CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50760

MEDICAL REVIEW(S)

MEDICAL OFFICER'S REVIEW OF NEW DRUG APPLICATIONS
NDA 50-760 AMOXIL 200mg and 400mg SUSPENSIONS Q12 HOURS
NDA 50-761 AMOXIL 200mg and 400mg CHEWABLE TABLETS Q12 HOURS

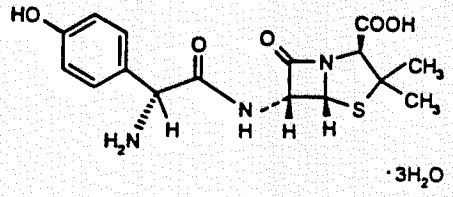
Applicant:
SmithKline Beecham Pharmaceuticals
One Franklin Plaza
Philadelphia, PA 19101

Contact:
Sharon Shapowal, R. Ph.
Associate Director, U.S. Regulatory Affairs
215-751-3468

Date submitted:	April 15, 1998
Date received by reviewer:	May 5, 1998
Review begun:	October 13, 1998
Review completed:	February 4, 1999

DRUG IDENTIFICATION

Generic Name:	amoxicillin
Trade Name:	Amoxil
Pharmacologic Class:	a semisynthetic penicillin-class antibiotic as a trihydrate
Dosage Form:	suspension, chewable tablets
Dose:	200mg/5mL and 400mg/5mL; 200mg and 400mg
Route of Administration:	oral
Chemical structure:	D-(-)-alpha-amino-p-hydroxybenzyl penicillin trihydrate.



Molecular formula and weight:
The amoxicillin molecular formula is $C_{16}H_{19}NO_5S.3H_2O$ and the molecular weight is 419.45.

PROPOSED LABELLING (taken from revised label received 1/21/99 by fax)

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

Medical reviewer's comments:
The applicant has not proposed any changes to the list of indications and microorganisms for which Amoxil is currently approved.

RELATED DRUGS

NDA 50-720 Augmentin 875mg tablets q 12 hours
NDA 50-725 Augmentin 200mg and 400mg oral suspensions q 12 hours
NDA 50-726 Augmentin 200mg and 400mg chewable tablets q 12 hours
NDA 50-754 Amoxil 500mg and 875mg swallow tablets q 12 hours

MATERIALS REVIEWED

Two volumes of the clinical data section were submitted for each NDA. The volumes contained the pharmacokinetic/ pharmacodynamic justification, the proposed label and 21 pharmacokinetic/pharmacodynamic references.

The final report for Study 2333/057, a bioequivalence study which compared the new Amoxil 400-mg swallow tablet, the new Amoxil 400mg/5mL suspension, and the approved Augmentin 400-mg/57mg/5mL oral suspension, was also reviewed.

LITERATURE REFERENCES

Craig, WA and Andes D. Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. Pediatr Infect Dis J. 1996: 15:255-9.

Craig WA. Pharmacokinetic/Pharmacodynamic Parameters: Rationale for Antibacterial Dosing of Mice and Men. Clin Infect Dis 1998:26:1-12.

Hyatt JM, McKinnon PS, Zimmer GS, and Schentag JJ. The Importance of Pharmacokinetic/ Pharmacodynamic Surrogate Markers to Outcome. Focus on Antibacterial Agents. Clin Pharmacokinetics 1995:28:143-160.

DRUG DEVELOPMENT AND REGULATORY BACKGROUND

March, 1992
Initial discussions took place between SB and the Division of Anti-Infective Drug Products of the Food and Drug Administration (FDA) regarding the development of q 12 hour dosing regimens for Augmentin.

May 27, 1993
Teleconference between the Dr. Rosemary Roberts, FDA primary medical reviewer (at the time), and SB to discuss the development of Augmentin for pediatric q 12 hour dosing. SB was advised that pharmacokinetic/pharmacodynamic data and the safety data from clinical trials in adults for lower respiratory tract infections (LTRI) (including

sinusitis), skin and skin structure infections (SSSI), and complicated and uncomplicated urinary tract infections (UTI) would suffice to register the Augmentin q 12 hour dosing products. Since acute otitis media is not a disease of adults, this indication would require a clinical study. Agreement was reached between SB and FDA that a single clinical-only study, without bacteriology, would be done for the acute otitis media indication.

