kinase inhibitor
OCPB Reviewer	Gene M. Williams, Ph.D.	Indication(s)	in combination with capecitabine, for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 (ErbB2)
OCPB Team Leader	Brian Booth, Ph.D.	Dosage Form	250 mg tablet
		Dosing Regimen	1250 mg QD
Date of Submission	Sept. 13, 2006	Route of Administration	oral
Estimated Due Date of OCPB Review		Sponsor	GlaxoSmithKline
PDUFA Due Date	March 13, 2007	Priority Classification	1P
Division Due Date			

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	x			
I. Clinical Pharmacology				
Mass balance:	x	1		
Isozyme characterization:	x	4	4	
Blood/plasma ratio:				
Plasma protein binding:	x	1	1	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	7	4	
multiple dose:	x	1	0	
Patients-				
single dose:	X	2	2	
multiple dose:	X	4	4	
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	2	2	
In-vivo effects of primary drug:				
In-vitro:	X	1	1	
Subpopulation studies -				
ethnicity:				

gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	x	1	1	
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:	x	1		
alternate formulation as reference:	x	1		
Bioequivalence studies -				
traditional design; single / multi dose:	x	1		
replicate design; single / multi dose:				
Food-drug interaction studies:	x	2	1	
In-Vitro Release BE				
(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		20	15	

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	x	
Comments sent to firm?		
QBR questions (key issues to be considered)	Drug interactions, new drug as cause as well as victim	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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

/s/

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2/26/2007 12:53:18 PM
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Roshni Ramchandani
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Brian Booth
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