BDG SYNTHESIS

Certificate of Analysis

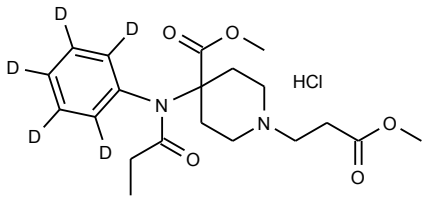
BDG Synthesis certifies that this reference material meets or exceeds the specifications stated herein.

Neil Beare, PhD, Director
12 April 2016

Name: **Remifentanil-d_5 HCl**

CAS Number: 132539-07-2 (unlabelled)

Structure:



Molecular Weight: $C_{20}H_{23}D_5N_2O_5 \cdot HCl = 417.94$

Lot Number: BDG 10744.2

Appearance: Off-white, crystalline solid

Corrected Purity: 97.2 % (HPLC) - 0.5 % (ethanol) - 0.7 % (acetone) = 96.0 %

Isotopic Purity: Under 0.5 % d_0

Re-test Date: 12 April 2021

Storage and Handling:

Temperature:	refrigerate for prolonged storage; may be handled and shipped at ambient temperature.
Humidity:	not believed to be hygroscopic; may be handled in normal laboratory atmosphere.
Light:	protect from strong sunlight.
Caution:	only experienced laboratory personnel should handle the material.

Identity and Purity

Proton NMR Spectrum

Identity: the signals are consistent with the proposed structure and in accord with literature where available. The complexity of the spectrum indicates two rotamers of the product are present in solution.
Isotopic Labelling: signals at the sites of deuteration are greatly diminished, compared with the spectrum of unlabelled material, indicating clean deuteration.
Residual Solvents: small amounts of ethanol (0.5 % *w/w*) and acetone (0.7 % *w/w*) are observed.
Impurities: a trace of an unidentified impurity is seen in the baseline.

Carbon-13 NMR Spectrum

Identity: the signals are consistent with the proposed structure and in accord with literature where available. Most signals are duplicated indicating that two rotamers of the product are present in solution.
Isotopic Labelling: signals at the sites of deuteration have collapsed to small multiplets compared with the spectrum of unlabelled material, indicating clean deuteration.

High-resolution Mass Spectrum (ESI+)

Found *m/z* 382.2391. $C_{20}H_{24}D_5N_2O_5$ $[M+H]^+$ requires *m/z* 382.2385. The deviation of 1.5 ppm is within normally accepted limits for the establishment of identity by HRMS. No signal for d_0 material was seen (detection limit about 0.5 %).

HPLC

A somewhat broadened, slightly tailing peak is observed (97.2 %). Note: in the absence of reference materials for preparing calibration curves, it is assumed that all peaks have the same detector response. Where possible, the conditions of analysis follow a pharmacopeial or literature method, or have been adapted from same.

Elemental Analysis

	Found:	C 57.40, H 5.87, D 2.44, N 6.50 %
$C_{20}H_{23}D_5N_2O_5 \cdot HCl$	Requires:	C 57.48, H 5.79, D 2.41, N 6.70 %

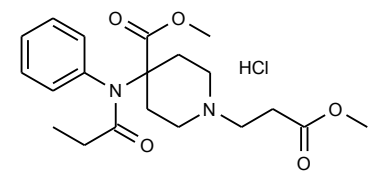
The elemental analyses fall within generally accepted limits for establishing the molecular formula given. The results may also be taken to imply the absence of significant quantities of water or inorganic salts (which have not been elsewhere tested for because of sample size limitations).

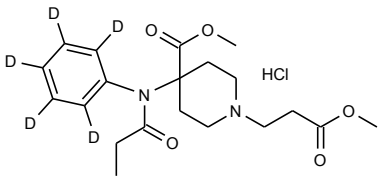
The available quantity of custom-synthesised material is always small, and this limits the extent and type of analytical data which can be obtained. This Certificate is presented in descriptive format for use by analytical chemists who are trained in the use of custom-synthesised materials. Custom materials often contain higher levels of residual solvents and/or water, and we urge you to use the corrected purity where needed rather than the raw HPLC purity. This compound is intended for use as an analytical reference material and it is not for human administration. Structures are shown with relative stereochemistry unless otherwise specified.

The re-test date is assigned from experience gained with the material in the laboratory and/or on storage. It is not possible to perform formal storage studies because of the small amount of material available.