May 31, 1996
Approval of NDA 50-725, 726 for Augmentin 7:1 formulations (suspension and chewable tablets) for pediatrics.

June 14, 1996
Proposal for Amoxil q12 hour dosing, similar to the one for Augmentin, was submitted in a letter to FDA.

July 17, 1996
Teleconference with FDA during which the acceptability of the rationale and the proposed development program was communicated to SB.

March 21, 1997
FDA requested inclusion of scientific rationale in the NDA to support the change in dosing schedule.

April 29, 1997
Teleconference between Sharon Shapowal, SB Regulatory Affairs, this medical officer and medical team leader, Brad Leissa to discuss filing of new Amoxil formulations. Dr. Leissa informed Ms. Shapowal that, in addition to the pharmacokinetic study, Chemistry and Manufacturing Controls data, proposed labelling, and the data pertaining to amoxicillin susceptible, non-beta-lactamase-producing pathogens from clinical trials conducted in support of NDAs 50-720, 50-725 and 50-726 for Augmentin should be summarized and submitted.

July 28, 1997
SB submitted a pivotal bioequivalence protocol 2333/057 entitled "A study to determine the bioequivalence of amoxicillin in novel chewable tablet and suspension formulations of Amoxil (400mg) to the standard marketed formulation of Augmentin (400/57mg) to support the Amoxil chewable tablets and suspension for q 12h dosing".

January 21, 1999
During a teleconference with S. Shapowal, SB Regulatory Affairs, the reviewer was advised by Ms. Shapowal that a revised label, incorporating the approved changes of NDA 50-754 (Amoxil 500mg and 875mg swallow tablets), had been prepared by SB. The reviewer requested and received a fax copy of this revised label.
Additionally, the reviewer inquired about outstanding chemistry (18-month stability data) and PK/PD data (dissolution data) and was informed that some data had been submitted to the Division.

BACKGROUND

Amoxil (amoxicillin) is a semisynthetic antibiotic, an analog of ampicillin, with broad-spectrum activity against many Gram-positive and Gram-negative bacteria. Amoxil has been approved since the 1970s and continues to be used to treat many common infections. Originally developed as an alternative to ampicillin, with the same desirable efficacy, its better safety and bioavailability profiles have resulted in fewer episodes of gastrointestinal disturbance, better patient tolerability, and higher serum and tissue concentrations. These higher serum and tissue concentrations correspond with less frequent dosing for amoxicillin. Amoxicillin bioavailability nearly identical to that in adults, has been demonstrated in infants and children.

Currently, the Augmentin (amoxicillin-clavulanate) 200-mg and 400-mg formulations are approved for q12 hour dosing for the treatment of specific infections caused by beta-lactamase producing organisms. The approval of these regimens was based on pharmacokinetic data that demonstrated bioequivalence between the adult and pediatric formulations.

NON-CLINICAL STUDIES

CHEMISTRY/MANUFACTURING CONTROLS

Eighteen-month stability data is still pending at this time. Please refer to review by Chemist, Andrew Yu, Ph.D.

ANIMAL PHARMACOLOGY/TOXICOLOGY

There were no new pharmacology/toxicology studies performed to support the proposed labelling changes; as such, no review was done by K. Seethaler, Ph.D.

MICROBIOLOGY

The application contains no microbiologic data; the applicant has referenced the microbiologic data in NDA 50-720 to support approval of these formulations. See Microbiology review by Sousan Altaie, Ph.D.

HUMAN PHARMACOKINETICS/PHARMACODYNAMICS

The bioequivalence study and the Biopharmaceutics reviewer's comments are summarized in this review. Please refer to full review by He Sun, Ph.D.

INTRODUCTION TO CLINICAL TRIALS

RATIONALE

The purpose of these applications is to seek approval for the q 12-hour regimen of Amoxil, which was designed to achieve enhanced dosing convenience and preserve the efficacy relative to the already established q 8-hour regimen. In addition, this change will result in conformity between the Amoxil and Augmentin dosing schedules.

The major benefit expected from the proposed q12 hour dosing regimen, is the possibility of improved patient compliance, while providing efficacy equivalent to the Amoxil regimens dosed q8 hours. It is expected that the safety and efficacy profile of the twice-daily regimen should be comparable to that of the thrice-daily regimen. The Amoxil q12 hourly regimen is expected to exhibit efficacy similar to that of the Augmentin q12 hourly regimen against non beta-lactamase producing pathogens.

