Consistent with the terms of the Court's May 22, 2017 scheduling order, the record has been redacted for all information that plaintiff, Texas Department of Criminal Justice (Texas), has identified as confidential. In addition, Defendants have also redacted information that the drug's supplier and broker have separately advised the agency they consider confidential and private, as well as information the agency itself generally treats as confidential. This information has been redacted pending final FDA's review of confidentiality claims, and our filing of the record with these redactions does not necessarily reflect our agreement with all of the claims of confidentiality Defendants have received. Defendants explicitly reserve the right to make an independent determination regarding the proper scope of redactions at a later time. Should we identify any of Texas's redactions that are over-broad or otherwise improper, we will work with Texas's counsel to revise the redactions in the record.

Exhibit 14

CERTIFICATE

Pursuant to the provisions of Rule 44 of the Federal Rules of Civil Procedure, I hereby certify that John Verbeten, Director of the Operations and Policy Branch, Division of Import Operations and Policy, Office of Regional Operations, Office of Regulatory Affairs, United States Food and Drug Administration, whose declaration is attached, has custody of official records of the United States Food and Drug Administration.

In witness whereof, I have, pursuant to the provision of Title 42, United States Code, Section 3505, and FDA Staff Manual Guide 1410.23, hereto set my hand and caused the seal of the Department of Health and Human Services to be affixed this 20th day of April, 2011.

Karen Kennard

Karen Kennard, Acting Director
Division of Dockets Management
Office of Public Information and Library Services
Office of Shared Services
Office of Management

By direction of the Secretary of
Health and Human Services

DECLARATION OF JOHN VERBETEN

John Verbeten, being first duly sworn, declares as follows:

1. I am the Director of the Operations and Policy Branch, Division of Import Operations and Policy, Office of Regional Operations, Office of Regulatory Affairs, United States Food and Drug Administration.

2. In this capacity, I have custody of official records of the United States Food and Drug Administration.

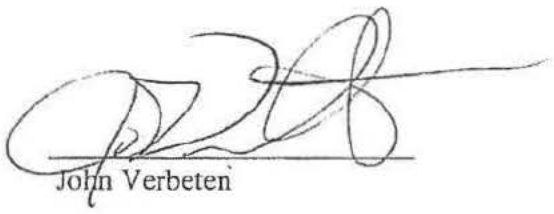
3. Attached is a certified and authentic copy of the following records of the Food and Drug Administration:

Administrative record relating to Beaty v. FDA et al., No. 11-00289 RJL (D.D.C.)

4. Copies of the attached administrative record are part of the official records of the United States Food and Drug Administration.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on April 18, 2011.



John Verbeten

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Description	Date	Bates Number
Letter from Charles Ryan, Director, Arizona Department of Corrections, to David Thomas, FDA Investigations re: Execution by Lethal Injection of Arizona Inmate Jeffrey Timothy Landrigan #082157	9/24/2010	000001
Letter from Charles Flanagan, Deputy Director, Arizona Department of Corrections, to David Thomas, FDA Investigations, enclosing Controlled Substance Registration Certificate	9/24/2010	000002-000003
Notice of FDA Action	9/29/2010	000004
Department of Treasury, U.S. Customs Service Entry/Immediate Delivery Form	10/7/2010	000005-00006
FDA's Operational and Administrative System for Import Support (OASIS) Screenshot for Entry # 112-9247186-3	n/a	000007
Letter from Dale Baich, Supervisor, Capital Habeas Unit, Office of the Federal Public Defender for the District of Arizona, to Ralph Tyler, Chief Counsel, FDA	10/23/2010	000008-000012
Department of Homeland Security, U.S. Customs and Border Protection Entry/Immediate Delivery Form	10/25/2010	000013-000015
FDA's OASIS Screenshot for Entry # 574-0251126-5	n/a	000016
Email from Patrick Bowen, FDA, to Distribution re: Import Bulletin #60-B08	10/27/2010	000017-000018
Email from Nima Abbaszadeh, U.K. Desk Officer, U.S. Department of State, to Ilisa Bernstein re: assistance on sodium thiopental question raised by UK Embassy, enclosing Letter from Ian Bond, Political Counsellor, British Embassy Washington, to Elizabeth Dibble, Deputy Assistant Secretary of State	11/4/2011	000019-000020
Email from Clare Bloomfield, British Embassy, to Murray Lumpkin, FDA, re: UK request for information on sodium thiopental	11/4/2010	000021
Email from Tom Smith, Department for Business, Innovation and Skills, to Murray Lumpkin re: Sodium Thiopental	11/5/2010	000022
Email from Murray Lumpkin to Tom Smith cc JM Sharfstein and Margaret Hamburg re: Substantive response from US FDA re: Sodium Thiopental	11/16/2010	000023-000024
Letter from Charles Ryan, Director, Arizona Department of Corrections, to Deborah Autor, Director, Office of Compliance, CDER, re: Entry #574-0251126-5 Thiopental Sodium	11/10/2010	000025-000026

Administrative Record Index

Letter from Charles Ryan, Director, Arizona Department of Corrections, to David Thomas, FDA Investigations, re: Inspection and Release of Entry #574-0251126-5, Thiopental Sodium	11/10/2010	000027
Letter from Dale Baich, Supervisor, Capital Habeas Unit, Office of the Federal Public Defender for the District of Arizona, to Thomas Emerick, Assistant Special Agent in Charge, FDA	11/17/2010	000028-000029
Department of Treasury Entry/Immediate Delivery Form	11/24/2010	000030-000031
FDA's OASIS Screenshot for Entry # 112-9938358-2	n/a	000032
Letter from Benjamin Rice, General Counsel, State of California, to Ruth Dixon, FDA	12/9/2010	000033
Sodium Thiopental Statement, Key Messages	12/29/2010	000034-000035
Email from Shelly Burgess to Nathan Koppel	1/4/2011	000036-000037
Letter from Coleen Klasmeier, Bradford Berenson (Sidley Austin), and Dale Baich (Office of the Federal Public Defender for the District of Arizona), to Margaret Hamburg, Commissioner, FDA	1/4/2011	000038-000050
Guidance for handling pending and future shipments of Sodium Thiopental	1/5/2011	000051-000057
Notice of FDA Action	1/6/2011	000058-000059
Notice of FDA Action	1/7/2011	000060-000061
Letter from Patricia Shafer, Acting District Director, New Orleans District Office, to Benjamin Rice, Chief Counsel, California Department of Corrections & Rehabilitation	1/7/2011	000062-000063
Letter from Alonza Cruse, District Director, Los Angeles District, to Carson McWilliams, Warden, Arizona State Prison Complex	n/a	000064
Miscellaneous		
FDA Establishment Inspection Report for Sandoz - Endorsement Excerpt	7/8/2009	000065
FDA Establishment Inspection Report for Sandoz - Summary Excerpt	7/29/2010	000066-000069
Form FDA 483 - Inspectional Observations for Sandoz	7/29/2010	000070

Ramos, Merly

From: Lumpkin, Murray
Sent: Tuesday, November 16, 2010 2:03 PM
To: 'tom.smith@bis.gsi.gov.uk'
Cc: Sharfstein, JM; Hamburg, Margaret
Subject: Substantive response from US FDA re: Sodium Thiopental

Dear Mr. Smith,

Thank you for your understanding and for your original inquiry. I do now have information that I hope will still be responsive to your time frame.

You asked for the "authoritative view from the FDA on the current usage of sodium thiopental for medical reasons within the United States.". Currently there is no sodium thiopental for sale in the United States, because the domestically manufactured supply has been unavailable for more than a year. There are no approved or permitted foreign sources of sodium thiopental. As a result, there is currently little to no current usage of sodium thiopental for medical reasons.

To your specific questions:

a) The question is whether it continues to be licensed for use within the US (and, if so, for what purposes);

There is no FDA-approved sodium thiopental for human use in the United States. Although the domestically manufactured supply is not approved, the product has been marketed and commercially available without FDA approval pursuant to FDA's Compliance Policy Guide on Marketed Unapproved Drugs. This document is available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070290.pdf.

b) The question is whether it does in practice continue to be used. Even relatively low levels of usage (as a percentage of anaesthetic procedures) would be relevant information to us.

Currently, sodium thiopental's use is very limited due to the shortage described above. When there is no shortage, there is minimal use of sodium thiopental for medical reasons. Experts consulted by FDA have stated that sodium thiopental would be used in well under 5% of patients presenting for a general anesthetic. There is one scenario where the use of sodium thiopental would likely increase: if there were to be another shortage of propofol, an anesthetic agent. If propofol is in shortage, sodium thiopental would most likely find increased use as an induction agent for general anesthesia. Propofol is not currently in shortage in the United States.

Again, I hope this is responsive to your request

Sincerely,

Murray M. Lumpkin, M.D., M.Sc.
Deputy Commissioner
International Programs
US Food and Drug Administration.

----- Original Message -----
From: Smith Tom (ITID) [mailto:tom.smith@bis.gsi.gov.uk]
Sent: Tuesday, November 16, 2010 09:01 AM
To: Lumpkin, Murray
Subject: RE: Apologies: Sodium Thiopental

Dear Mr Lumpkin,

Thank you. I do understand and appreciate your efforts.

Tom Smith
Head, Export Control Organisation
Department for Business, Innovation and Skills
3rd Floor, "Orchard 3", 1 Victoria Street

London SW1H 0ET
Tel: 0207 215 4355
Email: tom.smith@bis.gsi.gov.uk

-----Original Message-----
From: Lumpkin, Murray [mailto:Murray.Lumpkin@fda.hhs.gov]
Sent: 16 November 2010 11:45
To: Smith Tom (ITID)
Cc: Sharfstein, JM; Hamburg, Margaret
Subject: Apologies: Sodium Thiopental

Dear Mr Smith,
I am writing today to offer my sincerest apologies that the US FDA has been unable to supply you with the information you requested in time to be of help in your UK exporting agency's trial tomorrow. I know it is now afternoon in London, and your trial starts tomorrow morning (London time). Even checking on an almost daily basis, as of this morning, I still have not received departmental clearance on a communication to you that would be responsive to your request. I know we have been singularly unhelpful, and, for that, I am truly sorry. I do wish we could have been more helpful to you. Again, many sincere apologies.

If I do happen to receive clearance later today our time, I will, of course, send you what is cleared in the hopes it might be of help, even at that late hour.

Best regards,
Murray Lumpkin

Murray M. Lumpkin, MD, MSc
Deputy Commissioner
International Programs
US Food and Drug Administration.

Sodium Thiopental Statement, Key Messages
December 29, 2010

First, we would confirm the shipments are imported on or behalf of state correctional authorities.

Second, we would release the shipments with the following comment:

"FDA releases this shipment, which is being imported by or on behalf of state correctional authorities. In keeping with established practice, FDA does not review or approve products for the purpose of lethal injection. FDA has not reviewed the products in this shipment to determine their identity, safety, effectiveness, purity, or any other characteristics."

Third, we would use the following key messages and Q and A to respond to inquiries from the news media and other interested parties.

Key Messages

*The U.S. Food and Drug Administration (FDA) is charged by Congress with protecting the public health. Ensuring the safety and effectiveness of pharmaceuticals used for medical purposes is a core part of FDA's mission.

*Reviewing substances imported or used for the purpose of state-authorized lethal injection clearly falls outside of FDA's explicit public health role. FDA does not verify the identity, potency, safety, or effectiveness of substances imported for this purpose. FDA exercises similar enforcement discretion when these drugs are manufactured and purchased within the United States.

*Accordingly, FDA chooses to continue to defer to law enforcement on all matters involving lethal injection, consistent with the U.S. Supreme Court's ruling in Heckler v. Chaney (1985).

Q and A

1.) What has happened so far this year with the imports of sodium thiopental?

In 2009 and 2010, FDA permitted the importation of several shipments of sodium thiopental to state Departments of Correction. In doing so, FDA deferred to law enforcement in the use of substances for lethal injection, which is consistent with the agency's longstanding policy. The agency did not conduct any review of these products for safety, effectiveness or quality.

2.) What has changed?

Two things. In the context of two death penalty cases in the fall of 2010, it was suggested that FDA "approves" the importation of these drugs for use in lethal injections and/or reviews them for safety, effectiveness, and quality. In actuality, the FDA neither approves nor reviews these drugs for use in lethal injections and feels it necessary to clear up any confusion. Also, FDA reviewed its procedures for the importation of sodium thiopental in concert with CBP. The agencies decided that since FDA does not conduct a review of pharmaceuticals intended for lethal injection, FDA will continue to exercise its enforcement discretion and defer to CBP's system for processing importations. The agencies are working together to develop a system for future shipments that avoids any confusion about whether FDA evaluates shipments of drugs intended for lethal injection.

3.) Is the importation of unapproved sodium thiopental for lethal injection illegal?

In deferring to law enforcement on matters involving pharmaceuticals for lethal injection, FDA is exercising enforcement discretion. This approach by the agency was upheld by the Supreme Court in Heckler v. Chaney (1985). Among the reasons cited by the Court for its decision not to review FDA's non-enforcement against lethal injection drugs is that agencies are responsible for prioritizing their enforcement resources to most effectively achieve their statutory missions. Again, FDA similarly defers to law enforcement with respect to transport of these substances within the United States.

4.) What will happen to any shipments that are currently pending?

FDA is releasing these with the comment: "FDA releases this shipment, which is being imported by or on behalf of state correctional authorities. In keeping with established practice, FDA does not review or approve products for the purpose of lethal injection. FDA has not reviewed the products in this shipment to determine their identity, safety, effectiveness, purity, or any other characteristics."

Dohm, Julie

From: Burgess, Shelly
Sent: Tuesday, January 04, 2011 9:50 AM
To: 'Koppel, Nathan'
Subject: FW: update
Importance: High

Nathan - As discussed, the following is the latest FDA position on sodium thiopental.

The U.S. Food and Drug Administration (FDA) is charged by Congress with protecting the public health. Ensuring the safety and effectiveness of pharmaceuticals used for medical purposes is a core part of FDA's mission.

Reviewing substances imported or used for the purpose of state-authorized lethal injection clearly falls outside of FDA's explicit public health role. FDA does not verify the identity, potency, safety, or effectiveness of substances imported for this purpose. FDA exercises similar enforcement discretion when these drugs are manufactured and purchased within the United States.

Accordingly, FDA chooses to continue to defer to law enforcement on all matters involving lethal injection, consistent with the U.S. Supreme Court's ruling in Heckler v. Chaney (1985).

Following is information that addresses the import of sodium thiopental -

So far this year with the imports of sodium thiopental , inn 2009 and 2010, FDA permitted the importation of several shipments of sodium thiopental to state Departments of Correction. In doing so, FDA deferred to law enforcement in the use of substances for lethal injection, which is consistent with the agency's longstanding policy. The agency did not conduct any review of these products for safety, effectiveness or quality.

In the context of two death penalty cases in the fall of 2010, it was suggested that FDA "approves" the importation of these drugs for use in lethal injections and/or reviews them for safety, effectiveness, and quality. In actuality, the FDA neither approves nor reviews these drugs for use in lethal injections and feels it necessary to clear up any confusion. Also, FDA reviewed its procedures for the importation of sodium thiopental in concert with CBP. The agencies decided that since FDA does not conduct a review of pharmaceuticals intended for lethal injection, FDA will continue to exercise its enforcement discretion not to review these shipments and allow processing through CBP's automated system for importations. The agencies are working together to develop a system for future shipments that avoids any confusion about whether FDA evaluates shipments of drugs intended for lethal injection.

Is the importation of unapproved sodium thiopental for lethal injection illegal?

In deferring to law enforcement on matters involving pharmaceuticals for lethal injection, FDA is exercising enforcement discretion. This approach by the agency was upheld by the Supreme Court in Heckler v. Chaney (1985). Among the reasons cited by the Court for its decision not to review FDA's non-enforcement against lethal injection drugs is that agencies are responsible for prioritizing their enforcement resources to most effectively achieve their statutory missions. Again, FDA similarly defers to law enforcement with respect to transport of these substances within the United States.

What will happen to any shipments for correctional facilities that are currently pending?

*FDA is releasing these with the comment: "FDA releases this shipment, which is being imported by or on behalf of state correctional authorities. In keeping with established practice, FDA does not review or approve products for the purpose of lethal injection. FDA has not reviewed the products in this shipment to determine their identity, safety, effectiveness, purity, or any other characteristics."

I will try to find someone to speak with you. I hope this is helpful.

Best,
Shelly

Exhibit 15

Goodman & Gilman's

The Pharmacological Basis of THERAPEUTICS

eleventh edition

McGRAW-HILL
MEDICAL PUBLISHING DIVISION

New York Chicago San Francisco Lisbon London Madrid Mexico City Milan New Delhi
San Juan Seoul Singapore Sydney Toronto

classes of anesthetics, as mutations in various regions (and subunits) of the $GABA_A$ receptor selectively affect the actions of various anesthetics (Belelli *et al.*, 1997; Krasowski and Harrison, 1999). Notably, none of the general anesthetics competes with GABA for its binding site on the receptor. The capacity of propofol and etomidate to inhibit the response to noxious stimuli is mediated by a specific site on the β_3 subunit of the $GABA_A$ receptor (Jurd *et al.*, 2003), whereas the sedative effects of these anesthetics are mediated by the same site on the β_2 subunit (Reynolds *et al.*, 2003). These results indicate that two components of anesthesia *can* be mediated by $GABA_A$ receptors; for anesthetics other than propofol and etomidate, which components of anesthesia *are* produced by actions on $GABA_A$ receptors remains a matter of conjecture.