BDG SYNTHESIS

Proton NMR Spectrum of Remifentanil HCl (top) and Remifentanil-d_5 HCl (bottom) in DMSO-d_6





Lot Number: BDG 10744.2

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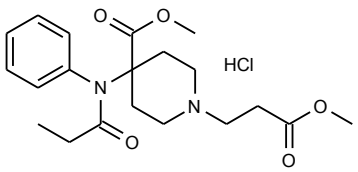
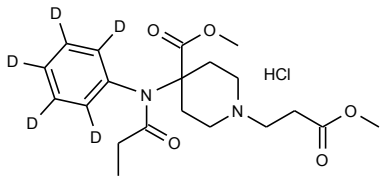
Carbon-13 NMR Spectrum of Remifentanil HCl (top) and Remifentanil-d_5 HCl (bottom) in DMSO-d_6





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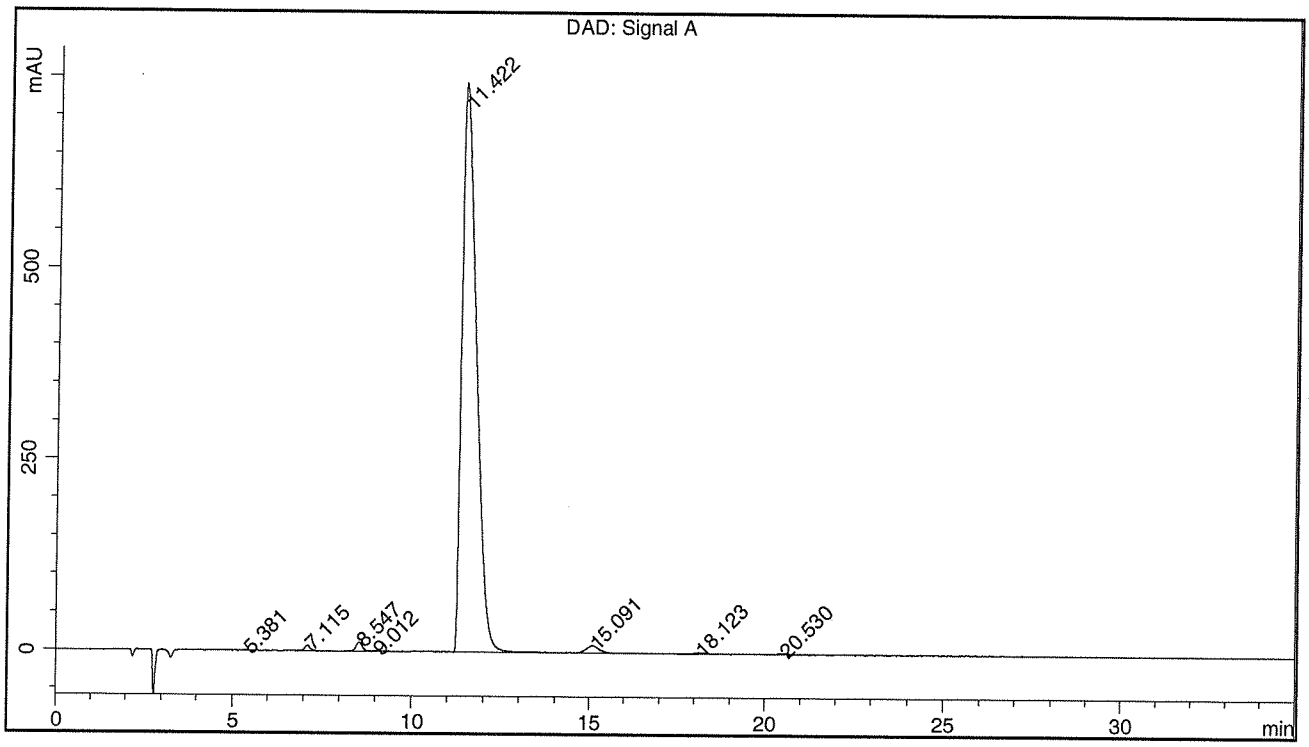
BDG - Analysis of Remifentanil-d5 HCl

Column : Phenomenex Luna C18(2) 5um 250 x 4.6 mm
Guard : Phenomenex Security Guard C18 RP 4 x 3 mm
Mobile Phase : 75:25:0.1 Water : Acetonitrile : Trifluoroacetic Acid
Flow Rate : 1.0 mL/min
Sample Solvent : 7:3 Water : Acetonitrile
Column Temperature : 20C
Injection Volume : 10 uL
Detection : UV at 210 nm

Sample Name	BDG 10744.2	Instrument	AnalyticalLC01
Acquisition	12/04/2016, 09:43:21	Method (rev.)	LC10373d (9)
Sequence	BDG_12Apr2016a - Reprocessed	Vial Position	4
Operator	solvation010\cerityadmin	Injection	1 of 1



Area Percent Report

Peak#	RT	Peak Height	Peak Area	Width	Area %
1	5.38 min	0.9982	7.8106	0.1153 min	0.037 %
2	7.12 min	7.0148	78.7966	0.1751 min	0.368 %
3	8.55 min	11.9588	153.4730	0.1937 min	0.718 %
4	9.01 min	0.9824	16.4121	0.2149 min	0.077 %
5	11.42 min	744.0649	20793.8485	0.4180 min	97.235 %
6	15.09 min	9.5387	245.6428	0.3724 min	1.149 %
7	18.12 min	1.7301	51.5638	0.3797 min	0.241 %
8	20.53 min	1.0725	37.5549	0.4245 min	0.176 %