The applicant is convinced that the benefits of improved compliance outweigh the risk of a potential diminished efficacy from the slightly lower T>MIC for Amoxil q12 hour dosing regimens for pathogens of low MIC. An overall improvement in the risk-benefit ratio between the q12-hour and q8-hour Amoxil regimens is expected.

The rationale given to register the new Amoxil q12 hour formulations is the same that used to gain approval for the Augmentin q12 hour formulations in 1996. It is anticipated that since the disease processes are similar in adults and children, the results of clinical studies conducted for the approved indications for Augmentin should be applicable to the indications being sought in NDAs 50-760 and 50-761.

NDAs 50-760 and 50-761 focus on novel formulations for Amoxil chewable tablets and Amoxil oral suspensions. The sponsor believes that, given the linear kinetics of the amoxicillin, the results of the bioequivalence study with the Amoxil 400mg formulations should be sufficient to register the novel amoxicillin-200mg chewable tablet and amoxicillin 200mg/5mL oral suspension formulations.

Primary Objective

The purpose of these NDAs is to seek marketing approval for two new q12 hour dosing regimens for Amoxil for pediatric patients; the first regimen, Amoxil 200 mg q12 hours, is an alternative to the currently approved dose of 125 mg q 8 hours, and the second, Amoxil 400 mg q12 hours, is an alternative to the currently approved dose of 250 mg q 8 hours. Both dosing regimens will be available as chewable tablets and suspensions.

HUMAN PHARMACOKINETICS/PHARMACODYNAMICS

Study 2333-057: "A study to determine the bioequivalence of amoxicillin in novel chewable tablet and suspension formulations of Amoxil (400mg) to the standard marketed formulation of Augmentin (400/57mg) to support the Amoxil chewable tablets and suspension for q 12h dosing".

This single dose, randomized, open-label, 3-part crossover study was conducted in the US. Each subject received a dose of Amoxil chewable tablet, Amoxil oral suspension, and the currently approved and marketed Augmentin suspension. Each dose was given concurrent with a light breakfast after an overnight fast, at least 3 days apart. Volunteers could not ingest anything other than water for 3 hours after the dosing.

Primary Objective	to demonstrate the bioequivalence of Amoxil 400mg chewable tablet and Amoxil 400mg/5mL oral suspension to Augmentin 400/57mg/5mL oral suspension
Study drug	Amoxil 400mg chewable tablet; Amoxil 400mg/5mL oral suspension; Augmentin 400mg/57mg/5mL oral suspension (reference formulation), a single dose of each, at least 3 days apart
Labs/follow-up	Blood specimen collection 0 (baseline), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 12 hours after dosing
Patient Population-enrolled Evaluable	27 healthy males and females;19-58 years of age 24
Primary parameters	AUC $_{(0\text{-inf})}$; C_{max}

Medical reviewer's comments:
The applicant has concluded that, given the established linear pharmacokinetics of amoxicillin, the results of this study with Amoxil the 400mg formulations should be sufficient to register the new Amoxil 200mg formulations also. Therefore, no clinical trial data were collected with the new Amoxil 200mg chewable tablet and 200mg/5mL oral suspension.

RESULTS

Of 27 subjects enrolled, 1 was withdrawn before dosing because of a vasovagal response during cannulation. Two subjects withdrew, for personal reasons, after the first dose of study drug. The results in the following tables are based on 24 subjects who completed all study periods.

Table 1. Amoxicillin Pharmacokinetic Parameter Estimates after the oral administration of three different dosage forms

Parameter	Amoxil chewable tablets 400mg	Amoxil Suspension 400mg/5mL	Augmentin Suspension 400mg/57mg/5mL
AUC (0-infinity) (μg.h/mL)	17.9 (2.4)	17.1 (3.1)	18.0 (3.1)*
C_{max} (μg/mL)	5.2 (1.6)	5.9 (1.6)	5.6 (1.5)
Tmax (hours)**	1.5 (0.5 - 4)	1.0 (1 - 4)	1.3 (0.5 – 3)

Data presented as mean (+/- SD) for n=24 and represent amoxicillin values
* n=23, one patient was excluded due to inability to calculate AUC (0-infinity) and t1/2 with this formulation
** Data presented as median (range)

Safety
There were no reports of deaths or serious adverse experiences.