Structurally closely related to the $GABA_A$ receptors are other ligand-gated ion channels including glycine receptors and neuronal nicotinic acetylcholine receptors. Glycine receptors may play a role in mediating inhibition by anesthetics of responses to noxious stimuli. Clinical concentrations of inhalational anesthetics enhance the capacity of glycine to activate glycine-gated chloride channels (glycine receptors), which play an important role in inhibitory neurotransmission in the spinal cord and brainstem. Propofol (Hales and Lambert, 1988), neurosteroids, and barbiturates also potentiate glycine-activated currents, whereas etomidate and ketamine do not (Mascia *et al.*, 1996). Subanesthetic concentrations of the inhalational anesthetics inhibit some classes of neuronal nicotinic acetylcholine receptors (Violet *et al.*, 1997; Flood *et al.*, 1997). However, these actions do not appear to mediate anesthetic immobilization (Eger *et al.*, 2002); rather, neuronal nicotinic receptors could mediate other components of anesthesia such as analgesia or amnesia.

The only general anesthetics that do not have significant effects on $GABA_A$ or glycine receptors are ketamine, nitrous oxide, cyclopropane, and *xenon*. These agents inhibit a different type of ligand-gated ion channel, the *N*-methyl-D-aspartate (NMDA) receptor (*see* Chapter 12). NMDA receptors are glutamate-gated cation channels that are somewhat selective for calcium and are involved in long-term modulation of synaptic responses (long-term potentiation) and glutamate-mediated neurotoxicity. Ketamine inhibits NMDA receptors by binding to the *phencyclidine* site on the NMDA receptor protein (Anis *et al.*, 1983), and the NMDA receptor is thought to be the principal molecular target for ketamine's anesthetic actions. Nitrous oxide (Mennerick *et al.*, 1998; Jevtovic-Todorovic *et al.*, 1998), cyclopropane (Raines *et al.*, 2001), and xenon (Franks *et al.*, 1998; de Sousa *et al.*, 2000) are potent and selective inhibitors of NMDA-activated currents, suggesting that these agents also may produce unconsciousness *via* actions on NMDA receptors.

Inhalational anesthetics have two other known molecular targets that may mediate some of their actions. Halogenated inhalational anesthetics activate some members of a class of K^+ channels known as two-pore domain channels (Gray *et al.*, 1998; Patel *et al.*, 1999); other two-pore domain channel family members are activated by xenon, nitrous oxide, and cyclopropane (Gruss *et al.*, 2004). These channels are important in setting the resting membrane potential of neurons and may be the molecular locus through which these agents hyperpolarize neurons. A second target is the molecular machinery involved in neurotransmitter release. In *Caenorhabditis elegans*, the action of inhalational anesthetics requires a protein complex (syntaxin, SNAP-25, synaptobrevin) involved in synaptic neurotransmitter release (van Swinderen *et al.*, 1999). These molecular interactions may explain in part the capacity of inhalational anesthetics to cause presynaptic inhibition in the hippocampus and could contribute to the amnesic effect of inhalational anesthetics.

Summary. Current evidence supports the view that most intravenous general anesthetics act predominantly through $GABA_A$ receptors and perhaps through some interactions with other ligand-gated ion channels. The halogenated inhalational agents have a variety of molecular targets, consistent with their status as complete (all components) anesthetics. Nitrous oxide, ketamine, and xenon constitute a third category of general anesthetics that are likely to produce unconsciousness *via* inhibition of the NMDA receptor and/or activation of two-pore-domain K^+ channels. The molecular mechanisms of general anesthetics are reviewed by Rudolph and Antkowiak (2004).

PARENTERAL ANESTHETICS

Pharmacokinetic Principles

Parenteral anesthetics are small, hydrophobic, substituted aromatic or heterocyclic compounds (Figure 13–1). Hydrophobicity is the key factor governing their pharmacokinetics (Shafer and Stanski, 1992). After a single intravenous bolus, these drugs preferentially partition into the highly perfused and lipophilic tissues of the brain and spinal cord where they produce anesthesia within a single circulation time. Subsequently blood levels fall rapidly, resulting in drug redistribution out of the CNS back into the blood. The anesthetic then diffuses into less perfused

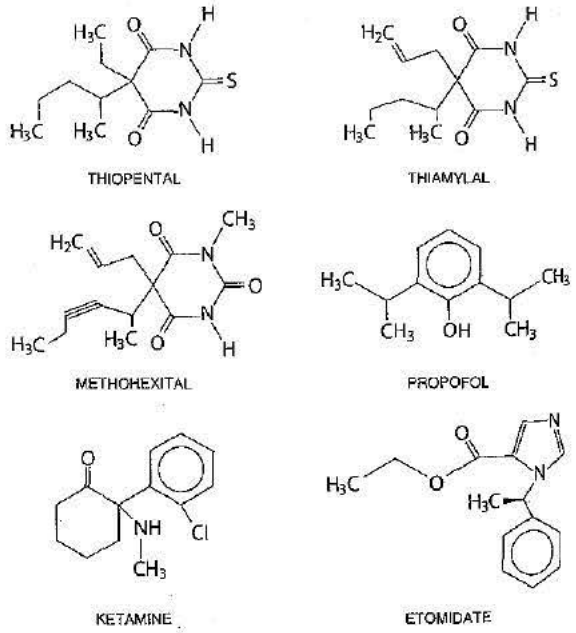

Figure 13–1. *Structures of parenteral anesthetics.*

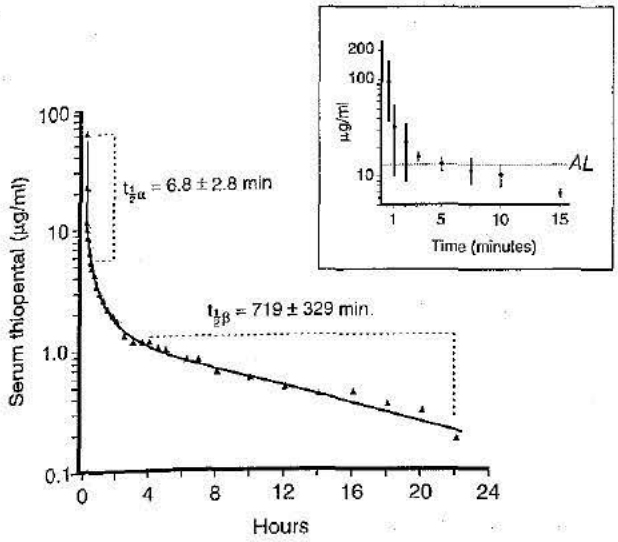

Figure 13–2. Thiopental serum levels after a single intravenous induction dose. Thiopental serum levels after a bolus can be described by two time constants, $t_{\frac{1}{2}}\alpha$ and $t_{\frac{1}{2}}\beta$. The initial fall is rapid ($t_{\frac{1}{2}}\alpha$ <10 min) and is due to redistribution of drug from the plasma and the highly perfused brain and spinal cord into less well-perfused tissues such as muscle and fat. During this redistribution phase, serum thiopental concentration falls to levels at which patients awaken (AL, awakening level; *see* inset—the average thiopental serum concentration in 12 patients after a 6-mg/kg intravenous bolus of thiopental). Subsequent metabolism and elimination is much slower and is characterized by a half-life ($t_{\frac{1}{2}}\beta$) of more than 10 hours. (Adapted with permission from Burch and Stanski, 1983.)

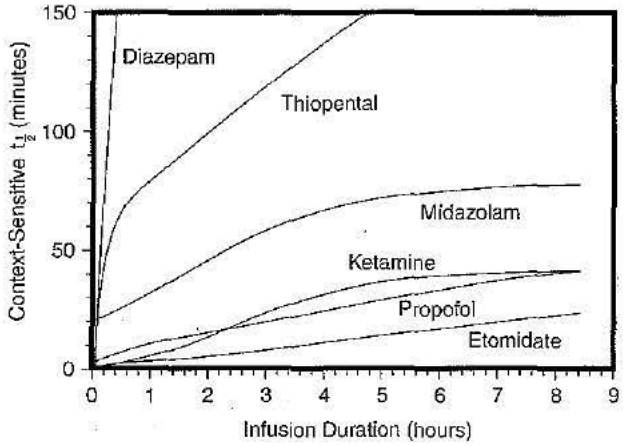

Figure 13–3. Context-sensitive half-time of general anesthetics. The duration of action of single intravenous doses of anesthetic/hypnotic drugs is similarly short for all and is determined by redistribution of the drugs away from their active sites (*see* Figure 13–2). However, after prolonged infusions, drug half-lives and durations of action are dependent on a complex interaction between the rate of redistribution of the drug, the amount of drug accumulated in fat, and the drug's metabolic rate. This phenomenon has been termed the *context-sensitive half-time*; that is, the half-time of a drug can be estimated only if one knows the context—the total dose and over what time period it has been given. Note that the half-times of some drugs such as etomidate, propofol, and ketamine increase only modestly with prolonged infusions; others (*e.g.*, diazepam and thiopental) increase dramatically. (Reproduced with permission from Reves *et al.*, 1994.)

tissues such as muscle and viscera, and at a slower rate into the poorly perfused but very hydrophobic adipose tissue. Termination of anesthesia after single boluses of parenteral anesthetics primarily reflects redistribution out of the CNS rather than metabolism (Figure 13–2). After redistribution, anesthetic blood levels fall according to a complex interaction between the metabolic rate and the amount and lipophilicity of the drug stored in the peripheral compartments (Hughes *et al.*, 1992; Shafer and Stanski, 1992). Thus, parenteral anesthetic half-lives are "context-sensitive," and the degree to which a half-life is contextual varies greatly from drug to drug, as might be predicted based on their differing hydrophobicities and metabolic clearances (Table 13–2 and Figure 13–3). For example, after a single bolus of thiopental, patients usually emerge from anesthesia within 10 minutes; however, a patient may require more than a day to awaken from a prolonged thiopental infusion. Most individual variability in sensitivity to parenteral anesthetics can be accounted for by pharmacokinetic factors (Wada *et al.*, 1997). For example, in patients with lower cardiac output, the relative perfusion of and fraction of anesthetic dose delivered to the brain is higher; thus, patients in septic shock or with cardiomyopathy usually require lower doses of anesthetic. The elderly also typically require a smaller anesthetic dose, primarily because of a smaller initial volume of distribution (Homer and Stanski, 1985). As described below, similar principles govern the pharmacokinetics of the hydrophobic inhalational anesthetics, with the added complexity of drug uptake by inhalation.

SPECIFIC PARENTERAL AGENTS

Barbiturates

Chemistry and Formulations. Anesthetic barbiturates are derivatives of barbituric acid (2,4,6-trioxohexahydropyrimidine), with either an oxygen or sulfur at the 2-position (Figure 13–1). The three barbiturates used for clinical anesthesia are *sodium thiopental, thia-*

Table 13–2
Pharmacological Properties of Parenteral Anesthetics

DRUG	FORMULATION	IV INDUCTION DOSE (mg/kg)	MINIMAL HYPNOTIC LEVEL (μg/ml)	INDUCTION DOSE DURATION (min)	$T_{1/\beta}$ (hours)	CL (ml·min^{-1}·kg^{-1})	PROTEIN BINDING (%)	V_{ss} (L/kg)
Thiopental	25 mg/ml in aqueous solution + 1.5 mg/ml Na_2CO_3; pH = 10–11	3–5	15.6	5–8	12.1	3.4	85	2.3
Methohexital	10 mg/ml in aqueous solution + 1.5 mg/ml Na_2CO_3; pH = 10–11	1–2	10	4–7	3.9	10.9	85	2.2
Propofol	10 mg/ml in 10% soybean oil, 2.25% glycerol, 1.2% egg PL, 0.005% EDTA or 0.025% Na-MBS; pH = 4.5–7	1.5–2.5	1.1	4–8	1.8	30	98	2.3
Etomidate	2 mg/ml in 35% PG; pH = 6.9	0.2–0.4	0.3	4–8	2.9	17.9	76	2.5
Ketamine	10, 50, or 100 mg/ml in aqueous solution; pH = 3.5–5.5	0.5–1.5	1	10–15	3.0	19.1	27	3.1

SOURCES: Thiopental: Clarke *et al.*, 1968; Burch and Stanski, 1983; Hudson *et al.*, 1983; Hung *et al.*, 1992; methohexital: Brand *et al.*, 1963; Clarke *et al.*, 1968; Kay and Stephenson, 1981; Hudson *et al.*, 1983; McMurray *et al.*, 1986; propofol: Kirkpatrick *et al.*, 1988; Langley and Heel, 1988; Shafer *et al.*, 1988; etomidate: Doenicke, 1974; Meuldermans and Heykants, 1976; Fragen *et al.*, 1983; Hebron *et al.*, 1983; ketamine: Chang and Glazko, 1974; Clements and Nimmo, 1981; White *et al.*, 1982; Dayton *et al.*, 1983. ABBREVIATIONS: $t_{1/\beta}$, β phase half-life; *CL*, clearance; *Vss*, volume of distribution at steady state; EDTA, ethylenediaminetetraacetic acid; Na-MBS, Na-metabisulfite; PG, propylene glycol; PL, phospholipid.

mylal, and *methohexital.* Sodium thiopental (PENTOTHAL) has been used most frequently for inducing anesthesia. The barbiturate anesthetics are supplied as racemic mixtures despite enantioselectivity in their anesthetic potency (Andrews and Mark, 1982). Barbiturates are formulated as the sodium salts with 6% sodium carbonate and reconstituted in water or isotonic saline to produce 1% (methohexital), 2% (thiamylal), or 2.5% (thiopental) alkaline solutions with pHs of 10 to 11. Once reconstituted, thiobarbiturates are stable in solution for up to 1 week, methohexital for up to 6 weeks if refrigerated. *Mixing with more acidic drugs commonly used during anesthetic induction can result in precipitation of the barbiturate as the free acid; thus, standard practice is to delay the administration of other drugs until the barbiturate has cleared the intravenous tubing.*

Dosages and Clinical Use. Recommended intravenous dosing for parenteral anesthetics in a healthy young adult is given in Table 13–2.

The typical induction dose (3 to 5 mg/kg) of thiopental produces unconsciousness in 10 to 30 seconds with a peak effect in 1 minute and duration of anesthesia of 5 to 8 minutes. Neonates and infants usually require a higher induction dose (5 to 8 mg/kg), whereas elderly and pregnant patients require less (1 to 3 mg/kg) (Homer and Stanski 1985; Jonmarker *et al.*, 1987; Gin *et al.*, 1997). Dosage calculation based on lean body mass reduces individual variation in dosage requirements. Doses can be reduced by 10% to 50% after premedication with benzodiazepines, opiates, or α_2 adrenergic agonists, because of their additive hypnotic effect (Short *et al.*, 1991; Nishina *et al.*, 1994; Wang *et al.*, 1996). Thiamylal is approximately equipotent with and in all aspects similar to thiopental. Methohexital (BREVITAL) is threefold more potent but otherwise similar to thiopental in onset and duration of action. Thiopental and thiamylal produce little to no pain on injection; methohexital elicits mild pain. Veno-irritation can be reduced by injection into larger non-hand veins and by prior intravenous injection of lidocaine (0.5 to 1 mg/kg). Intra-arterial injection of thiobarbiturates can induce a severe inflammatory and potentially necrotic reaction and should be avoided. Thiopental often evokes the taste of garlic just prior to inducing anesthesia. Methohexital and to a lesser degree the other barbiturates can produce excitement phenomena such as muscle tremor, hypertonus, and hiccups. For induction of pediatric patients without IV access, all three drugs can be given per rectum at approximately tenfold the IV dose.

Pharmacokinetics and Metabolism. Pharmacokinetic parameters for parenteral anesthetics are given in Table 13–2. As discussed above, the principal mechanism limiting anesthetic duration after single doses is redistribution of these hydrophobic drugs from the brain to other tissues. However, after multiple doses or infusions, the duration of action of the barbiturates varies considerably depending on their clearances.

Methohexital differs from the other two intravenous barbiturates in its much more rapid clearance; thus, it accumulates less during prolonged infusions (Schwilden and Stoeckel, 1990). Because of their slow elimination and large volumes of distribution, prolonged infusions or very large doses of thiopental and thiamylal can produce unconsciousness lasting several days. Even single induction doses of thiopental and to a lesser degree methohexital can produce psychomotor impairment lasting up to 8 hours (Korttila *et al.*, 1975; Beskow *et al.*, 1995). Methohexital had been used frequently for outpatient procedures for which rapid return to an alert state is particularly desirable, but for this use it now has been largely replaced by propofol (*see* below). All three barbiturates are primarily eliminated by hepatic metabolism and renal excretion of inactive metabolites; a small fraction of thiopental undergoes desulfuration to the longer-acting hypnotic pentobarbital (Chan *et al.*, 1985). Each drug is highly protein bound (Table 13–2). Hepatic disease or other conditions that reduce serum protein concentration will decrease the volume of distribution and thereby increase the initial free concentration and hypnotic effect of an induction dose.

Side Effects. Nervous System. Besides producing general anesthesia, barbiturates reduce the cerebral metabolic rate, as measured by cerebral oxygen consumption ($CMRO_2$), in a dose-dependent manner. Induction doses of thiopental reduce $CMRO_2$ by 25% to 30% with a maximal decrease of 55% occurring at two to five times that dose (Stullken *et al.*, 1977). As a consequence of the decrease in $CMRO_2$, cerebral blood flow and intracranial pressure are similarly reduced (Shapiro *et al.*, 1973).

