



PHILIP MORRIS
U.S.A.
RICHMOND, VIRGINIA

March 9, 2001

Covance Laboratories Inc.
3301 Kinsman Boulevard
Madison, WI 53704

**Re: Amendment No. 1 to the Research Services Agreement Between
Covance Laboratories Inc. and Philip Morris Incorporated, dated October 17, 2000**

Gentlemen:

Covance Laboratories Inc., ("CONSULTANT") and Philip Morris Incorporated ("COMPANY") have entered into a Research Services Agreement effective October 17, 2000 (the "Agreement"). Pursuant to Article 20, CONSULTANT and COMPANY agree to amend the Agreement as follows, effective as of March 1, 2001:

1. Article 1, Scope of Services and General Obligations, ATTACHMENT A, shall be replaced in its entirety by the revised Attachment A attached to this Amendment.
2. Article 2, Term of Agreement, shall be amended to extend the term of the Agreement until June 30, 2001.
3. Article 3, Compensation, first paragraph, (ii), shall be replaced with the following:
(ii) pay CONTRACTOR, upon completion of the method development, the remaining fifty percent (50%) of the total cost of the services specified in Attachment A for the method development within thirty (30) days of receipt of CONTRACTOR's invoice, said amount not to exceed ONE HUNDRED NINETEEN THOUSAND AND NINETY-SIX DOLLARS AND FIFTY CENTS (119,096.50).
4. Article 3, Compensation, first paragraph, (iv), shall be replaced with the following:
(iv) pay CONTRACTOR upon completion of the method development, an advance payment of ONE HUNDRED THIRTY THOUSAND AND SIX HUNDRED AND NINETY DOLLARS AND FIFTY CENTS (\$130,690.50) representing fifty percent (50%) of the total cost of the validation services specified in the Supplement to Attachment A;
5. Article 3, Compensation, first paragraph, (v), shall be replaced with the following:
(v) pay CONTRACTOR upon completion of the validation services, the remaining fifty percent (50%) of the total cost of the services specified in

Attachment A for the validation of methods, said amount not to exceed ONE HUNDRED THIRTY THOUSAND AND SIX HUNDRED AND NINETY DOLLARS AND FIFTY CENTS (\$130,690.50).

6. Article 3, Compensation, first paragraph, delete the word "and" before (vi) and add the following after the semicolon at the end of item (vi):

(vii) pay CONTRACTOR FIFTEEN THOUSAND DOLLARS (\$15,000.00) for Advertising Expenses as specified in Attachment A; and (viii) pay CONTRACTOR SIXTY FIVE THOUSAND AND ONE HUNDRED AND TWENTY-ONE DOLLARS (\$65,121.00) for Miscellaneous Expenses outlined in Attachment A upon receipt of detailed invoices.

7. Article 3, Compensation, first paragraph, last sentence, shall be replaced with the following sentence:

Notwithstanding the foregoing, COMPANY shall not be obligated to make any payments under this Agreement in excess of an aggregate amount of FIVE HUNDRED AND SEVENTY THREE THOUSAND AND FOUR HUNDRED AND FIVE DOLLARS (\$573,405.00), unless COMPANY specifically so agrees in writing.

If Covance Laboratories Inc. is in agreement with this amendment, please so indicate by having an authorized representative of Covance Laboratories Inc. sign both originals of this letter and return one of them to me.

In all other respects, the Agreement shall remain in full force and effect.

Sincerely yours,

PHILIP MORRIS INCORPORATED

By: _____



Richard P. Solana, Ph.D

Vice President, Worldwide Scientific Affairs

Accepted and agreed
as of the date of this letter:

COVANCE LABORATORIES INC.

By: _____

Printed

Name: _____

Title: _____

ANALYTICAL ELEMENTS OF THE TOTAL EXPOSURE PILOT STUDY

Determination of Nicotine and Metabolites in Human Urine (Revised)

It is proposed that the determination of nicotine, cotinine, 3-hydroxycotinine and their respective glucuronides in human urine will be performed at Covance Harrogate (UK). An additional week has been added to method development to cover any unforeseen circumstances.

Analysis will be developed and validated using the following cost structure estimate:

4 weeks development/feasibility @ £6,660 (\$9,790) per week	£26,400 (\$38,808)
Method validation	£25,000 (\$36,750)

Haemoglobin adducts of 3- and 4-aminobiphenyl (Revised)

It is proposed that the analysis of 3- and 4-aminobiphenyl adducts of haemoglobin will be performed at Covance Harrogate (UK). An additional week has been added to method development to cover any unforeseen circumstances.

5 weeks establishment @ £6,660 (\$9,790) per week	£33,000 (\$48,510)
Method validation	£23,400 (\$34,398)

11-dehydro-thromboxane B₂ (Revised)

Covance Harrogate (UK) was requested to terminate validation work on thromboxan B₂ and validate 11-dehydro-thromboxane B₂.

Validation of thromboxane B ₂	£3,000 (\$4,410)
Validation of 11-dehydro-thromboxane B ₂	£15,000 (\$22,050)

8-epi-prostaglandin F2 Alpha

It is proposed that the analysis for 8-epi-prostaglandin F2 alpha be performed in Covance Harrogate (UK).