Table 2. Treatment emergent adverse experiences

Adverse experience	Amoxil chewable tablet 400mg	Amoxil suspension 400mg/5mL	Augmentin suspension 400mg/57mg/5mL
Subjects exposed	24	25	25
Headache	7	4	6
Nausea	0	0	2
Vomiting	0	0	1
Pharyngitis	0	0	1
Diarrhea	0	2	0
Cystitis	0	1	0
Conjunctivitis	1	0	0
Purpura	1	0	0
Toothache	1	0	0
Number with AE	9	6	7

Medical reviewer's comments:
1. Based on the results of study 2333-057, the Biopharmaceutics reviewer has concluded that:

a) Both the novel chewable tablet and suspension formulations of Amoxil 400mg are bioequivalent to the amoxicillin component of the standard marketed formulation of Augmentin 400mg/57mg/5mL. Although bioequivalence between the chewable and suspension formulations of Amoxil was not demonstrated, these results are acceptable because each of the new 400mg formulations was bioequivalent to the reference, Augmentin suspension.

b) An in vivo *study of the lower strength (200mg) formulations was waived because the 200mg and 400mg formulations are proportional in formulation ingredients.*

c) The dissolution studies for the Amoxil 200mg and 400mg formulations are acceptable.

d) The label should include language to reflect that food effect studies for each formulation, although recommended by the Biopharmaceutics reviewer, were not performed.

2. Headache was the most frequently reported adverse event, occurring with similar frequency across the 3 study groups. Other adverse events were reported infrequently.

EFFICACY STUDIES

Using the same rationale that was applied to win approval of the Augmentin pediatric q 12-hour dosages, that is, the results of clinical studies in adults would equally apply to children, no clinical efficacy studies in pediatric patients were submitted to support these applications. The applicant has referenced the bacteriologic efficacy data from clinical studies submitted in NDA 50-720 (Augmentin q 12 hours). The applicant notes that, in these trials, there was no difference overall in the bacteriologic efficacy seen between the Augmentin q8 hour and q12 hour dosing regimens in patients with beta-lactamase negative organisms (where clavulanate would not be expected to make a difference in the bacteriologic outcome).

As LRTI, UTI (complicated and uncomplicated), and SSSI are similar diseases in adults and children, these data, are applicable to pediatric patients. The tables and data which follow were taken from the medical officer, Dr. Alex Rakowsky's review of NDA 50-720 for Augmentin q 12 hours in adults and summarize the results of Augmentin q8 hours vs. Augmentin q 12 hours for the eradication of beta-lactamase negative organisms.

Bacteriologic Efficacy data from Augmentin Clinical studies, NDA 50-720. Protocol 25000/231

Comparison of the safety and efficacy of Augmentin 500/125mg po q 12 hours vs. Augmentin 250/125 mg po q 8 hours in the treatment of uncomplicated skin and skin structure infections

In his review of NDA 50-720 in 1996, Dr. Rakowsky defined the follow-up visit as the test-of cure-visit for the bacteriologic response, and patients in foreign studies who had confirmation of pre-therapy organisms at a local lab were included in the FDA evaluable population. This accounted for the differences in the numbers of pathogens considered for efficacy when compared with the applicant's results.

Table Bacteriologic Efficacy by specific organism at the follow-up visit--Beta-lactamase-negative organisms

Pre-therapy organisms	Augmentin 250-mg q 8h		Augmentin 500-mg q 12h	
	n/N	%	n/N	%
S. aureus	8/14	57.1	12/17	70.6
Streptococcus Group A	4/8	50	5/5	100
S. viridans	2/3	66.7	2/3	66.7
Enterococcus	1/2	50	2/4	50
E. coli	2/3	66.7	4/5	80

Medical reviewer's comments:
At a dose of Amoxil 500-mg q12 hours, the results from the medical officer's review showed lower success rates when compared with the applicant's results; however, the number of pathogens is small.