Because it markedly lowers cerebral metabolism, thiopental has been used as a protectant against cerebral ischemia. At least one human study suggests that thiopental may be efficacious in ameliorating ischemic damage in the perioperative setting (Nussmeier *et al.*, 1986). Thiopental also reduces intraocular pressure (Joshi and Bruce, 1975). Presumably in part due to their CNS depressant activity, barbiturates are effective anticonvulsants. Thiopental in particular is a proven medication in the treatment of status epilepticus (Modica *et al.*, 1990).

Cardiovascular. *The anesthetic barbiturates produce dose-dependent decreases in blood pressure.* The effect is due primarily to vasodilation, particularly venodilation, and to a lesser degree to a direct decrease in cardiac contractility. Typically, heart rate increases as a compensatory response to a lower blood pressure, although barbiturates also blunt the baroreceptor reflex.

Hypotension can be severe in patients with an impaired ability to compensate for venodilation such as those with hypovolemia, cardiomyopathy, valvular heart disease, coronary artery disease, cardiac tamponade, or β adrenergic blockade. Thiopental is not contraindicated in patients with coronary artery disease because the ratio of myocardial oxygen supply to demand appears to be adequately maintained within a patient's normal blood pressure range (Reiz *et al.*, 1981). None of the barbiturates has been shown to be arrhythmogenic.

Respiratory. *Barbiturates are respiratory depressants.* Induction doses of thiopental decrease minute ventilation and tidal volume with a smaller and inconsistent decrease in respiratory rate (Grounds *et al.*, 1987); reflex responses

to hypercarbia and hypoxia are diminished by anesthetic barbiturates (Hirshman *et al.*, 1975), and at higher doses or in the presence of other respiratory depressants such as opiates, apnea can result. With the exception of uncommon anaphylactoid reactions, these drugs have little effect on bronchomotor tone and can be used safely in asthmatics (Kingston and Hirshman, 1984).

Other Side Effects. Short-term administration of barbiturates has no clinically significant effect on the hepatic, renal, or endocrine systems. A single induction dose of thiopental does not alter tone of the gravid uterus, but may produce mild transient depression of newborn activity (Kosaka *et al.*, 1969). True allergies to barbiturates are rare (Baldo *et al.*, 1991); however, direct drug-induced histamine release is occasionally seen (Sprung *et al.*, 1997). Barbiturates can induce fatal attacks of porphyria in patients with acute intermittent or variegate porphyria and are contraindicated in such patients. Unlike inhalational anesthetics and succinylcholine, barbiturates and all other parenteral anesthetics apparently do not trigger malignant hyperthermia (Rosenberg *et al.*, 1997).

Propofol

Chemistry and Formulations. Propofol now is the most commonly used parenteral anesthetic in the United States. The active ingredient in propofol, 2,6-diisopropylphenol, is essentially insoluble in aqueous solutions and is formulated only for IV administration as a 1% (10 mg/ml) emulsion in 10% soybean oil, 2.25% glycerol, and 1.2% purified egg phosphatide. In the United States, disodium EDTA (0.05 mg/ml) or sodium metabisulfite (0.25 mg/ml) is added to inhibit bacterial growth. Nevertheless, significant bacterial contamination of open containers has been associated with serious patient infection; propofol should be either administered or discarded shortly after removal from sterile packaging.

Dosage and Clinical Use. The induction dose of propofol (DIPRIVAN) in a healthy adult is 1.5 to 2.5 mg/kg; propofol has an onset and duration of anesthesia similar to thiopental (Table 13–2). As with barbiturates, dosages should be reduced in the elderly and in the presence of other sedatives and increased in young children. Because of its reasonably short elimination half-life, propofol often is used for maintenance of anesthesia as well as for induction. For short procedures, small boluses (10% to 50% of the induction dose) every 5 minutes or as needed are effective. An infusion of propofol produces a more stable drug level (100 to 300 μg/kg per minute) and is better suited for longer-term anesthetic maintenance. Infusion rates should be tailored to patient response and the levels of other hypnotics. Sedating doses of propofol are 20% to 50% of those required for general anesthesia. However, even at these lower doses, caregivers should be vigilant and prepared for all of the side effects of propofol discussed below, particularly airway obstruction and apnea. Propofol elicits pain on injection that can be reduced with lidocaine and the use of larger arm and antecubital veins. Excitatory phenomena during induction with propofol occur at about the same frequency as with thiopental, but much less frequently than with methohexital (Langley and Heel, 1988).

Pharmacokinetics and Metabolism. The pharmacokinetics of propofol are governed by the same principles that apply to barbiturates. Onset and duration of anesthesia after a single bolus are similar to thiopental (Langley and Heel, 1988). Recovery after multiple doses or infusion has been shown to be much faster after propofol than after thiopental or even methohexital (Doze *et al.*, 1986; Langley and Heel, 1988).

Propofol's shorter duration after infusion can be explained by its very high clearance, coupled with the slow diffusion of drug from the peripheral to the central compartment (Figure 13–3). The rapid clearance of propofol explains its less severe hangover compared with barbiturates, and may allow for a more rapid discharge from the recovery room. Propofol is metabolized in the liver to less active metabolites that are renally excreted (Simons *et al.*, 1988); however, its clearance exceeds hepatic blood flow, and anhepatic metabolism has been demonstrated (Veroli *et al.*, 1992). Propofol is highly protein bound, and its pharmacokinetics, like those of the barbiturates, may be affected by conditions that alter serum protein levels (Kirkpatrick *et al.*, 1988).

Side Effects. Nervous System. The CNS effects of propofol are similar to those of barbiturates.

Propofol decreases $CMRO_2$, cerebral blood flow, and intracranial and intraocular pressures by about the same amount as thiopental (Langley and Heel, 1988). Like thiopental, propofol has been used in patients at risk for cerebral ischemia (Ravussin and de Tribolet, 1993); however, no human outcome studies have been performed to determine its efficacy as a neuroprotectant. Results from studies on the anticonvulsant effects of propofol have been mixed; some data even suggest it has proconvulsant activity when combined with other drugs (Modica *et al.*, 1990). Thus, unlike thiopental, propofol is not a proven acute intervention for seizures.

Cardiovascular. Propofol produces a dose-dependent decrease in blood pressure that is significantly greater than that produced by thiopental (Grounds *et al.*, 1985; Langley and Heel 1988). The fall in blood pressure can be explained by both vasodilation and mild depression of myocardial contractility (Grounds *et al.*, 1985). Propofol appears to blunt the baroreceptor reflex or is directly vagotonic because smaller increases in heart rate are seen for any given drop in blood pressure after doses of propofol (Langley and Heel, 1988). As with thiopental, propofol should be used with caution in patients at risk for or intolerant of decreases in blood pressure.

Respiratory and Other Side Effects. At equipotent doses, propofol produces a slightly greater degree of respiratory

Exhibit 16

The history of barbiturates a century after their clinical introduction

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Abstract: The present work offers an analysis of the historical development of the discovery and use of barbiturates in the field of psychiatry and neurology, a century after their clinical introduction. Beginning with the synthesis of malonylurea by von Baeyer in 1864, and up to the decline of barbiturate therapy in the 1960s, it describes the discovery of the sedative properties of barbital, by von Mering and Fischer (1903), the subsequent synthesis of phenobarbital by this same group (1911), and the gradual clinical incorporation of different barbiturates (butobarbital, amobarbital, secobarbital, pentobarbital, thiopental, etc). We describe the role played in therapy by barbiturates throughout their history: their traditional use as sedative and hypnotic agents, their use with schizophrenic patients in so-called "sleep cures" (Klaesi, Cloetta), the discovery of the antiepileptic properties of phenobarbital (Hauptmann) and their use in the treatment of epilepsy, and the introduction of thiobarbiturates in intravenous anesthesia (Lundy, Waters). We also analyze, from the historical perspective, the problems of safety (phenomena of dependence and death by overdose) which, accompanied by the introduction of a range of psychoactive drugs in the 1950s, brought an end to barbiturate use, except in specific applications, such as the induction of anesthesia and the treatment of certain types of epileptic crisis.

Keywords: barbiturates, history of medicine, sedative-hypnotic drugs, "sleep cures", epilepsy, anesthesia

Introduction

Throughout the history of humanity, numerous therapeutic agents have been employed for their hypnotic and/or sedative properties, though the true effectiveness of many of them has been fairly limited (Alamo et al 1998). It suffices to mention alcohol itself (in different forms, such as hydromel or wine) or the alkaloids of opium and other narcotic plants (hemp, jimsonweed, belladonna, henbane, etc). More recently, around the late 19th and early 20th centuries, agents such as paraldehyde, chloral hydrate, and bromides were used, until the discovery, at the beginning of the 20th century, of the sedative and hypnotic properties of barbiturates, thanks to the prior synthesis of malonylurea by Adolf von Baeyer in 1864.

The clinical introduction of barbiturates begun a century ago (1904) when the Farbwerke Fr Bayer and Co brought onto the market the first agent of this type, diethyl-barbituric acid, giving rise to profound changes in the pharmacological approach to the psychiatric and neurological disorders of the time. A large number of previously untreatable patients gained access to treatment and improved their prognosis. The most significant results were obtained in the treatment of patients with serious neuroses and psychoses and with severe emotional repression, who as a result of being administered barbiturates, especially intravenously, overcame their inhibitions, thus facilitating psychotherapeutic treatment. Barbiturates were also useful in the treatment of sleep disorders as well as being the first truly effective

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pharmacological tools for the management of epileptic seizures. Furthermore, they opened up the field of intravenous anesthesia, playing a prominent role in anesthetic induction, above all for minor operations.

In the course of the 20th century, more than 2500 barbiturates were synthesized, 50 of which were eventually employed clinically. Their use was widespread and many still have some use today. One hundred years after the introduction in clinical pharmacology of the original compound, oxybarbiturates, in general, continue to be the selected drugs in the treatment of some serious forms of insomnia and in some types of epilepsy. Similarly, some thiobarbiturates and some ultrashort-acting barbiturates are still used today as inducers of general anesthesia. Nevertheless, currently, 5 or 6 derivates of barbiturates are sufficient to cover the therapeutic applications that still require them.

Sedative and anticonvulsant drugs in the pre-barbiturate era

Although, as mentioned, the therapeutic agents historically employed for their sedative, hypnotic, or anticonvulsant effects have been quite numerous, the most specific drugs in this regard have their origin in the 19th century. Such is the case of choral hydrate, different alkaloids and, above all, bromides (Hollister 1983; Sneader 1985; Scott 1992; Lehmann 1993; Shorvon and Sander 1996; Shorter 1997; Alamo et al 1998; Healy 2002).

The second half of the 19th century is called by some authors, such as Shorter (1997), the "alkaloids era". Alkaloids were introduced into psychiatry as sedatives and hypnotics, thanks to the isolation of morphine from opium, in 1805, by the German pharmacist Friedrich Sertürner. In 1861, Wilhelm Griesinger, in the second edition of his *Die Pathologie und Therapie der Psychischen Krankheiten*, defended the use of opium in sleep disorders, pointing out the improvements it brought about in patients suffering from anxiety. However, the alkaloids that met with most success were those isolated from different species of the *Solanaceae* family: plants known for their hallucinogenic effects, such as hyoscyamus, whose sedative and hypnotic properties were described by the Viennese pharmacologist Karl Schroff in 1868. In 1839, chemists at the E Merck company in Darmstadt (Germany) had already isolated hyoscyamine, another alkaloid, which became popular in the late 19th century, forming part of many of the "cocktails" administered in neuropsychiatric institutions at that time (Woodward 1994). Finally, the year 1880 saw the isolation of hyoscine (called scopolamine in North America), an alkaloid that was also widely used in psychiatric cocktails, such as the famous Hyoscine Co A, which contained hyoscine, morphine, and atropine, and was administered to highly excited and aggressive manic patients (Norton 1979).

The first drug that could truly be called hypnotic is chloral hydrate. Synthesized in 1832 by Justus von Liebig, a chemist from Giessen, it was not analyzed as a hypnotic until 1869 by the Berlin pharmacologist Oskar Liebreich. The hypothetical mechanism to which its action was ascribed was based on the mistaken belief that, in vivo, chloral hydrate was capable of transforming itself into formic acid and chloroform, whose properties were already known at that time (Sourkes 1992). Very soon, chloral hydrate substituted morphine and the *Solanaceae* alkaloids, given its convenience, as it could be administered without the need for injection, allowing treatment in the home and making it unnecessary to confine patients to neuropsychiatric institutions (Shorter 1997).

Nevertheless, it would be the bromides that were most widely used in the second half of the 19th century, either as sedatives or for the treatment of epilepsy, having been introduced for these applications by the internist and obstetrician Sir Charles Locock in 1857. It was in that year that Locock reported his results in the treatment with bromides in women with what the author has named as catamenial or hysteriform epileptic seizures, obtaining positive outcomes in 14 women out of a sample of 15. From that time on, bromides were widely introduced in asylums and similar institutions throughout Europe, given their sedative and antiepileptic properties, the relevant function in the latter case being to reduce the expression of the epileptic patients' sexuality. Another contribution in relation to the neuropsychiatric use of bromides was made by the British doctor Neil MacLeod, who in 1897, while working in Shanghai, carried out the first "sleep cure" with these salts. MacLeod called it "the bromide sleep" (MacLeod 1900), and some authors, such as Shorter (1997), have considered this technique as the first pharmacological therapy that, within psychiatry, succeeded in improving the symptoms of psychiatric patients. However, the main problem with bromides resided in their high toxicity (neurological and gastrointestinal disorders, irritability, hallucinations, deliria, and lethargy), given their long half-life (elimination taking around 12 days) and their capacity for accumulation in tissue; as a result, they were gradually phased out after the introduction of barbiturates in the early part of the 20th century (Balme 1976).

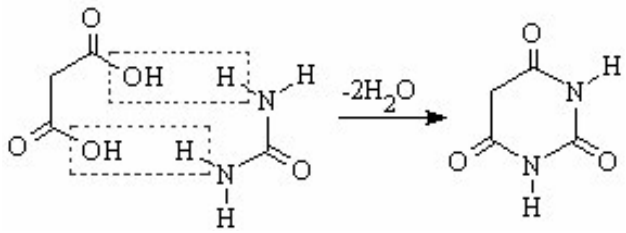

Figure 1 Synthesis of barbituric acid, from the combination of malonic acid (left) and urea (right).

Other substances used as hypnotics and sedatives and eventually as anticonvulsants were also introduced in the 19th century and the early decades of the 20th century. Such is the case of paraldehyde, discovered by Wildenbusch in 1829 and introduced into clinical practice by Vincenzo Cervello in 1882; and sulphonal, whose hypnotic action was discovered by chance by Eugen Baumann and Alfred Kast in 1887 (Kast 1888). Finally, those seeking to treat epilepsy turned, as well as to potassium bromide, chloral hydrate, or hyoscine, to a whole host of substances of more questionable efficacy, including opium, belladonna, atropine, stramonium, strophanthus, *cannabis indica*, and zinc oxide.

The discovery and clinical introduction of barbiturates as sedative and hypnotic agents

Between the 1920s and the mid-1950s, practically the only drugs used as sedatives and hypnotics were barbiturates (Lehmann and Ban 1970). From a chemical point of view, these drugs are closed-chain ureic compounds, whose nucleus is malonylurea (a combination of urea, a product present in animal excrement, and malonic acid, an acid derivative taken from apples) (Figure 1). Barbiturates were synthesized in 1864 by Adolf von Baeyer, though the synthetic process was developed and perfected by the French chemist Edouard Grimaux in 1879, making possible the subsequent widespread development of barbiturate derivatives (Carter 1951). Von Baeyer, a disciple of Robert W Bunsen and Friedrich A Kekulé, taught at the universities of Strasbourg and Munich, was the founder of what was to become the Bayer Chemical Co, and received the Nobel Prize in Chemistry in 1905 for his contribution to the development of organic chemistry (Figure 2a).

There are various hypotheses about the origin of the term "barbiturates" (Dundee and McIlroy 1982). According to one of these, Baeyer may have used this name for the compounds for sentimental reasons, in honor of his friend Barbara (Cohen 1943). Other authors, however, claim that the name derives from the fact that Baeyer celebrated his discovery in a tavern near his home that was frequented by artillery officers, who themselves were celebrating the day of their patron, St Barbara (Sharpless 1970). A third possibility is that the term is inspired by the "barbed" appearance of the crystals of these ureic compounds (Fieser 1944). In any case, it is clear that the union of the elements "barb(ara)" and "urea" forms the basis of the name.