Method development and validation	£6,600 (\$9,702)
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Determination of Malondialdehyde in Plasma and Urine (Addition)

It is proposed that the determination of malondialdehyde in human urine will be performed at Covance Harrogate (UK).

Analysis will be developed and validated using the following cost structure estimate:

3 weeks development/feasibility @ £6,660 (\$9,790) per week	£19,980 (\$29,371)
Method validation (£10,400/matrix)	£20,800 (\$30,576)
Audit of subcontractor facility	£8,500 (\$12,495)

Determination of Caffeine and Metabolites in Urine (Addition)

It is proposed that the determination of caffeine and metabolites will be performed at Covance Madison (US).

2 weeks method development @ \$10,000 per week	\$20,000
Method validation	\$20,000

Acetonitrile in Exhalate

It is proposed that the analysis of acetonitrile in exhaled air will be performed at Covance Madison (US).

Analysis will be developed and validated using the following cost structure estimate:

Estimated cost for method development:	\$30,000
Estimated cost for method validation:	\$30,000

Acetonitrile in blood

It is proposed that the analysis of acetonitrile in blood will be performed at Covance Madison (US).

Analysis will be developed and validated using the following cost structure estimate:

Estimated cost for method development:	\$25,000
Estimated cost for method validation:	\$10,000

NNAL and NNAL-glucuronide in Human Urine

It is proposed that the analysis of NNAL and NNAL-glucuronide will be performed at Covance Madison (US).

Analysis will be developed and validated using the following cost structure estimate:

Method development/establishment	\$34,000
Method validation	\$51,000

The above price estimates do not include costs associated with any required custom syntheses for analytical standard materials. It is possible that some of these standards will require custom synthesis. Costs for the synthesis of standard materials will be passed on to Philip Morris.

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COVANCE ANALYTICAL METHOD DEVELOPMENT SUMMARY

Analytes	Activity	Covance Labs UK Harrogate North Yorkshire UK	Covance Labs US Madison Wisconsin USA
Nicotine and metabolites in 24 h urine	Development Validation	\$38,808 \$36,750	Not Applicable
	Estimate total	\$75,558	---
Malondialdehyde in plasma and urine	Development Validation Audit	\$29,371 \$30,576 \$12,495	Not Applicable
	Estimate total	\$72,442	---
Caffeine and metabolites in urine	Development Validation	Not Applicable	\$20,000 \$20,000
	Estimate total	---	\$40,000
Hb adducts of 3- and 4- aminobiphenyl	Development Validation	\$48,510 \$34,398	Not Applicable
	Estimate total	\$82,908	---
Acetonitrile in exhalate and blood	Development Validation	Not Applicable	\$25,000 (blood) \$30,000 (exhalate) \$10,000 (blood) \$30,000 (exhalate)
	Estimate total	---	\$95,000
NNK metabolites in 24 h urine	Development Validation	Not Applicable	\$34,000 \$51,000
	Estimate total	---	\$85,000
8-epi- prostaglandin F2 alpha	Development Validation	\$9,702	Not Applicable
	Estimate total	\$9,702	---

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**COVANCE ANALYTICAL METHOD DEVELOPMENT SUMMARY
(CONTINUED)**

Analytes	Analytes	Covance Labs UK Harrogate North Yorkshire UK	Covance Labs US Madison Wisconsin USA
11-dehydro- Thromboxane B₂	Development Validation	\$26,460	Not Applicable
	Estimate total	\$26,460	---
Sub-Total	Development	\$116,689	\$109,000
	Validation	\$150,381	\$111,000
Total Development and Validation		\$267,070	\$220,000

Conversion rates are based on \$1.47 to £1

**PROTOCOL AND QUESTIONNAIRE DEVELOPMENT FOR
THE TOTAL EXPOSURE PILOT STUDY**

TASK	
Protocol Development	\$15,000
Questionnaire Development	\$10,000
Advertising (one ad in various print media) - Addition	\$15,000
Consulting	
Director Level - \$300/hour estimate 80 hours	\$24,000
Manager Level - \$195/hour estimate 40 hours	\$7,800
Total	\$71,800

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ANALYTICAL ELEMENTS OF THE TOTAL EXPOSURE PILOT STUDY
MISCELLANEOUS ITEMS
(costs not included in summary table)

Specific equipment required for analysis

- Savant centrifugal evaporator	£10,900 (\$16,023)
- Modified fridge for housing dialysis vessels	£600 (\$882)
- Stirring equipment for dialysis vessels	£1,400 (\$2,058)
- Large ultrasonic bath	£1,700 (\$2,499)

11-dehydro-thromboxane B₂ and 8-epi-prostaglandin F2 Alpha

Water purifier for ultra-pure water production	£4,700 (\$6,909)
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Meeting/Travel Costs (UK)

£20,000 (\$29,400)

Analytical Standards

£5,000 (\$7,350)

Administrative costs associated with the sourcing and purchasing of reference standard materials

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