Protocol 25000/233

Comparison of the safety and efficacy of Augmentin 875/125mg po q 12 hours vs. Augmentin 500/125 mg po q 8 hours in the treatment of complicated urinary tract infections and pyelonephritis

The medical reviewer, Dr. Rakowsky, accepted any visit greater than 4 days after the completion of study therapy as the first follow-up visit, and the test-of-cure visit. Therefore, depending on the protocol, the results in the table below represent patients who had the first follow-up visit at 5-9 days post-therapy and 2-4 weeks after the completion of therapy.

Table Pre-therapy ampicillin-susceptible uropathogens at first follow-up– Beta-lactamase-negative organisms

Pre-therapy organisms	Augmentin 500-mg q 8h		Augmentin 875-mg q 12h	
	n/N	%	n/N	%
E. coli	31/57	54.4	30/58	51.7
P. mirabilis	2/4	50	2/2	100
Enterococcus spp.	5/8	62.5	4/7	57.1

Medical reviewer's comments:
In general, the bacteriologic efficacy results for Augmentin 875-mg q 12h from the medical officer's review were lower than those from the applicant's analysis, especially for E. coli. *As with the results of study 25000/231 for skin and skin structure infections, the numbers of* P. mirabilis *and* Enterococcus spp. *are small.*

Protocol 25000/234

Comparison of the safety and efficacy of Augmentin 875/125mg po q 12 hours vs. Augmentin 500/125 mg po q 8 hours in the treatment of lower bacterial respiratory infections.

(Results taken from Medical review by Alex Rakowsky)

Tables Bacteriologic successes at the End of Therapy by Beta-lactamase-negative Pre-therapy Organism (Per Protocol bacteriologically evaluable population)

Community Acquired Pneumonia

Pre-therapy organisms	Augmentin 500-mg q 8h		Augmentin 875-mg q 12h	
	n/N	%	n/N	%
S. pneumoniae	23/25	92	22/23	95.6
H. influenzae	14/15	93.3	13/20	70
M. catarrhalis	1/1	100	3/3	100
S. aureus	1/1	100	1/1	100

Acute Exacerbation of Chronic Bronchitis

Pre-therapy organisms	Augmentin 500-mg q 8h		Augmentin 875-mg q 12h	
	n/N	%	n/N	%
S. pneumoniae	10/13	76.9	6/7	85.7
H. influenzae	7/12	58.3	11/14	78.6
M. catarrhalis	1/1	100	3/3	100
S. aureus	0/1	0	2/2	100

Medical reviewer's comments:
When compared with those of the applicant, the reviewer's bacteriologic efficacy results for Augmentin 875-mg q 12h were lower for S. pneumoniae *and* H. influenzae.
No data were provided for infections of the upper respiratory tract, but the pathogens are the same as those seen in lower respiratory tract infections.

CONCLUSIONS

1. *The results of study 2333/057, the bioequivalence study in adults, have shown that the new Amoxil 400-mg chewable tablet and Amoxil 400-mg suspension are bioequivalent to the amoxicillin component of the marketed Augmentin 400-mg/5mL suspension. Because the two formulations are similar in formulation constitutes, an in vivo study of the lower strength formulations was not needed. The results of this study with Amoxil 400-mg suspension and chewable tablets should be sufficient to register the new Amoxil 200-mg chewable tablet and 200-mg/5mL oral suspension also.*

2. *There were no significant differences in adverse events amongst the groups.*

3. *The microbiologic data from NDA 50-720, for the treatment of beta-lactamase-negative organisms in adult infections, are acceptable to support the requested claims in pediatric patients.*

RECOMMENDATIONS

1. *Pending the results of 18-month stability data, NDAs 50-760 and 50-761, which seek to register the new Amoxil 200-mg and 400-mg chewable tablets and oral suspension q12 hours, are recommended for approval for the indications currently listed in the approved Amoxil label.*

2. *The remarkable labelling revisions are outlined below.*

Redacted 3

pages of trade secret and/or confidential commercial information

/S/

Mamodikoe Makhene, M.D.
Medical Officer/HFD-520

cc:
Original ~~IND~~ NDA
HFD-520
HFD-520/DepDir/LGavrilovich
HFD-520/MO/MMakhene
HFD-520/Pharm/KSeethaler
HFD-520/Micro/SAltaie
HFD-880/Chem/AYu
HFD-520/Biopharm/HSun
HFD-520/PM/JCintron