(a) (b) (c)

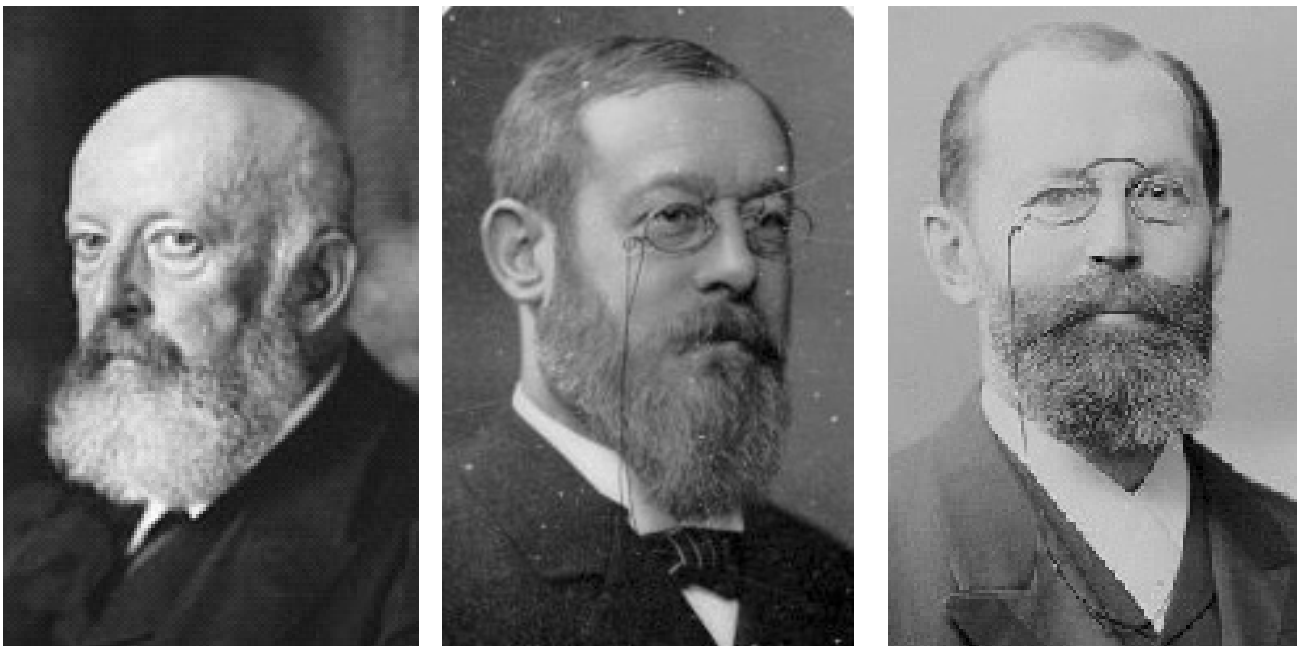

Figure 2 (a) Adolf von Baeyer (1835–1917); (b) Josef von Mering (1849–1908); (c) Emil Fischer (1852–1919).

From malonylurea to barbital

The first of the barbiturates to come onto the market was diethyl-barbituric acid, also known as barbital, malonal, or gardenal. Synthesized in 1881 by Conrad and Guthzeit, on treating the argentic salt of barbituric acid with ethyl iodide, it was introduced clinically as a hypnotic by the German companies E Merck (Darmstadt) and F Bayer and Co (Elberfeld) in 1904, thanks to the work of Josef Freiherr von Mering (Figure 2b) and Emil Fischer (Nobel Prize in Chemistry, 1902) (Figure 2c).

Von Mering, who taught pharmacology at the University of Halle, had observed that some of the synthetic compounds obtained towards the end of the 19th century and commercialized as hypnotics, such as sulphonal, contained in their molecular structure a carbon atom with two ethyl groups. Furthermore, knowing of von Baeyer's work with derivatives of urea, von Mering decided to study the hypnotic properties of diethyl-acetylurea, and found that it was even more potent than sulphonal. The next step was to analyze the properties of 5,5-diethyl-barbituric acid, for which he turned to Fischer, an old friend from his student days. At that time, Fischer, doyen of the German organic chemists, was Professor of Chemistry at the University of Berlin. Moreover, Fischer was well acquainted with the chemistry of malonylurea, as he had been von Baeyer's assistant in Munich for eight years. Together with his nephew Alfred Dilthey, he tested the new, resynthesized product, demonstrating, in dogs, that its hypnotic power was far greater than that of von Mering's diethyl-acetylurea (Sneader 1985). When Fischer told his friend von Mering about this finding, the latter happened to be in the Italian city of Verona, and it was this that prompted him to call the new drug Veronal® (Cohen 1943; Sharpless 1970). Nevertheless, other authors argue that the name Veronal (from Latin, verus = true) was coined by Fischer, who claimed to have found the "true" hypnotic compound (Sneader 1985). This new hypnotic drug was patented by Fischer in January 1903, and two months later the first scientific data on barbiturates were published in a brief report (Fischer and von Mering 1903). The licence for its commercialization in the USA was granted to the Winthrop Chemical Company.

The term barbital for diethyl-barbituric acid is a later development, coming as a result of the economic effects of World War I. After the United States entered the conflict, in 1917, Congress passed the Trading with the Enemy Act 1917, which permitted them as a kind of war booty to manufacture German products protected by patent, modifying their generic name and with the profits going to the American subsidiaries of the German companies (Sneader 1985). Thus, the American Medical Association approved the name barbital, whilst in the United Kingdom, through a similar mechanism, diethyl-barbituric acid came to be called barbitone. From this point on the two endings "-al" and "-one" could be found in the nomenclature of barbiturates.

Veronal had hypnotic, sedative, and anticonvulsant properties (Figure 3a). It could calm manic patients and help melancholic patients to sleep, and was an effective inducer of sleep in insomniacs. The first trials with barbital were carried out by Hermann von Husen (1904), a young psychiatrist affected by sleep disorders, who tried the new drug on himself. After taking 0.5 g of Veronal the first night and 1 g the following night, he reports:

> In both cases, after 10–15 minutes, I fell into a growing state of dejection that led to deep sleep after around 30 minutes. After half a gram of Veronal I slept for 8 hours, and after a whole gram, around 9 hours. On the first morning I awoke fresh and rested; on the second morning, after the higher dose, I found it difficult to get out of bed (von Husen 1904, p 59).

The consolidation of barbiturate therapy: phenobarbital

By means of small modifications to the chemical structure of the barbituric acid molecule, more than 2500 different agents were synthesized. The first barbital analogs, numbering around 18, were synthesized and tested by the group made up of von Mering, Fischer, and Dilthey. One of them, perhaps that most widely used subsequently, was phenobarbital, synthesized by Hörlein in 1911, on substituting one of the ethyl groups by a phenyl radical. Phenobarbital was employed in therapy as a hypnotic for the first time in 1912 by Loewe, Juliusburger, and Impens, and that same year it was commercialized by F Bayer and Co, under the name Luminal®. Phenobarbital, with a more prolonged pharmacological action than its predecessor, soon became "king of the barbiturates", both in hospitals and in outpatient care (Shorter 1997). This drug opened up the way, moreover, to another important therapeutic application of barbiturates, as will be mentioned later: the treatment of epilepsy.

Both Veronal (barbital) and Luminal (phenobarbital), the first two representatives of the series of barbiturates, were accepted by the international pharmacopoeia, such as the *United States Pharmacopoeia* (USP X) in 1926, and the *British Pharmacopoeia* in 1914 and 1932, respectively.

Later, both drugs were also included in the *Pharmacopoeia Internationalis*.

Clinical introduction of the new barbiturates

The new barbiturates brought substantial advantages compared with their classical predecessors, such as a greater potency and duration of action, as well as a wider therapeutic range. However, of the several thousand that were synthesized, only about 50 came onto the market, and of these no more than a couple of dozen were regularly used in clinical practice. The next barbiturate to be used successfully in therapy was butobarbital, whose history begins in World War I. The British war effort required large quantities of acetone for the manufacture of explosives (Sneader 1985), and one of the solutions was provided by Chaim Weizmann, who would later become the first president of the state of Israel. Weizmann found that the bacteria *Clostridium acetobutylicum* was capable of transforming materials rich in starch into acetone and butyric alcohol, and at low industrial cost. After the war, the cost of butyric alcohol, a chemical that was as useful as it was expensive, fell drastically, thus permitting its use for obtaining numerous synthetic drugs. In 1920, Roger Adams (Abbott Laboratories, Chicago, USA) synthesized the ester of 5-butyl-5-ethyl-malonic acid, an intermediate stage in the synthesis of a butyl analog of barbital, which was finally synthesized by Arthur Dox (Parke Davis and Company, Detroit, USA) in 1922, and marketed the following year by Abbott Laboratories, under the name Neonal® (Sneader 1985). Butobarbital (butethal in the USA) was three times as strong as barbital and its period of action was much shorter due to its lipophilicity, which greatly lowered the possibility of "rebound" drowsiness the day after administration.

In the years that followed, new barbiturates continued to come onto the market. In 1923, it was amobarbital (Amytal®), synthesized by Shonle and Moment (Eli Lilly Company, Indianapolis, USA) by adding a carbon atom to the butyl chain of butobarbital; and in 1929, Horace A Shonle also synthesized secobarbital (Seconal®). Both barbiturates had quite similar pharmacological properties to those of butobarbital (Sneader 1985). The next drugs of this series to be introduced were pentobarbital (Nembutal®), synthesized by Volwiler and Tabern (Abbott Laboratories) in 1930, and thiopental (Pentothal®). The latter, a sulfur derivative of pentobarbital, presented at the American Chemical Society congress in San Francisco in August 1935 (Tabern and Volwiler 1935), would revolutionize intravenous

(a)

(b)

Figure 3 (a) Elixir Veronal from Dr Bustamante's Laboratories it is a "Practical treatment of insomnia". They have also added audaciously "Secure and harmless". Finally they say that "it tastes good and acts smoothly, being absorbed by the organism". (b) Advertisement for Abbott sodium pentobarbital in an American medical journal of 1933, highlighting its "short but powerful hypnotic effect and prolonged sedative action from small dosage".

Table 1 Mean and maximum dosage of the pharmacological agents used as hypnotics before the benzodiazepine era

Drug	Dosage per administration: Mean dosage	Dosage per administration: Maximum dosage	Daily maximum dosage
Ethchlorvynol	250 mg	500 mg	750 mg
Chloral hydrate	500 mg	1000 mg	1000 mg
Paraldehyde	3 mL	8 mL	8 mL
Glutethimide	250 mg	500 mg	500 mg
Methyprylon	200 mg	400 mg	400 mg
Methaqualone	200 mg	400 mg	600 mg
Phenobarbital	50–100 mg	200 mg	200 mg
Amobarbital	50–100 mg	200 mg	200 mg
Secobarbital	100 mg	200 mg	200 mg
Pentobarbital	100 mg	200 mg	200 mg
Sodium tripental	250 mg	500–1000 mg	–

NOTE: The doses indicated correspond only to the hypnotic use of these drugs. The maximum doses of the barbiturates are not considered when they are used as anticonvulsants.

anesthesia and would be the only representative of the thiobarbiturate family to be officially recognized, being accepted first by the *British Pharmacopoeia* (1942, 7th Add) and subsequently by the *United States Pharmacopoeia* (1947, USP XIII) and the *Pharmacopoeia Internationalis* (1951, Volume I). Figure 3b shows an advertisement for pentobarbital in an American journal of the time.

Table 1 shows the recommended dosages of barbiturates used as hypnotics together with those of other drugs also used as hypnotics prior to the clinical introduction of benzodiazepines at the end of the 1950s. Among these last agents, chemically different from barbiturates although with similar pharmacological actions, we have to mention glutethimide (USV Pharmaceutical Corporation, 1954), methyprylon (Hoffmann-La Roche, 1955), methaqualone (King George Medical College, Lucknow, India, 1956; William H Rorer Inc, 1965), chlormethiazole (Hoffmann-La Roche, 1956), and ethchlorvynol (Pfizer, 1956). Most of these drugs were introduced as barbiturate substitutes, due to the fact that they seemed to offer a wider margin of safety. However, the clinical experience has demonstrated that their addiction liability and the severity of withdrawal symptoms were similar to those of barbiturates, and most of them were removed from the market some years later.

The role of barbiturates in "sleep cures" for schizophrenic patients

The hypnotic properties of some barbiturates were rapidly applied to the treatment of psychotic patients, thanks to their induction of a state of deep and prolonged sleep. The pioneer of these techniques was the Italian psychiatrist Giuseppe Epifanio, working at the University Psychiatric Clinic in Turin, who described his technique in an article published in 1915. The lack of impact of this development on the international scientific community can be attributed to the fact that it was published only in an Italian journal, and in the middle of the Great War (Epifanio 1915). It was on 25th March 1913 that Epifanio administered the first dose of Luminal to a girl aged 19 (FL) affected by manic-depressive psychosis, extending the treatment over a period of 4 days. The patient fell into a "deep sleep" that lasted until 9th April, was discharged at the end of June, and was in remission during the next two years. This case marked the beginning of what Manfred Bleuler would describe in 1955 as "the first of the great physical therapies" for mental disorders (Windholz and Witherspoon 1993).

However, the clinical introduction of these techniques is historically associated with Jakob Klaesi, a psychiatrist at the University Psychiatric Clinic in Zurich (Psychiatrische Universitätsklinik, Burghölzli, Switzerland). His "sleep cures" ("Dauerschlaf", "Dauernarkose"), proposed in 1920 within the framework of the 59th Assembly of the Swiss Psychiatry Society (28th November 1920), enjoyed great prestige at the time and directly involved the use of barbiturates. Klaesi's initial proposal was that his techniques for inducing deep hypnosis, taken from Epifanio, would facilitate communication between patient and psychotherapist ("to achieve a better relationship between doctor and patient") (Shorter 1997, p 204). Klaesi introduced his method in Switzerland, and based it on pre-medication with morphine (0.01 mL) and scopolamine (0.001 mL) and the subsequent administration (intravenous or subcutaneous), over at least 6–7 days, of Somnifen® (Figure 4), a mixture of diethyl and dipropenyl-barbituric acid and diethylamine (2–4 mL), manufactured by the Hoffmann-LaRoche company. The percentage improvements reported by Klaesi, in samples of schizophrenic patients, ranged from 25% to 33%, which is 10% higher than the rates of spontaneous remission in this type of patient (Klaesi 1922). These cures ("prolonged sleep therapy") acquired great popularity during the 1920s, with numerous variations as regards methodology and applications (agitated schizophrenic patients, delirium tremens, autism, morphine dehabituation, etc), though the administration of Somnifen was always involved (Windholz and Witherspoon 1993). Nevertheless, it is important to consider a fact mentioned in the first publication on the effectiveness of the method in schizophrenic patients: three of the 26 patients recruited died during the study due to

Figure 4 The packaging of Somnifen®, produced by Hoffmann-LaRoche.

bronchopneumonia or hemorrhages in the cardiac muscles (Klaesi 1922). A few years later, some authors set the mortality rate with Somnifen at around 5% (Müller 1927).

The legacy of Somnifen was taken up at the same Swiss clinic in Burghölzli by pharmacologist Max Cloetta and psychiatrist Hans W Maier, who sought a compound that would be better tolerated. In 1934, they prepared a compound based on paraldehyde, amylen hydrate, chloral hydrate, alcohol, ephedrine hydrate, digalen, and isopropyl-allyl-barbituric acid, which they called Cloettal® or "Cloetta Mixture", and which was rectally administered (Cloetta and Meier 1934). This preparation was widely used in schizophrenic patients, not only in the Zurich clinic (Boss, Monnier), but also elsewhere, such as in the Soviet Union by Ivan P Pavlov (Windholz and Witherspoon 1993). The most rigorous study with this mixture was carried out in Burghölzli by Marcel Monnier, who, with a sample of 125 schizophrenic patients, applied strict exclusion criteria (elderly patients and those with renal or respiratory disorders) before applying the preparation. Only 84 patients were given the Cloetta Mixture, and 53 of them improved (40 were even discharged from the hospital). Nevertheless, two patients died during the treatment as a result of respiratory complications associated with the medication (Monnier 1936).

Eliot Slater, of the Maudsley Hospital in London, recalled that "sleep cures" were "the only treatment we had back in the 1930s that was of any value in acute psychotic disorders" (Slater 1975, p 74). After this initial period, the use of "sleep cures" based on barbiturates began to decline due in part to problems of safety, as well as to the clinical introduction of new biological therapies for the treatment of schizophrenic patients such as Sakel's (1935) insulin shocks or the cardiazolic shocks of von Meduna (1937). Even so, as Shorter (1997) points out, "the story of barbituric narcosis has a corollary". This refers to the work of D Ewen Cameron in the mid-1950s at the Psychiatry Department of the Allan Memorial Institute in Montreal (Canada). Financed by the Central Intelligence Agency (CIA), Cameron developed his technique of "psychic driving" (Cameron 1956), a prototype version of what would come to be known commonly as "brainwashing". With this technique, in which barbiturates were also used, Cameron intended to take advantage of prolonged sleep to force his patients to listen to propaganda messages, which, in this case, were designed to quicken their recovery. In spite of its aims, eminently clinical, this work was widely criticized in the mass media at the time.

Barbiturates as antiepileptic agents

With phenobarbital, in addition to confirmation of the excellent hypnotic effect of barbiturates, it was demonstrated that these drugs had significant anticonvulsant properties. The discovery of these properties took place in 1912, the year of their commercialization, and provided another example of serendipity in the field of psychopharmacology. Alfred Hauptmann, resident psychiatrist in Freiburg, was given responsibility for the care of epileptic inpatients. Finding it impossible to sleep properly because of the continual convulsive seizures of his patients, Hauptmann decided to administer them some of the new hypnotics on the market, among them phenobarbital. Surprisingly, Hauptmann observed that the incidence of seizures in patients treated with low doses of phenobarbital fell notably, not only during the night, but also during the day (Hauptmann 1912). One of Hauptmann's most important conclusions was that phenobarbital not only reduced the number of seizures, but also their intensity, allowing many patients to leave the institutions and enjoy a normal working life.

It was in this way that the anticonvulsant properties of barbiturates were discovered, phenobarbital being the first truly effective drug for the treatment of epilepsy (Iváñez and Díez-Tejedor 1998). Table 2 shows, by way of example,

Table 2 Anticonvulsant drugs used at the National Hospital (Queen Square) in London, before and after the clinical introduction of phenobarbital in the treatment of epilepsy

1910		1930	
Drugs of definite benefit	**Drugs of doubtful benefit**	**Drugs of definite benefit**	**Drugs of doubtful benefit**
Bromides	Monobromate of camphor	Bromides	Zinc salts
Chloral hydrate	Eosinate of sodium	Bromide combinations	Iron
Glycerophosphates	Chloretone	**Phenobarbital**	Digitalis
Borax	Antipyrin	Borax	Strophanthus
Belladonna		Double tartrate of	Calcium
Zinc salts		borax and potassium	Opiates
Opium		Belladonna	Hypnotics
Strychnine		Nitroglycerine	
Chloride of calcium			
Atropine			

Adapted from Shorvon and Sander (1996).

the anticonvulsant agents commonly employed in the treatment of epilepsy before and after the introduction of phenobarbital.

However, the international acceptence of phenobarbital as an antiepileptic drug was seriously delayed, due first of all to the scarce significance outside Germany of the journal in which Hauptmann published the reports of his work (*Münchener Medizinische Wochenschrift*), and secondly, to the outbreak of World War I. Indeed, phenobarbitone was not commercialized in Great Britain until 1923, by the Winthrop Chemical Company. In one of his first reports on the use of phenobarbitone in England, Charles Brooks, Colony Medical Officer at the Chalfont Centre in London, noted its particular efficacy in severe cases of convulsions and in epileptic conditions with associated mental deficiency. Brooks also mentioned that if the barbiturate did not show a certain degree of effectiveness in the first months of treatment, the result of the therapy would not be satisfactory, so that it would be necessary to find an alternative (Brooks 1922). In a later report, Brooks made a close examination of patterns of use of phenobarbitone, concluding that it was more effective than bromides, but that it was not particularly useful in patients with low-intensity seizures (Brooks 1923).

It was precisely the Chalfont Centre that published, at the end of the 1920s, one of the first therapeutic guides for newly admitted epileptic patients, written by F Haward (Shorvon and Sander 1996). According to this guide, potassium bromide was the first-choice treatment, though it should be substituted by phenobarbital if there was no remission in the seizures within a given period of time (Table 2). If after three months of treatment the improvement was not clear, the guide recommended treatment with a combination of Luminal® and potassium bromide. Moreover, it set down the recommended dosage for phenobarbitone: 1 grain (65 grams) in the morning and another at night for adult patients, and 1/2 grain in the case of children; the dose was to be increased gradually, according to the clinical response, but should never exceed 6 grains per day (Haward 1928). At the beginning of the 1930s, the use of phenobarbital superseded definitively that of bromides in the treatment of epileptic seizures, despite the first reports of pharmacological tolerance and the risk of seizures when withdrawal was too abrupt. Phenobarbital is currently the most widely-prescribed antiepileptic drug in the world (Shorvon 2000), even though in the developed countries it has passed onto a secondary plane in therapy, for the treatment of partial and generalized seizures, due to its profile of adverse effects.

In the years following the discovery of the antiepileptic properties of phenobarbital, there were studies of numerous barbiturate derivatives in the field of epilepsy, the most important being mephobarbital (Prominal®) (Weese 1932) and, above all, deoxybarbital or primidone (Mysoline®). Primidone was synthesized by Bogue and Carrington (Imperial Chemical Industries Ltd, ICI, Manchester, UK) in 1949, demonstrating its antiepileptic activity in patients with generalized seizures in 1952 (Handley and Stewart 1952). Initially, primidone awoke great therapeutic interest, as it was thought that its anticonvulsant effectiveness may be greater than that of other available barbiturates, and without sedative effects (Bogue and Carrington 1953), but this interest soon waned after it was demonstrated that phenobarbital was a metabolite of this drug, together with phenyl-ethyl-malonamide (Butler and Waddell 1956). Comparative clinical studies carried out with phenobarbital and its prodrug, primidone, showed no differences between

the two (Oleson and Dam 1967). Currently, primidone is still considered as being of some use in partial and secondary generalized seizures, but is not a first-choice drug. Unlike phenobarbital, it cannot be used in epileptic status, since no galenic formulation has been developed for its parenteral administration.

The discovery by Houston Merritt and Tracy Putnam (Boston City Hospital, USA) in 1938 of the anticonvulsant properties of phenytoin (the first drug to show that an antiepileptic need not be a hypnotic), in 1944 of trimethadione, and in the late 1950s of carbamazepine, extended the spectrum of antiepileptic drugs, resulting in decreased use of barbiturates in these applications.

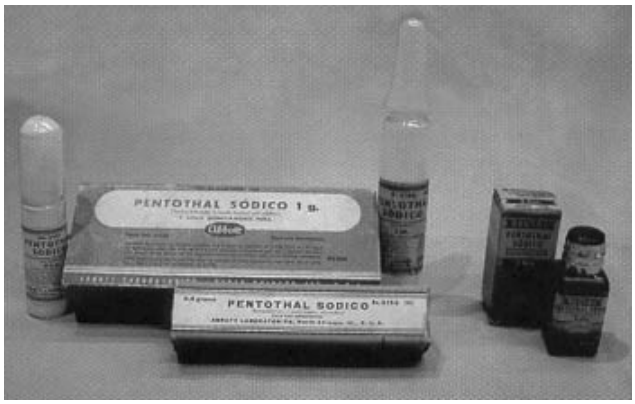

Figure 5 The packaging of Abbott Pentothal® at the time of its clinical introduction in the late 1930s. Pieces from the Museum of the Buenos Aires Anaesthesiology Association (Argentina).

The use of barbiturates in intravenous anesthesia

Despite the existence of some publications on the use of Somnifen® as a general anesthetic as early as 1921 by the French anesthetist Daniel Bardet – who noted that his patients woke up very slowly and with serious headaches (Bardet 1921) – the first barbiturate to be used systematically in anesthesia was sodium sec-butyl-(2-bromo-allyl)-barbiturate (Pernocton®). This was introduced into the field by the German obstetrician Bumm in 1927 (Bumm 1927). Subsequently, as new barbiturates were synthesized for their oral administration as sedatives, sodium salts of the same drugs were formulated, which could be administered intravenously and used as anesthetics (Dundee and McIlroy 1982). Notable among the pioneers in this field is John S Lundy of the Mayo Clinic (Rochester, USA), who introduced sodium amobarbital (1929) and sodium pentobarbital (1930) in anesthesia.

The addition of a methyl group to the butobarbital molecule, by the chemists Kropp and Taub at Bayer (IG Farbenindustrie, Leverkusen) in the early 1930s, gave rise to hexobarbital, whose sodium salt (Evipal®), introduced into clinical anesthesia in 1932 (Weese and Scharpff 1932), constituted the first barbiturate agent that induced anesthesia. Ten years after its introduction, more than 10 million people had undergone operations with the help of this drug (Adams 1944). The duration of hexobarbital's action was shorter than that of its predecessors, given its greater lipophilicity, but under its effect some muscular movements occurred. This problem was solved through the next modification of the chemical structure of the basic nucleus of the barbiturates, the addition of a sulfur group to pentobarbital. Thus born were the agents that would revolutionize intravenous anesthesia, the thiobarbiturates, thanks to the work of Volwiler and Tabern of Abbott Laboratories (Tabern and Volwiler 1935). These agents were studied as anesthetics at the Mayo Foundation (Rochester) by John Lundy's group, who gave the sulfur derivative of pentobarbital the name Thionembutal®. Its sodium salt was marketed as Pentothal (Figure 5). The team led by Ralph M Waters at the University of Wisconsin Medical School (Madison, USA) were the first to begin clinical administration of Pentothal, and published their results in 1936 (Pratt et al 1936). This agent rapidly displaced the rest of the barbiturates as an anesthetic, partly due to the swiftness of its onset and its short action period, and it currently remains the preferred intravenous anesthetic in many types of surgical intervention. Despite the anesthetic efficacy of both hexobarbital and thiopental, the barbiturates most commonly employed in surgery in the mid-20th century, they were not without their clinical problems. Such problems were brought to the public eye in particularly unfortunate fashion after the involvement of these agents, apparently due to malpractice, in numerous cases of death in patients treated in states of shock after the Japanese attack on Pearl Harbor in December 1941. Some authors went as far as describing these drugs as providing the "ideal form of euthanasia" (Halford 1943).

After World War II the search for anesthetic barbiturates continued, and new compounds such as thiobutobarbital (Horatz and Stürtzbecher 1952) were introduced, though the only one that truly challenged thiopental was methohexital (Brietal®), developed by SM Chernish's group at Lilly Research Laboratories (Indianapolis, USA) in 1956. In clinical trials, methohexital showed itself to be more potent than thiopental and to lead to quicker recovery in patients; it was recommended for use as an anesthetic

inducer in minor outpatient surgery (Taylor and Stoelting 1960). The subsequent development of other anesthetic agents for intravenous administration (hydroxydione, alphaxalone, etomidate, propofol, etc) led to a reduction in the use of barbiturates in this context.

The peak and decline of barbiturate therapy

As mentioned earlier, chemists from different universities and pharmaceutical companies managed to synthesize over 2500 barbiturate derivates. The differential pharmacokinetic properties of these agents made it possible to draw up a practical clinical classification, based on the duration of their pharmacological action (Hollister 1983). Thus, the barbiturates in the category of short or intermediate action (secobarbital, amobarbital, pentobarbital) were employed initially as hypnotics, whilst those of prolonged action (phenobarbital) were widely used as anxiolytics and anticonvulsants; ultrashort-acting agents, notably sodium thiopental, were especially useful as anesthetic inducers for minor operations (Table 3). From time to time, some barbiturates have been used in the treatment of other disorders. One such case is the use of primidone in the management of essential tremor (Koller et al 2000), while another is that of combinations of barbiturates and analgesics (salicylates, codeine, etc) in the treatment of headaches, migraines, and other types of pain (Wolf et al 1941), though such applications are considered counterproductive today.

Some barbiturates, such as sodium amytal and sodium pentothal (the latter being known as "the truth serum") were widely known and used as coadjuvant agents for the exercise of narcoanalysis, as initially developed by Bleckwenn in 1930 (Bleckwenn 1930a, 1930b). In principle, the application of an infusion of barbiturates reverted temporarily the catatonic state of certain schizophrenic patients. These cures for catatonia allowed patients, for a few hours, to maintain conversations and interact with their environment, before returning to their state of lethargy. Despite the fact that the response was somewhat brief, these cures were quite customary in European asylums in the 1930s and 1940s. But a variety of this technique became widespread during and after World War II: it consisted of the intravenous administration of a short-acting barbiturate, which had a disinhibiting effect (potentiating positive transfers) and facilitated the subsequent exercise of psychotherapy (a phenomenon referred to as "cathartic abreaction") (Lehmann 1993). This technique was also called by other authors the "induced crepuscular method".

It was during the 1930s and 1940s that barbiturates attained their greatest popularity and were most widely used, putting them in a position that could be compared, according to Hollister (1983), to that currently held by benzodiazepines. The barbiturates most commonly used at that time were phenobarbital, sodium amobarbital, sodium secobarbital, sodium pentobarbital, and sodium thiopental. Despite their widespread use during the first half of the 20th century, no barbiturate succeeded in eliminating the main drawbacks of these drugs, which were the phenomena of dependence and death by overdose (Johns 1977). Among the paradoxes of destiny is the possible death through overdose of the two scientists who introduced the first barbiturate, Fischer and von Mering, after some years of dependence upon these substances (Escohotado 1996). To reduce these problems, from a legal perspective, a series of laws were passed aimed at regulating the distribution and sale of barbiturates. The first of these came into force in California in 1929. However, its effects were limited, if we consider, for example, that the production of barbiturates in the USA increased by more than 400% from 1933, with some 70 tons of these drugs sold in 1936. The problem continued during the following decade, and it became necessary to arrange special conferences for all those involved, such as that held in Washington, under the auspices of the American Pharmaceutical Association, on 12th October 1945 (*Conference on the Regulation of Use and Distribution of Barbiturates*). Barbiturate use in the pre-benzodiazepine period was such that, in the USA alone, production of these drugs reached, in 1955, the quantity

Table 3 Classification and principal clinical applications of the barbiturates most commonly employed before World War II

	Barbiturates	Trade name	Chemical name	Clinical indications
Long-acting	Phenobarbital	Luminal	5-ethyl-5-phenylbarbituric acid	Sedative
Intermediate-acting	Amobarbital	Amytal	5-ethyl-5-isopentylbarbituric acid	Hypnotic
Short-acting	Pentobarbital	Nembutal	5-ethyl-5-(1-methylbutyl)-barbituric acid	Hypnotic and anticonvulsant
	Secobarbital	Seconal	5-allyl-5-(1-methylbutyl)-barbituric acid	Hypnotic
Ultrashort-acting	Thiopental	Pentothal	5-ethyl-5-(1-methylbutyl)-thiobarbituric acid	Anesthesia inducer

Adapted from Hollister (1983).

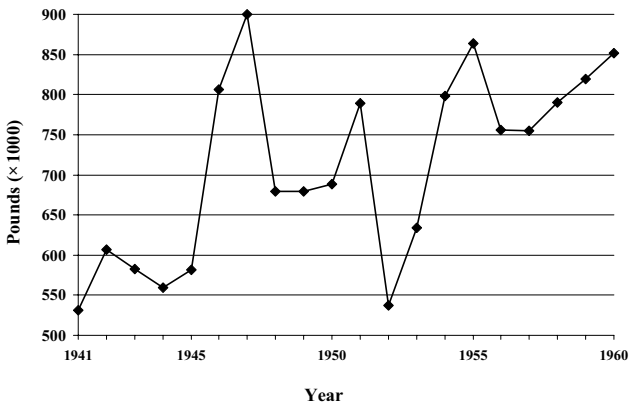

Figure 6 Evolution of annual barbiturates production in USA for the period 1941–1960. Adapted from Fort (1964).

necessary for the treatment of 10 million people throughout an entire year. Figure 6 shows the industrial production of barbiturates and their derivatives in the USA during the 1940s and 1950s.

The capacity of barbiturates to cause dependence was described in the medical literature as early as one year after the commercialization of barbital ("the Veronal habit"), though reliable evidence of the potential of these drugs to generate abuse was not available until the 1950s (Glatt 1962). In fact, doses 4–6 times higher than the therapeutic dose as hypnotics of the short-acting barbiturates (400–600 mg/day of amobarbital, secobarbital, or pentobarbital) brought about, if the treatment was sufficiently prolonged, authentic withdrawal syndromes when use was stopped. In order to palliate these effects, the Narcotics Expert Committee at the World Health Organization recommended (at their sessions of 7th–12th January, 1952, and 18th–24th October, 1956) that barbiturates should only be available on medical prescription. In spite of this, and according to different estimates, in 1965 there were 135 000 barbiturate addicts in England, whilst in the United States it was declared, by a special drug-dependence committee set up by President Kennedy in 1962, that there may be as many as 250 000 Americans addicted to barbiturates. Indeed, the USA currently produces 30 barbiturate pills per inhabitant per year (Escohotado 1996). Some barbiturates (amobarbital and pentobarbital) have even found their way into mixtures with amphetamine derivatives (*goofballs*), such as Dexamyl®, a combination of dextroamphetamine and amobarbital.

In relation to the frequent cases of death by overdose, given the small therapeutic margin of these substances, it should be pointed out that this was a common method in suicide attempts. It suffices to recall, in this regard, the famous case of Marilyn Monroe, on whose death certificate it clearly states "acute poisoning by overdose of barbiturates" (Figure 7). The lethal effect of these compounds was such that a mixture of barbiturates with other substances

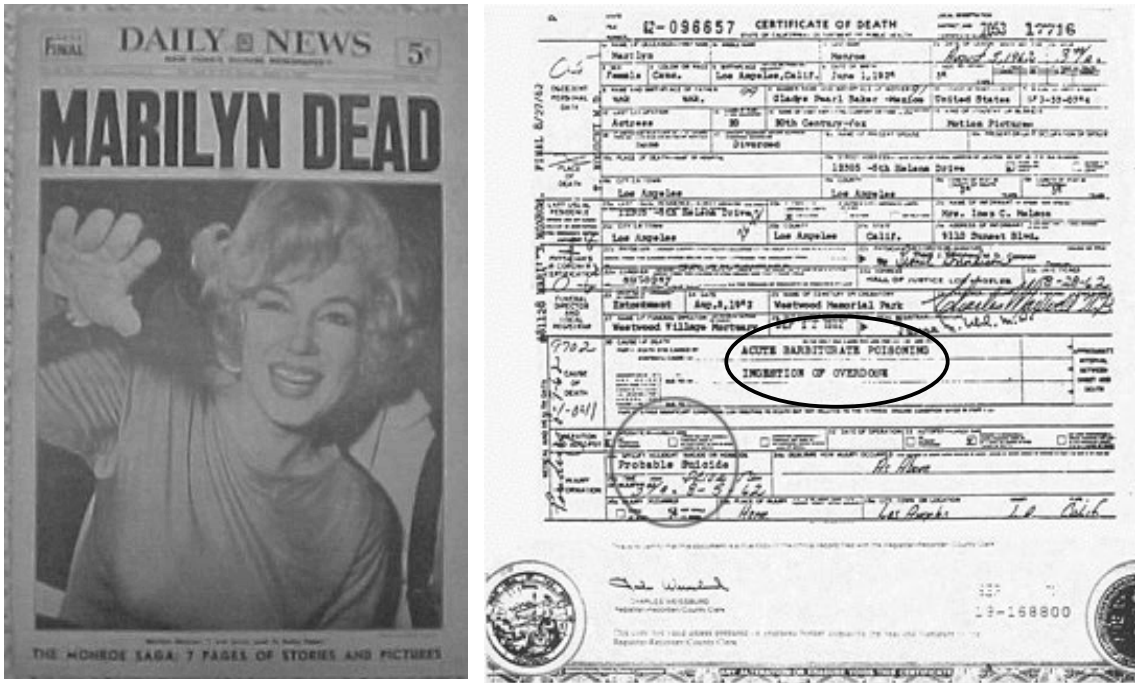

Figure 7 Death certificate of the actress Marilyn Monroe, issued on 28th August 1962. The circles indicate cause of death ("Acute barbiturate poisoning. Ingestion of overdose") and the intentionality ("Probable suicide").