Concurrence Only:
HFD-520/DivDir/GChikami
HFD520/TmLdrMO/MAlbuerne
4/15/99
NDA 4/5/99

HFD-520 Trostle

JAN 25 1999

Joint Medical/Microbiology Consultation

NDA 50-542 Amoxil® (amoxicillin) capsules, powder for oral suspension and chewable tablets
NDA 50-754 Amoxil® (amoxicillin) tablets
NDA 50-760 Amoxil® (amoxicillin) for oral suspension
NDA 50-761 Amoxil® (amoxicillin) chewable tablets

Date Consult Received:	12/16/98
Consulting Division:	Division of Anti-Infective Drug Products
Sponsor:	SmithKline Beecham Pharmaceuticals
Drug Name:	Amoxil® (amoxicillin)
Category:	β-Lactam
Date Consultation Received:	December 16, 1998
Date Review Started:	January 20, 1999
Date Review Completed:	January 20, 1999

Regulatory Background

Currently approved NDAs include 50-542 and 50-754. Two NDAs (50-760 and 50-761) were submitted on April 15, 1998 and are currently under review in DAIDP. These submissions propose a change in the dosing regimen of amoxicillin from thrice daily to twice daily in pediatric patients and provide for new strength of chewable tablets and oral suspension. The new Amoxil suspension and chewable tablets are matched in amoxicillin content to the Augmentin (amoxicillin/clavulanate potassium) suspensions and chewable tablet formulations previously approved for q 12h dosing.

All current formulations of Amoxicillin are described in a single package insert. This package insert was recently revised (Please refer to Medical Officer's labeling review of NDA 50-542/S-011 that was submitted on October 6, 1997) to include information on the approved 14-day triple therapy regimen that includes lansoprazole 30 mg bid, clarithromycin 500 mg bid, plus amoxicillin 1 gram bid and the dual therapy 14-day regimen including lansoprazole 30 mg tid plus amoxicillin 1 gram tid. Subsequently, DSPIDP has approved two 10-day triple therapy *H. pylori* regimens that contain amoxicillin: Lansoprazole 30 mg bid + Clarithromycin 500 mg bid, + Amoxicillin 1 gram bid, and Omeprazole 20 mg bid + Clarithromycin 500 mg bid, + Amoxicillin 1 gram bid. The Amoxicillin label does not include recent changes incorporated into the clarithromycin, omeprazole, and lansoprazole labels which address these two 10-day PPI-based regimens.

Purpose of Consultation

The purpose for the consultation is "to revise the currently approved labeling for adequacy of the *Helicobacter pylori* sections".

Conclusions

Reviewer Comments: *There are four sections of the current amoxicillin label that contains information on H. pylori:* **CLINICAL PHARMACOLOGY,** *subsection* **Microbiology, INDICATIONS AND USAGE** section, **PRECAUTIONS,** *subsection* **Adverse Reactions, DOSAGE AND ADMINISTRATION** *section, and* **CLINICAL STUDIES** *section. These sections should be revised to update the AMOXIL label*

so that it is consistent with recently approved clarithromycin, omeprazole and lansoprazole labels. Changes that should be incorporated are described below. The data used to revise the Amoxil label was taken directly from the clarithromycin, lansoprazole, and omeprazole package inserts.

CLINICAL PHARMACOLOGY Section, Microbiology Subsection

Reviewer Comment: The subsection **"Susceptibility for *Helicobacter pylori*"** *should be revised as follows:*

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

Recommendation
The Sponsor should be made aware of the proposed labeling changes as suggested above.

/S/

Robert J. Hopkins M.D., M.P.H., & T.M.
Medical Team Leader, DSPIDP

/S/

Shukal Bala Ph.D.
Acting Microbiolgy Team Leader, DSPIDP

Concurrence
HFD-590/DepDivDir/RAlbrecht (for) 1/25/99

cc: Original NDAs
HFD-520 files
HFD-590 files
HFD-520/PM/Strostle
HFD-590/PM/RAnderson
HFD-530/Micro/SAltaie
HFD-520/TL/MAlbuerne
HFD-590/MO/RHopkins
HFD-520/CPMS/Jbona
HFD-590/DepDivDir/RAlbrecht
HFD-590/Div.Dir./MGoldberger
HFD-520/Act.Div.Dir./GChikami