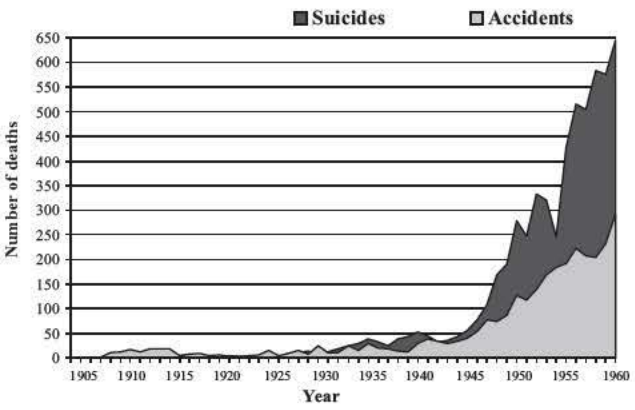

Figure 8 Deaths from overdose of barbiturates in England and Wales during the period 1905–1960 (Registrar-General's Statistical Review for England and Wales). Includes both accidental deaths and suicides. Adapted from Glatt (1962).

was even employed in some USA states for the execution of prisoners sentenced to death. Furthermore, there are classic reports of fatal overdose due to the "automatism phenomenon", whereby the patient would take his or her dose, only to forget that he or she had already taken it, given the amnesic effect of the drug, and take it again, this process being repeated several times (Richards 1934). Figure 8 shows the evolution of number of deaths (accidental or suicide) by barbiturate overdose in England and Wales for the period 1905–1960. In this regard, and in the city of New York alone, in the period 1957–1963, there were 8469 cases of barbiturate overdose, with 1165 deaths (Sharpless 1970), whilst in the United Kingdom, between 1965 and 1970, there were 12 354 deaths attributed directly to barbiturates (Barraclough 1974). These data should not surprise us, since in a period of just one year (1968), 24.7 million prescriptions for barbiturates were issued in the United Kingdom (Plant 1981). In view of these data, the Advisory Council Campaign in Britain took measures restricting the prescription of these drugs. Meanwhile, the prescription of prolonged-acting sedative barbiturates was strongly opposed through citizens' action campaigns such as CURB (Campaign on the Use and Restrictions of Barbiturates), especially active during the 1970s.

Furthermore, during the 1950s, when the use of barbiturates was at its peak, there took place a veritable revolution in the approach to psychiatric disorders, thanks to the introduction into clinical practice of the first pharmacological tools aimed specifically at treating these patients (Caldwell 1970; Jacobsen 1986; Ayd 1991; Lehmann 1993; Frankenburg 1994; López-Muñoz et al 2000; Ban 2001; Healy 2002). This "psychopharmacological revolution" began with the discovery and clinical use, from 1952, of chlorpromazine (López-Muñoz et al 2004), culminating in the commercialization of the first benzodiazepine, chlordiazepoxide, in 1960. The discovery of benzodiazepines was actually made possible, in part, by the 60 years of clinical and basic research provided by barbiturates, whose therapeutic life, from that time on, began to decline.

Barbiturates today

Currently, the use of barbiturates is circumscribed to quite specific therapeutic applications (Charney et al 2001). Thus, phenobarbital and butabarbital are still used as sedatives in cases of gastrointestinal and asthmatic functional disorders, as well as to antagonize the adverse central stimulant effects of some drugs, such as ephedrine, dextroamphetamine, or theophylline. Phenobarbital is also used in cases of withdrawal syndromes of hypnosedative agents. In the field of neurology, barbiturates (phenobarbital and primidone) are still employed, not only in the treatment of certain types of epilepsy (partial and tonic-clonic generalized seizures), but also in the emergency treatment of some types of convulsions, such as those associated with tetanus, eclampsia, cerebral hemorrhage, status epilepticus, or different forms of poisoning. As intravenous anesthetic inducers, ultrashort-acting barbiturates are of use, mainly thiopental and methohexital, the latter also being administered rectally in children or as a sedative in some diagnostic imaging explorations. Table 4 shows the therapeutic applications of barbiturates that have survived to the present day.

In addition to these approved indications, the barbiturates present other current uses. Phenobarbital is capable of improving the hepatic transport of bilirubin in patients with hemolytic jaundice, so that it can be used in newborn babies to treat hyperbilirubinemia and kernicterus. At a diagnostic level, amobarbital, in low doses, can be injected directly into the carotid artery prior to neurosurgery to identify the dominant cerebral hemisphere. Finally, anesthetic doses of barbiturates can attenuate post-surgical cerebral edemas and have positive effects in cases of cardiac and cerebral ischemia, reducing the size of the infarcted region. Moreover, barbiturates have been used since the 1970s in the management of acute traumatic brain injury in their capacity to reduce intracranial pressure (Marshall et al 1979). The mechanism through which high-dose barbiturates appear to exert their intracranial pressure-lowering effects is double: reduction of metabolism (with the consequent lower oxygen demand by cerebral tissue)

Table 4 Barbiturates currently employed and therapeutic applications

Barbiturate	Routes of administration	Therapeutic uses
Amobarbital	Oral, IM, IV	Insomnia Preoperative sedation Emergency management of seizures
Aprobarbital	Oral	Insomnia
Butabarbital	Oral	Insomnia Preoperative sedation
Mephobarbital	Oral	Epilepsy Daytime sedation
Methohexital	IV	Induction/maintenance of anesthesia
Pentobarbital	Oral, rectal, IM, IV	Insomnia Preoperative sedation Emergency management of seizures
Phenobarbital	Oral, IM, IV	Epilepsy Status epilepticus Daytime sedation
Primidone	Oral	Epilepsy
Secobarbital	Oral, rectal, IM, IV	Insomnia Preoperative sedation Emergency management of seizures
Thiopental	Rectal, IV	Induction/maintenance of anesthesia Preoperative sedation Emergency management of seizures

Adapted from Charney et al (2001).
Abbreviations: IM, intramuscular; IV, intravenous.

and modifications in vascular tone (Kassell et al 1980). Additionally some direct neuroprotective effects, such as membrane stabilization or inhibition of free radical-mediated lipid peroxidation, have been postulated (Piatt and Schiff 1984). Despite results of the multicenter randomized clinical trial published by Eisenberg et al (1988) that demonstrated the efficacy of high-dose barbiturates in severely head-injured patients with intractable intracranial pressure elevations, recent collaborations, based in Cochrane methodology, concluded that there is no evidence of health improvement in this type of patient (Roberts 2000).

The barbiturates introduced clinically one century ago were the first pharmacological agents to have demonstrated – in an historical period that was therapeutically inhospitable – a real efficacy in different neuropsychiatric disorders. They were the first-line treatment as hypnotics and anticonvulsants during the first half of the 20th century. The clinical results obtained in the last years in other indications such as the treatment (acute or prophylactic) of traumatic brain injury, although contradictory, seems to confirm that, from the pharmacological perspective, the barbiturates continue furnishing certain novelties and that in their history the last page has not yet been written.

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Exhibit 17

PDR
55
EDITION
2001

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...SALLY RELATED: Incidence less than 1% ... 3 or more patients, regardless of severity ... reactions reported only from ... experience or in the literature, not seen in ... considered rare and are italicized.

... Arrhythmia, bigeminy, abnormal electrocardiogram, myocardial ischemia, vasodilation.
Hepatitis.
... Agitation, dizziness.
... Asthma, dyspnea, hypoxia.

...SHIP UNKNOWN: Incidence less than ... 3 or more patients, regardless of ...

... Fever.
... Hemorrhage, myocardial infarct.
... Nutrition: Increased creatinine phosphokinase.
... System: Myalgia.
... Pruritis.

...TIONS for information regarding pediatric ... hyperthermia.
...dings: Transient elevations in glucose and ... count may occur as with use of other anes-

...USE AND DEPENDENCE

... drug abuse liability, and dependence associ... SUPRANE® (desflurane, USP) have not been ...

...AGE

... overdosage, or suspected overdosage, take ... measures: discontinue administration of SU... (desflurane, USP), maintain a patent airway, ini... controlled ventilation with oxygen, and ... cardiovascular function.

...AND ADMINISTRATION

...RANE® (desflurane, USP) from a vaporizer ... and designated for use with desflu...

...tion of general anesthesia must be individu... the patient's response (see INDIVIDUAL... DOSE). The following two tables provide ... based upon age and drug interaction ... ASA physical status I or II pa...

...OF AGE ON MAC OF DESFLURANE
...EAN ± SD (percent atmospheres)

...	O_2 100%	...	N_2O 60%
...6	9.2 ± 0.0	-	-
...5	9.4 ± 0.4	-	-
...4	10.0 ± 0.7	5	7.5 ± 0.8
...3	9.1 ± 0.6	-	-
...	-	5	6.4 ± 0.4
...4	8.6 ± 0.6	-	-
...5	8.1 ± 0.6	-	-
...4	7.3 ± 0.0	4	4.0 ± 0.3
...5	6.0 ± 0.3	6	2.8 ± 0.6
...6	5.2 ± 0.6	6	1.7 ± 0.4

... crossover pairs (using up-and-down method ...)

... sodiazepines decrease the amounts of SU... (desflurane, USP) required to produce anesthesia. ... is based on studies of drug interaction ...

...desflurane, USP) MAC WITH FENTANYL OR MIDAZOLAM
...EAN ± SD (percent reduction)

	18-30 years	31-65 years
	6.4 ± 0.0	6.3 ± 0.4
...yl	3.5 ± 1.9 (46%)	3.1 ± 0.6 (51%)
...l	3.0 ± 1.2 (53%)	2.3 ± 1.0 (64%)
	6.9 ± 0.1	5.9 ± 0.6
...olam	-	4.9 ± 0.9 (16%)
...olam	-	4.9 ± 0.5 (17%)

...desflurane, USP) decreases the doses of neu...cking agents required (see PRECAUTIONS, ...).
...intenance of anesthesia with inflow rates of ...s, the alveolar concentration of desflurane ... within 10% of the inspired concentration ...

THIOPENTAL SODIUM

Cat/Kit Number	Thiopental Sodium for Injection, USP	Diluent Volume	Reconstituted Concentration (%)	NDC Number
Syringe Kits[1]				
2580-0101	500 mg	20 mL	2.5	10019-258-96
Injection Kits[2]				
2630-0101	1 g	40 mL	2.5	10019-253-99
2540-0101	2.5 g	100 mL	2.5	10019-252-97
2550-0101	5 g	200 mL	2.5	10019-255-98

[1] Syringe Kits contain 1 vial of Thiopental Sodium for Injection, USP; 1 vial of 0.9% Sodium Chloride Injection, USP; 1 sterile syringe and needle.
[2] Injection Kits contain 1 vial of Thiopental Sodium for Injection, USP; 1 vial of Sterile Water for Injection, USP; sterile transfer spikes.

SAFETY AND HANDLING

Occupational Caution: There is no specific work exposure limit established for SUPRANE® (desflurane, USP). However, the National Institute for Occupational Safety and Health Administration has recommended an 8-hr, time-weighted average limit of 2 ppm for halogenated anesthetic agents in general (0.5 ppm when coupled with exposure to N_2O).

The predicted effects of acute overexposure by inhalation of SUPRANE® (desflurane, USP) include headache, dizziness or (in extreme cases) unconsciousness.

There are no documented adverse effects of chronic exposure to halogenated anesthetic vapors (Waste Anesthetic Gases or WAGs) in the workplace. Although results of some epidemiological studies suggest a link between exposure to halogenated anesthetics and increased health problems (particularly spontaneous abortion), the relationship is not conclusive. Since exposure to WAGs is one possible factor in the findings for these studies, operating room personnel, and pregnant women in particular, should minimize exposure. Precautions include adequate general ventilation in the operating room, the use of a well-designated and well-maintained scavenging system, work practices to minimize leaks and spills while the anesthetic agent is in use, and routine equipment maintenance to minimize leaks.

STORAGE

Store at room temperature, 15°–30°C (59°–86°F). SUPRANE® (desflurane, USP) has been demonstrated to be stable for the period defined by the expiration dating on the label.

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400-447-05

THIOPENTAL SODIUM

℞

[thi-ō-pent-ăl sō-dē-ŭm]

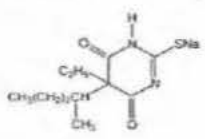
For Injection, USP

DESCRIPTION

Thiopental Sodium for Injection, USP is a thiobarbiturate, the sulfur analogue of sodium pentobarbital.

The drug is prepared as a sterile lyophilized powder and, after reconstitution with an appropriate diluent, is administered by the intravenous route.

Thiopental Sodium, USP is chemically designated sodium 5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate and has the following structural formula:



The drug is a yellowish, hygroscopic powder, stabilized with anhydrous sodium carbonate as a buffer (60 mg/g of Thiopental Sodium).

HOW SUPPLIED

Thiopental Sodium for Injection, USP, (Lyophilized) is available as follows:

[See table above]

Syringe Kits and Injection Kits are individually packaged. Store product prior to reconstitution at controlled room temperature 15°–30°C (59°–86°F).

Store reconstituted solution in a cool place and use within 24 hours of mixing. Administer only clear solution.

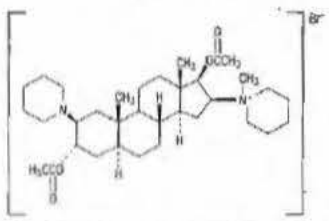
VECURONIUM BROMIDE

for Injection

℞ **only**

DESCRIPTION

Vecuronium Bromide for Injection is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2β, 3α, 5α, 16β, 17β)-3, 17-bis(acetyloxy)-2-(1-piperidinyl)androstan-16-yl]-1-methyl-, bromide. The structural formula is:



Its molecular formula is $C_{34}H_{57}BrN_2O_4$ with molecular weight 637.74.

Vecuronium Bromide for Injection is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Each 10 mL vial contains:

Vecuronium Bromide 10 mg; Citric Acid Anhydrous 20.75 mg; Sodium Phosphate Dibasic Anhydrous 16.25 mg; Mannitol (to adjust tonicity) 97 mg. pH is adjusted with sodium hydroxide and/or phosphoric acid if necessary. pH: 3.5–4.5.

Each 20 mL vial contains: Vecuronium Bromide 20 mg; Citric Acid Anhydrous 41.5 mg; Sodium Phosphate Dibasic Anhydrous 32.5 mg; Mannitol (to adjust tonicity) 194 mg. pH is adjusted with sodium hydroxide and/or phosphoric acid if necessary. pH: 3.5–4.5. When reconstituted with Bacteriostatic Water for Injection, USP, CONTAINS 0.9% w/v BENZYL ALCOHOL WHICH IS NOT FOR USE IN NEWBORNS.

HOW SUPPLIED

Vecuronium Bromide for Injection is supplied as follows:

NDC Number	Packaging Configuration	Vial Size
10019-481-01	Vecuronium Bromide for Injection 10 mg (diluent not supplied) Shelf pack carton of 10 individual vials.	10 mL
10019-482-02	Vecuronium Bromide for Injection 20 mg (diluent not supplied) Shelf pack carton of 10 individual vials.	20 mL

Store at controlled room temperature 15°–30°C (59°–86°F). PROTECT FROM LIGHT.

EDUCATIONAL MATERIAL

Educational Resources

Baxter Pharmaceutical Products Inc offers a wide range of educational materials free of charge to physicians, nurse-anesthetists, post-anesthesia nurses and hospital pharmacists. They are available from Baxter PPI sales representatives or by writing to: Baxter Pharmaceutical Products Inc, 95 Spring Street, New Providence, NJ 07974, or by calling (800) 262-3784.

) considered rare and are italicized.
Arrhythmia, bigeminy, abnormal electrocardiogram, myocardial ischemia, vasodilation.
Hepatitis.
: Agitation, dizziness.
Asthma, dyspnea, hypoxia.

ONSHIP UNKNOWN: Incidence less than 1 in 3 or more patients, regardless of 3)

r: Fever.
Hemorrhage, myocardial infarct.
lutrition: Increased creatinine phosphokinase.
System: Myalgia.
dages: Pruritis.

IONS for information regarding pediatric ant hyperthermia.
lings: Transient elevations in glucose and count may occur as with use of other anes-

AND DEPENDENCE

Drug abuse liability, and dependence associ-PRANE® (desflurane, USP) have not been

E

f overdosage, or suspected overdosage, take actions: discontinue administration of SU-flurane, USP), maintain a patent airway, ini- or controlled ventilation with oxygen, and quate cardiovascular function.

D ADMINISTRATION

ANE® (desflurane, USP) from a vaporizer esigned and designated for use with desflu-

ration of general anesthesia must be individu- on the patient's response (see INDIVIDUAL- DOSE). The following two tables provide potency based upon age and drug interaction edominately ASA physical status I or II pa-

T OF AGE ON MAC OF DESFLURANE
EAN ± SD (percent atmospheres)

N	O_2 100%	N	N_2O 60%
6	9.2 ± 0.0	-	-
5	9.4 ± 0.4	-	-
4	10.0 ± 0.7	5	7.5 ± 0.8
3	9.1 ± 0.6	-	-
-	-	5	6.4 ± 0.4
4	8.6 ± 0.6	-	-
5	8.1 ± 0.6	-	-
4	7.5 ± 0.0	4	4.0 ± 0.3
4	6.0 ± 0.3	6	2.8 ± 0.6
6	5.2 ± 0.6	6	1.7 ± 0.4

r of crossover pairs (using up-and-down method response)

benzodiazepines decrease the amounts of SU- (desflurane, USP) required to produce anesthesia. wing table is based on studies of drug interaction action).

(desflurane, USP) MAC WITH FENTANYL OR MIDAZOLAM
MEAN ± SD (percent reduction)

	18-30 years	31-65 years
	6.4 ± 0.0	6.3 ± 0.4
tanyl	3.5 ± 1.9 (46%)	3.1 ± 0.6 (51%)
tanyl	3.0 ± 1.2 (53%)	2.3 ± 1.0 (64%)
am	6.9 ± 0.1	5.9 ± 0.6
tazolam	-	4.9 ± 0.9 (16%)
dazolam	-	4.9 ± 0.5 (17%)

(desflurane, USP) decreases the doses of neu- blocking agents required (see PRECAUTIONS, actions).
maintenance of anesthesia with inflow rates of ert, the alveolar concentration of desflurane be within 10% of the inspired concentration. gure 1 in Pharmacokinetics section.)

LIED

(desflurane, USP), NDC 10019-641-24, is pack- ber-colored bottles containing 240 mL desflu-

Injection Kits[2]				
2530-0101	1 g	40 mL	2.5	10019-253-99
2540-0101	2.5 g	100 mL	2.5	10019-252-97
2550-0101	5 g	200 mL	2.5	10019-255-98

[1] Syringe Kits contain 1 vial of Thiopental Sodium for Injection, USP; 1 vial of 0.9% Sodium Chloride Injection, USP; 1 sterile syringe and needle.
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SAFETY AND HANDLING

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There are no documented adverse effects of chronic exposure to halogenated anesthetic vapors (Waste Anesthetic Gases or WAGs) in the workplace. Although results of some epidemiological studies suggest a link between exposure to halogenated anesthetics and increased health problems (particularly spontaneous abortion), the relationship is not conclusive. Since exposure to WAGs is one possible factor in the findings for these studies, operating room personnel, and pregnant women in particular, should minimize exposure. Precautions include adequate general ventilation in the operating room, the use of a well-designated and well-maintained scavenging system, work practices to minimize leaks and spills while the anesthetic agent is in use, and routine equipment maintenance to minimize leaks.

STORAGE

Store at room temperature, 15°–30°C (59°–86°F). SUPRANE® (desflurane, USP) has been demonstrated to be stable for the period defined by the expiration dating on the label.

℞ only

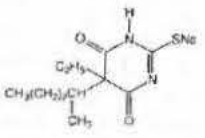
BAXTER
Mfd. and Mktd. by affiliates of
Baxter Healthcare Corporation
Deerfield, IL 60015 USA
Revised: June 1998
For Product Inquiry 1 800 ANA DRUG
400-447-05

THIOPENTAL SODIUM

[thī-ō-pent-āl sō-dē-ūm]
For Injection, USP

DESCRIPTION

Thiopental Sodium for Injection, USP is a thiobarbiturate, the sulfur analogue of sodium pentobarbital.
The drug is prepared as a sterile lyophilized powder and, after reconstitution with an appropriate diluent, is administered by the intravenous route.
Thiopental Sodium, USP is chemically designated sodium 5-ethyl-5-(1-methylbutyl)-2-thiobarbiturate and has the following structural formula:



The drug is a yellowish, hygroscopic powder, stabilized with anhydrous sodium carbonate as a buffer (60 mg/g of Thiopental Sodium).

HOW SUPPLIED

Thiopental Sodium for Injection, USP, (Lyophilized) is available as follows:
[See table above]
Syringe Kits and Injection Kits are individually packaged. Store product prior to reconstitution at controlled room temperature 15°–30°C (59°–86°F).
Store reconstituted solution in a cool place and use within 24 hours of mixing. Administer only clear solution.

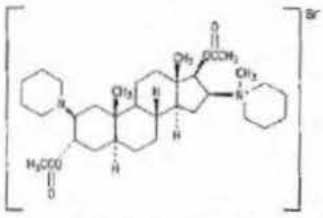
VECURONIUM BROMIDE

for Injection
℞ only

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION

Vecuronium Bromide for Injection is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2β, 3α, 5α, 16β, 17β)-3, 17-bis(acetyloxy)-2-(1-piperidinyl)androstan-16-yl]-1-methyl-, bromide. The structural formula is:



Its molecular formula is $C_{34}H_{57}BrN_2O_4$ with molecular weight 637.74.
Vecuronium Bromide for Injection is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Each 10 mL vial contains:
Vecuronium Bromide 10 mg; Citric Acid Anhydrous 20.75 mg; Sodium Phosphate Dibasic Anhydrous 16.25 mg; Mannitol (to adjust tonicity) 97 mg. pH is adjusted with sodium hydroxide and/or phosphoric acid if necessary. pH: 3.5–4.5.
Each 20 mL vial contains: Vecuronium Bromide 20 mg; Citric Acid Anhydrous 41.5 mg; Sodium Phosphate Dibasic Anhydrous 32.5 mg; Mannitol (to adjust tonicity) 194 mg. pH is adjusted with sodium hydroxide and/or phosphoric acid if necessary. pH: 3.5–4.5. When reconstituted with Bacteriostatic Water for Injection, USP, CONTAINS 0.9% w/v BENZYL ALCOHOL WHICH IS NOT FOR USE IN NEWBORNS.

HOW SUPPLIED

Vecuronium Bromide for Injection is supplied as follows:

NDC Number	Packaging Configuration	Vial Size
10019-481-01	Vecuronium Bromide for Injection 10 mg (diluent not supplied) Shelf pack carton of 10 individual vials.	10 mL
10019-482-02	Vecuronium Bromide for Injection 20 mg (diluent not supplied) Shelf pack carton of 10 individual vials.	20 mL

Store at controlled room temperature 15°–30°C (59°–86°F). PROTECT FROM LIGHT.

EDUCATIONAL MATERIAL

Educational Resources
Baxter Pharmaceutical Products Inc offers a wide range of educational materials free of charge to physicians, nurse-anesthetists, post-anesthesia nurses and hospital pharmacists. They are available from Baxter PPI sales representatives or by writing to: Baxter Pharmaceutical Products Inc, 95 Spring Street, New Providence, NJ 07974, or by calling (800) 262-3784.

For information on over-the-counter drugs, consult **PDR For Nonprescription Drugs.**

Exhibit 18

Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only

Guidance for Industry and Food and Drug Administration Staff

Document issued on: November 25, 2013

The draft of this document was issued on June 1, 2011.

For questions regarding this document contact Elizabeth Mansfield, by phone at (301) 796-4664, or by email at elizabeth.mansfield@fda.hhs.gov. For questions relating to devices regulated by CBER, contact the Office of Communications, Outreach and Development, CBER at 301-827-1800 or 800-835-4709.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of In Vitro Diagnostic Device Evaluation and Safety

Center for Biologics Evaluation and Research

Preface

Public Comment

You may submit written comments and suggestions at any time for Agency consideration to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, rm. 1061, (HFA-305), Rockville, MD, 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number 2011-D-0305. Comments may not be acted upon by the Agency until the document is next revised or updated.

Additional Copies

Additional copies are available from the Internet at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm[insert specific number].htm or http://www.fda.gov/cber/guidelines.htm. You may also send an e-mail request to dsmica@fda.hhs.gov to receive an electronic copy of the guidance or send a fax request to 301-847-8149 to receive a hard copy. Please use the document number 1723 to identify the guidance you are requesting.

Or, contact:

Office of Communication, Outreach and Development, HFM-40

Center for Biologics Evaluation and Research

Food and Drug Administration

1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448

Internet: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm

Tel: 800-835-4709 or 301-827-1800

E-mail: ocod@fda.hhs.gov

Table of Contents

Distribution of In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only

Guidance for Industry and Food and Drug Administration Staff

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

FDA is issuing this guidance document to provide the current thinking of the Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation and Research (CBER) on when in vitro diagnostic (IVD) products[1] are properly labeled "for research use only" (RUO) or "for investigational use only" (IUO)[2]. FDA is concerned that the distribution of unapproved and uncleared IVD products labeled RUO or IUO, but intended for purposes other than research or investigation (for example, for clinical diagnostic use[3]), has led, in some cases, to the clinical diagnostic use of products with unproven performance characteristics, and with manufacturing controls that are

[1] "*In vitro diagnostic products* are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the act), and may also be biological products subject to section 351 of the Public Health Service Act." Title 21, Code of Federal Regulations (CFR), section 809.3(a).

[2] This guidance is only intended to apply to IVD products that have not been approved, cleared or licensed for any use, and it is not intended to address off-label uses of any approved, cleared or licensed products.

[3] Throughout this guidance document, references to "clinical diagnostic use" and "use in clinical diagnosis" include use in making medical treatment decisions.

inadequate to ensure consistent manufacturing of the finished product. Use of such tests for clinical diagnostic purposes may mislead healthcare providers and cause serious adverse health consequences to patients, who are not aware that they are being diagnosed with or treated based on the results of tests with research or investigational products. FDA is issuing this guidance to clarify the requirements applicable to RUO and IUO IVD products, including that RUO and IUO labeling must be consistent with the manufacturer's intended use of the device.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Regulatory Requirements for Research Use Only and Investigational Use Only IVD products

Section 520(g) of the FD&C Act, 21 U.S.C. 360j(g), provides for the exemption of devices intended for investigational use from certain requirements of the Act if such devices comply with the procedures and conditions prescribed by that section and by regulation. For example, devices intended for investigational use that meet applicable requirements may be exempted from premarket notification and premarket approval requirements of sections 510, 515, 520(g)(2)(A) of the Act (21 U.S.C. 360, 360e, 21 U.S.C. 360j(g)(2)(A)); *see also* 21 CFR 812.1(a). A product's intended use refers to the "objective intent" of those responsible for labeling the product.[4] Intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article.[5]

Device Investigations Subject to IDE Regulation
FDA's investigational device exemption (IDE) regulation is found at 21 CFR part 812. Under 21 CFR 812.5, investigational devices must bear a label that states the following: "CAUTION--Investigational device. Limited by Federal (or United States) law to investigational use." The labeling may not represent that the device is safe or effective for the purposes for which it is being investigated. 21 CFR 812.5(b). The IDE regulation also prohibits certain conduct by sponsors and investigators pertaining to the investigation and distribution of investigational devices, among other practices. See 21 CFR 812.7.

Device Investigations Exempt from IDE Regulation
Investigations of diagnostic devices that meet the criteria at section 812.2(c)(3) are exempt from the regulations at 21 CFR 812, with the exception of section 812.119. The criteria at section 812.2(c)(3) include specifying that testing:

[4] See, 21 CFR 801.4
[5] See, id.

- be non-invasive,
- not require an invasive sampling procedure that presents a significant risk,
- not by design or intention introduce energy into a subject, and
- not be used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

The criteria in section 812.2(c)(3) also include compliance with labeling requirements section CFR 809.10(c), which exempts shipments and other deliveries of IVDs from certain labeling requirements if either (1) the device complies with part 812, or (2) the investigation is not subject to part 812 and one of the following conditions is met:

(i) For a product in the laboratory research phase of development, and not represented as an effective in vitro diagnostic product, all labeling bears the statement, prominently placed: "For Research Use Only. Not for use in diagnostic procedures."

(ii) For a product being shipped or delivered for product testing prior to full commercial marketing (for example, for use on specimens derived from humans to compare the usefulness of the product with other products or procedures which are in current use or recognized as useful), all labeling bears the statement, prominently placed: "For Investigational Use Only. The performance characteristics of this product have not been established."

For purposes of this guidance document, "labeled RUO" refers to IVD products labeled in accordance with section 809.10(c)(2)(i); "labeled IUO" refers to IVD products labeled in accordance with section 809.10(c)(2)(ii) unless otherwise specified. Examples of products that meet the criteria for these designations are provided in Section III.

Because these products are exempt from most regulatory controls, it is important that they are not distributed for clinical diagnostic uses.

Mere placement of an RUO or IUO label on an IVD product does not render the device exempt from otherwise applicable clearance, approval, or other requirements. FDA may determine that the device is intended for use in clinical diagnosis based on other evidence, including how the device is marketed.

In general, if evidence shows that an IVD product is inappropriately labeled RUO or IUO, and that the product does not qualify for an investigational device exemption under 520(g) of the Act, and is not cleared, approved, or 510(k)-exempt, the device would be misbranded under sections 502(a) and 502(o) of the Act, 21 U.S.C. 352(a), 352(o), and adulterated under section 501(f) of the Act, 21 U.S.C. 351(f).

III. Research Use Only and Investigational Use Only In Vitro Diagnostic Products

Both RUO and IUO products are IVD products currently under development and not approved for clinical diagnostic use. Because they are being shipped for investigations pertaining to product development and not clinical use, these products are exempt from most regulatory controls including IDE regulation. The term RUO refers to devices that are in the laboratory phase of development. The term IUO refers to devices that are in the product testing phase of development.

A. Research Use Only In Vitro Diagnostic Products

An RUO product is an IVD product that is in the laboratory research phase of development and is being shipped or delivered for an investigation that is not subject to part 812. During the research phase of development, the focus of manufacturer-initiated studies is typically to evaluate design, limited-scale performance, and issues such as usability of the test. Some examples of products FDA would consider to be in this research phase include:

- Tests that are in development to identify test kit methodology, necessary components, and analytes to be measured.
- Instrumentation, software, or other electrical/mechanical components under development to determine correct settings, subcomponents, subassemblies, basic operational characteristics, and possible use methods.
- Reagents under development to determine production methods, purification levels, packaging needs, shelf life, storage conditions, etc.

FDA also recognizes that there are certain products, such as instruments, systems, and reagents that are labeled for research use only and intended for use in the conduct of non-clinical laboratory research with goals other than the development of a commercial IVD product, i.e., these products are used to carry out research and are not themselves the object of the research. These include products intended for use in discovering and developing medical knowledge related to human disease and conditions. For example, instruments and reagents intended for use in research attempting to isolate a gene linked with a particular disease may be labeled for research use only when such instruments and reagents are not intended to produce results for clinical use.

B. Investigational Use Only In Vitro Diagnostic Products

An IUO product is an IVD product that is being shipped or delivered for product testing that is not subject to 21 CFR part 812 (with the exception of §812.119, Disqualification of clinical investigator) prior to full commercial marketing (for example, for testing of specimens derived from humans to compare the usefulness of the product with other products or procedures which are in current use or recognized as useful). Examples of IVD products under investigation that FDA considers to fall in this category include those that are being

evaluated in comparison studies that use archived or fresh specimens to determine performance characteristics.

IV. Appropriate Labeling and Distribution Practices for RUO and IUO Products

A. Labeling of RUO and IUO IVD Products

1. Research Use Only Labeling

With respect to IVD products that are appropriately labeled RUO, the RUO labeling is meant to serve as a warning, to prevent such products from being used in clinical diagnosis, patient management, or an investigation that is not exempt from 21 CFR part 812. In general, IVD products that are intended for clinical diagnosis or patient management must be labeled "For *In vitro* diagnostic use"[6] and be in compliance with all relevant regulations for *In vitro* diagnostic devices.

An IVD product should not be labeled RUO if it is intended for use in a clinical investigation subject to 21 CFR part 812 or for clinical diagnostic use outside an investigation (for example, in clinical diagnosis for standard medical practice). FDA would consider such an IVD product to be misbranded under section 502(a) of the Act, 21 U.S.C. 352(a), if it were labeled "For Research Use Only" or otherwise labeled solely for research use, because such labeling would be false or misleading.

2. Investigational Use Only Labeling

Similarly, with respect to IVD products that are appropriately labeled IUO, the IUO labeling is meant to serve as a warning that products so labeled should not be used in clinical diagnosis, patient management, or an investigation that is not exempt from 21 CFR part 812.

An IVD product should not be labeled IUO if it is intended for non-investigational purposes, such as in clinical diagnostic use outside of an investigation. FDA would consider such an IVD product to be misbranded under section 502(a) of the Act, 21 U.S.C. 352(a), if it was labeled with the statement: "For Investigational Use Only" or "Investigational device."[7]

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[6] 21 CFR 809.10(a)(4). Alternatively, some IVD products may be appropriately labeled as analyte specific reagents (see 21 CFR 864.4020 and 21 CFR 809.10(e)(1)(x) or (xi), or as general purpose reagents (see 21 CFR 864.4010 and 21 CFR 809.10(d)(1)(iv)).

[7] IVD products intended for investigational use in a manner that is not consistent with an exempted investigation (see 21 CFR 812.2(c) for a description of exempted investigations) must comply with the Investigational Device Exemption (IDE) requirements in 21 CFR part 812 in order to be exempt from many requirements otherwise applicable to medical devices. Instead of being labeled IUO, they must be labeled

B. Distribution Practices that are Inconsistent with RUO/IUO Designations

A product's intended use refers to the "objective intent" of those legally responsible for labeling the product[8], which may be determined by looking at the totality of circumstances surrounding the distribution of the article.[9] Overt expressions by the manufacturer, such as those present in labeling and advertising, may be sufficient to show determine that an IVD product is in appropriately labeled RUO or IUO, when such expressions demonstrate that the device is actually intended for clinical use despite the RUO or IUO labeling. Other evidence of the intended use of a product could include the design of the product, other statements by the manufacturer about the device, and how the device is sold and distributed by or on behalf of the manufacturer. The following are examples of evidence of intended uses that, depending on the totality of the circumstances surrounding the distribution of the article, would appear to conflict with RUO or IUO labeling:

- Written or verbal statements in any labeling, advertising, or promotion of the IVD product by or on behalf of the manufacturer, including any performance claims, instructions for clinical interpretation, clinical information, product names, or descriptors that claim or suggest that the IVD product may be used for any clinical diagnostic use, including a clinical investigation subject to part 812. This may include workshops or presentations that describe clinical uses of products labeled RUO or IUO that do not include appropriate statements and warnings about the research or investigational nature of the products;
- Written or verbal statements in any labeling, advertising, or promotion of the IVD product by or on behalf of the manufacturer that suggest that clinical laboratories can validate the test through their own procedures and subsequently offer it for clinical diagnostic use as a laboratory developed test.
    - Solicitation of business from clinical laboratories; for example, a manufacturer who produces only products labeled RUO whose sales force makes routine calls to clinical laboratories that do not perform research or clinical studies may be viewed as demonstrating its intent that its products be used for clinical purposes.
- Provision of certain types of specialized technical support [10] (e.g., assistance in performing clinical validation) to clinical laboratories.

"CAUTION—Investigational device. Limited by Federal (or United States) law to investigational use." 21 CFR 812.5.

[8] For the purposes of this guidance document, the term "manufacturer" 21 CFR 806.2(g) is taken as synonymous with "persons legally responsible for the labeling of devices" 21 CFR 801.4. The term "manufacturer" is used as a convenience throughout the guidance.

[9] See 21 CFR 801.4.

[10] Note: FDA is not referring here to generic maintenance support or software updates for an RUO or IUO IVD product.

Other practices, though not themselves in conflict with RUO or IUO labeling, may support a finding of a conflicting intended use when accompanied by behavior described above. For example, when there is a past history of distribution of a product intended for clinical diagnostic use as an analyte specific reagent (ASR), and the product is now labeled as RUO or IUO, without any change in distribution practices such as advertising to and solicitation of business from clinical laboratories, the "new" RUO/IUO labeling is likely to be inconsistent with the intended use of the manufacturer.

Other practices may or may not indicate an intended use that is consistent with RUO/IUO labeling, depending on the context. For example:

1. Instructions for use for an IVD product labeled RUO or IUO

FDA may consider all labeling for the product, including the content of the instructions for use and descriptive language in package inserts provided with the product as evidence of intended use.

In certain circumstances, such as when the use of an IVD product labeled for research use only is limited to use in the conduct of laboratory research that is unrelated to the development of IVDs, providing instructions for correctly using the product in a research manner (for example, mixing proportions, incubation times, storage conditions, etc.) would be considered to be consistent with research use only labeling. However, inclusion of clinical interpretive information, discussion of clinical significance, or other indications of clinical applicability included with any IVD products labeled for research use only would suggest that such products are not intended for research use only, but rather that they are intended for non-research clinical diagnostic purposes. FDA would consider the provision of such information as evidence of an intended use that would appear to conflict with research use only labeling, and requires compliance with all applicable device requirements under the FD&C Act.

FDA believes that those products that are being distributed for use in the research phase of IVD development may be unlikely to need instructions for use, as such products are still in their formative stages, and provision of instructions for using such products may not always be necessary. If basic instructions for use are needed in order to properly configure or use the device in the research phase of development, provision of these may be viewed as consistent with RUO labeling. For IVD products labeled IUO that are the subject of a clinical investigation by a sponsor other than the manufacturer, it is acceptable (and perhaps necessary) for the manufacturer to provide instructions for use to the sponsor of the study using the format described in 21 CFR 809.10(b).

2. Validation and verification of clinical diagnostic testing using IVD products labeled RUO or IUO

FDA views the activities of a manufacturer that aid the clinical laboratory in validation

or verification of a test that incorporates RUO or IUO labeled IVD products as evidence of the manufacturer's intended use. If the manufacturer of an IVD product labeled RUO or IUO were to assist in the validation or verification of the performance of a test for clinical diagnostic use that uses its RUO or IUO labeled IVD, that assistance would be considered to be evidence of a non-research or non-investigational intended use. FDA would consider such evidence along with the totality of the circumstances.

In contrast, the manufacturer of an appropriately labeled RUO or IUO device may provide support services such as general repair or maintenance, and general non-diagnostic use-specific technical support, because, in general, these would not constitute evidence of a non-research or non-investigational intended use.

FDA recommends that manufacturers assess the totality of the circumstances surrounding the sale and distribution of their RUO and IUO labeled IVD products to ensure that they are not engaging in practices that conflict with their labeling.

C. Other Relevant Practices

1. Use of a "certification program"

The totality of the circumstances surrounding the distribution and use of an RUO or IUO product should be considered when assessing its intended use. User certification programs, where users certify that they will not use RUO/IUO products in a manner inconsistent with the labeling, would be viewed as one factor to consider when assessing these circumstances. However, the existence of a certification program alone would not relieve manufacturers from their responsibilities to ensure that their labeling and distribution practices for RUO/IUO products are consistent with the product's RUO/IUO label.

2. Software labeled RUO or IUO

Software that is a stand-alone IVD product, or a component of or an accessory to another IVD product, which is labeled for research or investigational use only, may be distributed for research or investigational use to entities conducting research or investigations with the software.

V. FDA's Compliance Approach

Manufacturers must comply with all applicable requirements under the FD&C Act and FDA regulations for those IVD products that are intended for use in clinical diagnostic applications. For devices that are not used in research or investigation, these requirements generally include registration of the manufacturer and listing of the device(s), compliance with current Good Manufacturing Practices, and reporting of adverse events, among other general controls. There are also specific requirements for various device types, for example,

analyte specific reagents. *See* 21 CFR 809.10(e), 809.30, & 864.4020. While some IVD products, including some analyte specific reagents, are exempt from premarket notification, other products require premarket clearance or approval. Where the appropriate regulatory pathway is unclear, manufacturers are encouraged to discuss the matter with FDA.

When determining whether non-compliance with statutory and regulatory requirements warrant a regulatory and/or enforcement action, FDA intends to consider the totality of the circumstances concerning a manufacturer's sale and distribution of a product labeled as RUO or IUO.

In general, if evidence shows that an IVD product is inappropriately labeled RUO or IUO, and that the product does not qualify for an investigational device exemption under 520(g) of the Act, and is not cleared, approved, or 510(k)-exempt, the device would be misbranded under sections 502(a) and 502(o) of the Act, 21 U.S.C. 352(a), 352(o), and adulterated under section 501(f) of the Act, 21 U.S.C. 351(f).

REFERENCE 2

DEPARTMENT OF HOMELAND SECURITY
U.S. Customs and Border Protection
ENTRY/IMMEDIATE DELIVERY

Form Approved
OMB No. 1651-0024

BOX: [redacted] [redacted] AMS CARRIER [redacted]

19 CFR 142.3, 142.16, 142.22, 142.24 ABI CERTIFIED

1. ARRIVAL DATE	2. ELECTED ENTRY DATE	3. ENTRY TYPE CODE/NAME	4. ENTRY NUMBER
072415		01 CONSMPTION	[redacted]
5. PORT	6. SINGLE TRANS. BOND	7. BROKER/IMPORTER FILE NUMBER	
5309		[redacted]	
	8. CONSIGNEE NUMBER		9. IMPORTER NUMBER
	[redacted]		[redacted]
10. ULTIMATE CONSIGNEE NAME		11. IMPORTER OF RECORD NAME	
[redacted]		[redacted]	
12. CARRIER CODE	13. VOYAGE/FLIGHT/TRIP	14. LOCATION OF GOODS-CODE(S)/NAME(S)	
[redacted]	[redacted]	[redacted]	
15. VESSEL CODE/NAME			
16. U.S. PORT OF UNLADING	17. MANIFEST NUMBER	18. G.O. NUMBER	19. TOTAL VALUE
5501			[redacted]

20. DESCRIPTION OF MERCHANDISE
THIOPENTIAL-NA STERILE PWDR (LAW ENFORCEMENT ONLY

21. IT/BL/AWB CODE	22. IT/BL/AWB NO.	23. MANIFEST QUANTITY	24. H.S. NUMBER	25. COUNTRY OF ORIGIN	26. MANUFACTURER NO.
I	[redacted]		[redacted]	[redacted]	[redacted]
M	[redacted]	[redacted]			

27. CERTIFICATION

I hereby make application for entry/immediate delivery. I certify that the above information is accurate, the bond is sufficient, valid and current, and that all requirements of 19 CFR Part 142 have been met.

SIGNATURE OF APPLICANT

PHONE NO. [redacted] DATE 07/28/15

29. BROKER OR OTHER GOVT. AGENCY USE

02 FDA HOLD 07/27/15
14 FDA DOCUMENTS REQUIRED 07/27/15
02 FDA HOLD 07/28/15
14 FDA DOCUMENTS REQUIRED 07/28/15

28. CBP USE ONLY

☐ OTHER AGENCY ACTION REQUIRED, NAMELY:

☐ CBP EXAMINATION REQUIRED

☐ ENTRY REJECTED, BECAUSE:

DELIVERY AUTHORIZED:	SIGNATURE	DATE

PAPERWORK REDUCTION ACT STATEMENT: An agency may not conduct or sponsor an information collection and a person is not required to respond to this information unless it displays a current valid OMB control number and an expiration date. The control number for this collection is 1651-0024. The estimated average time to complete this application is 15 minutes. If you have any comments regarding the burden estimate you can write to U.S. Customs and Border Protection, Office of Regulations and Rulings, 799 9th Street, NW., Washington DC 20229.

CBP Form 3461 (10/09)

FDA 148

[redacted]

CUSTOM INVOICE

SHIPPER [redacted]	INVOICE NO & DATE [redacted]	EXPORTERS REF [redacted]
CONSIGNEE [redacted] **DEA Number:** [redacted] **Phone Number:** [redacted]	**Buyers Order No:** [redacted]	
PRE CARRIAGE BY [redacted]	PLACE OF RECEIPT OF PRE CARRIER	COUNTRY OF ORIGIN [redacted]
		COUNTRY OF FINAL DESTINATION **USA**
VESSEL / FLIGHT NO	PORT OF LOADING [redacted]	
PORT OF DISCHARGE	FINAL DESTINATION **Huntaville, Texas**	

DESCRIPTION OF GOODS MARKS & NO/ NO & KIND OF PACKAGE CONTAINER NO:	QUANTITY	AMOUT per unit (USD)	AMOUNT (USD)
Thiopenta Sodium USP 1gm Vial **Value Given For Custom Purpose:** [redacted]	1000 Vials	[redacted]	[redacted]
Declaration: We declare that this invoice shows the actual price of the goods Described and that all the particulars are true and correct	SIGNATURE / DATE	[redacted]	

242 - 243

[redacted]

[redacted]

TX002

Explanation for the Legitimate Use of Thiopental Being Imported Under 21 U.S.C. § 952

This product is being imported for use by the [redacted] law enforcement activities. The product complies with federal statutory and regulatory requirements. The [redacted] will not use this product for activities other than law enforcement activities.

[redacted]

June 8, 2015
Date

[redacted]

[redacted]

QUALITY CONTROL DEPARTMENT

CERTIFICATE OF ANALYSIS-FINISHED PRODUCT

Product Name [redacted] **Generic Name**	Thiopental Sodium for injection USP		
Manufactured by:	[redacted]	**Mfg. Date.**	06/15
		Exp. Date.	05/17
Batch No.	[redacted]	**Date Sampled.**	10/06/15
Batch Size.	[redacted]	**Qty Sampled.**	40 Units
Sampled by.	[redacted]	**Release Date.**	24/06/15
Specification	USP specification	**A.R. No**	[redacted]

S.No	TEST	SPECIFICATION	RESULT
1.	Description	Yellowish to white powder filled in colorless glass vials.	Yellowish to white powder filled in colorless glass vials.
2.	Identification	Should be positive for Thiopentone Sodium	Complies
3.	Average filled wt.	1.095 g ± 10 %	1.0210 g
4.	Reconstituted Solution	When reconstituted with SWFI solution is clear & free from Suspended matter.	Complies
5.	pH	10.2-11.2	10.6
6.	Particulate Matter	Should be free from particulate matter when examined visually	Complies
7.	Residual solvent s	Meets the requirements	Complies
8.	Appearance of Solution	10 .0 % w/v Test solutions in carbon dioxide free water is clear than reference standard solution.	Complies
9.	Bacterial Endotoxin	Not more than 1.0 EU/ mg	Less than 1.0 EU/mg
10.	Sterility Test	Should be sterile	sterile
11.	Assay: Each vial contains :	Result	Limit
	Thiopentone Sodium USP	989.1 mg	930. mg to 1070 mg

Remarks: The above Sample Complies as per USP Specification.

	Analyzed by	Checked by	Ap[redacted] C Manager)
Sign	[redacted]	[redacted]	
Date	24/06/15	24/06/15	

QP EYWFLAA
.FCCFBAA 281752

001 DFW 52866343

001-52866343

Shipper's Name and Address	Shipper's Account Number	Not Negotiable **Air Waybill** Issued by
[redacted]		[redacted]

Copies 1, 2 and 3 of this Air Waybill are originals and have the same validity.

Consignee's Name and Address	Consignee's Account Number
[redacted]	

It is agreed that the goods described herein are accepted in apparent good order and condition (except as noted) for carriage SUBJECT TO THE CONDITIONS OF CONTRACT ON THE REVERSE HEREOF. ALL GOODS MAY BE CARRIED BY ANY OTHER MEANS INCLUDING ROAD OR ANY OTHER CARRIER UNLESS SPECIFIC CONTRARY INSTRUCTIONS ARE GIVEN HEREON BY THE SHIPPER, AND SHIPPER AGREES THAT THE SHIPMENT MAY BE CARRIED VIA INTERMEDIATE STOPPING PLACES WHICH THE CARRIER DEEMS APPROPRIATE. THE SHIPPER'S ATTENTION IS DRAWN TO THE NOTICE CONCERNING CARRIER'S LIMITATION OF LIABILITY. Shipper may increase such limitation of liability by declaring a higher value for carriage and paying supplemental charge if required.

Issuing Carrier's Agent Name and City: [redacted]

Accounting Information

Agent's IATA Code: [redacted] Account No.

Airport of Departure (Addr. of First Carrier) and Requested Routing: DALLAS FT. WORTH

Reference Number | Optional Shipping Information

To	By First Carrier	Routing and Destination	to	by	to	by	Currency	CHGS Code	WT/VAL PPD	WT/VAL COLL	Other PPD	Other COLL	Declared Value for Carriage	Declared Value for Customs
IAH	[redacted]						USD	PPX		X			NVD	NCV

Airport of Destination: GEO BUSH INTERCONT | Requested Flight/Date: [redacted]

Amount of Insurance: XXX

INSURANCE - If carrier offers insurance, and such insurance is requested in accordance with the conditions thereof, indicate amount to be insured in figures in box marked "Amount of Insurance"

Handling Information - These commodities, technology or software were exported from the United States in accordance with the Export Administration Regulations. Diversion contrary to U.S. law prohibited.

SCI

No. of Pieces RCP	Gross Weight	kg/lb	Rate Class / Commodity Item No.	Chargeable Weight	Rate / Charge	Total	Nature and Quantity of Goods (incl. Dimensions or Volume)
3	60L	M		60	75.00	75.00	XXX VACINES NH
3	60		EPX-EXPEDITEFS NORMAL BO			75.00	

Prepaid	Weight Charge	Collect	Other Charges
	75.00		MYC24.00 SCC6.00 AWC15.00 XBC15.00

Valuation Charge

Tax: 7.50

Total Other Charges Due Agent

Total Other Charges Due Carrier: 60.00

I hereby certify that the particulars on the face hereof are correct and that insofar as any part of the consignment contains dangerous goods, **I hereby certify that the contents of this consignment are fully and accurately described above by proper shipping name and are classified, packaged, marked, and labeled, and in proper condition for carriage by air according to applicable governmental regulations.**

Signature of Shipper or his Agent

Total Prepaid	Total Collect
142.50	

Currency Conversion Rates	CC Charges in Dest. Currency	Executed on (date)	at (place)	Signature of Issuing Carrier or its Agent
1.0000000		25 JUL 2015		

FDA 152

For Carrier's Use only	Charges at Destination	Total Collect Charges
		USD [redacted]

AC 100/CPN 2943807 (REV. 05/2015)