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**BRIGARD &
CASTRO**
PROPIEDAD INTELECTUAL

Calle 70 A No. 4 - 41
BOGOTÁ - COLOMBIA
TEL: (571) 744 22 00
FAX: (571) 742 22 00
www.bc.com.co

As. 124.106

Señor

**DIRECTOR DIVISIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

E.

S.

D.

REF: Expediente No. **13 045.125**- solicitud de patente de invención
a favor de **HOSPIRA, INC.** Título: **FORMULACIÓN DE
PREMEZCLA DE DEXMEDETOMIDINA.**

RESPUESTA A EXAMEN DE FONDO

JUAN PABLO CADENA SARMIENTO, portador de la tarjeta profesional No. 57.492 del C.S.J., obrando como apoderado de la sociedad solicitante me permito dar respuesta al Oficio No. 7566 relacionado con la patentabilidad de la presente invención y notificado por fijación en lista el 1 de Julio de 2014.

A fin de subsanar todas y cada una de las objeciones emitidas por su Despacho en contra de la patentabilidad de la presente invención, nos permitimos poner a su disposición un nuevo pliego reivindicatorio que consta de diecisiete (17) reivindicaciones, las cuales fueron debidamente modificadas y adecuadas siguiendo las sugerencias manifestadas en el oficio técnico.

Con relación a dicho nuevo pliego reivindicatorio, vale la pena destacar que la materia allí reivindicada no excede el alcance de la invención reclamada previamente y que el mismo se encuentra completamente sustentado por las divulgaciones del capítulo descriptivo, razón por la cual solicitamos sea aceptado y examinado pertinentemente.

Sobre la claridad de dicho nuevo pliego reivindicatorio, es preciso mencionar que la expresión *"lista para el uso para la administración parenteral a un sujeto"*, al hacer parte del preámbulo de la reivindicación 1, no busca establecer ninguna característica técnica de la invención y por tanto, no existen faltas de claridad asociadas a la misma.

A pesar de ello, con el fin de hacer referencia a dicho atributo como característica técnica esencial de la presente invención, se incluyó la expresión *"en donde la composición farmacéutica líquida lista para el uso es administrable sin dilución a un sujeto"*, a partir de lo cual se da a entender que la composición reivindicada se formula como una premezcla lista para usarse que puede ser administrada a un sujeto sin necesidad de diluirla.

Teniendo en cuenta entonces que, además de la expresión *"en donde la composición farmacéutica líquida lista para el uso es administrable sin dilución a un sujeto"* recientemente incluida en la reivindicación 1, esta da a conocer el componente activo y su concentración en la formulación, afirmamos que la misma es completamente clara y comprensible para una persona normalmente versada en la materia.

Respecto a la reivindicación 8, encontramos que el señor Examinador afirma que la expresión *"la composición se formula como un volumen total"* no corresponde a una característica técnica de una composición. A pesar de ello, es nuestra intención destacar que la reivindicación en su totalidad revela y hace referencia al volumen total de la composición farmacéutica líquida lista para el uso, lo cual evidentemente corresponde a una característica técnica de la invención, razón por la que afirmamos que dicha reivindicación no recae en ninguna falta de claridad.

A raíz de lo anterior, solicitamos respetuosamente al señor Examinador llevar a cabo un análisis íntegro en donde evalúe la totalidad de la materia reclamada y no sólo frases y expresiones aisladas, ya que como es el caso de la reivindicación 8, esta enuncia de manera adecuada y clara la característica técnica que define a la presente

invención, guardando concordancia con el lenguaje habitualmente empleado en el campo técnico y en la práctica de patentes.

En cuanto a la reivindicación 10, consideramos oportuno expresar que la misma da a conocer una composición farmacéutica líquida lista para el uso caracterizada de la siguiente manera:

- Ingrediente activo: dexmedetomidina o una sal farmacéuticamente aceptable de la misma;
- Recipiente: Contenedor de vidrio sellado;
- Estabilidad: La concentración de dexmedetomidina no disminuye más de 2% tras ser almacenada por un periodo de tiempo de 5 meses;
- Administración: Administrable sin dilución a un sujeto.

Dicho esto, se hace evidente que las expresiones “*está dispuesta dentro de un contenedor de vidrio sellado*”, “*se almacena en el contenedor de vidrio por al menos cinco meses*” y “*exhibe no más de aproximadamente 2% de disminución en la concentración de dexmedetomidina*” hacen referencia a **características esenciales** y **limitaciones técnicas** de la presente invención, la cuales no representan en ningún momento “resultados a alcanzar” o faltas de claridad, razón por la que afirmamos que son completamente aceptables.

En este sentido, es necesario mencionar que la presente invención demuestra ser ventajosa en términos de estabilidad y capacidad de almacenamiento en comparación con formulaciones diluidas de dexmedetomidina, para lo cual resulta esencial que esta sea almacenada en un contenedor de vidrio sellado, razón por la que reiteramos que la expresión “*está dispuesta dentro de un contenedor de vidrio sellado*” constituye una característica técnica esencial de la presente invención.

De hecho, tal atributo constituye un factor determinante para dar solución al problema técnico que la misma enfrenta y resuelve de manera ventajosa, en base a lo cual solicitamos sea retirada la objeción que cuestiona la claridad de la reivindicación 10.

Asimismo, afirmamos que la expresión *"en donde cuando la composición farmacéutica líquida se almacena en el contenedor de vidrio por al menos cinco meses exhibe no más de 2% de disminución de la concentración de dexmedetomidina"* no enuncia ningún "resultado a alcanzar" sino una **limitación o condición técnica** bajo la cual se establece un parámetro que evidencia nuevamente una de las ventajas de la presente invención, la cual se relaciona directamente con su estabilidad y capacidad de almacenamiento.

De este modo, insistimos en que la reivindicación 10 constituye una divulgación clara y concisa de la presente invención por cuanto presenta las características esenciales y condiciones o limitaciones técnicas que la definen y la destacan por encima del arte previo, hecho por el cual solicitamos respetuosamente sea retirada la respectiva objeción.

Ahora bien, dada la objeción que afecta a las reivindicaciones 9 a 18, es de notar que la reivindicación 9 fue retirada del actual pliego reivindicatorio eliminando así cualquier tipo de redundancia con la materia descrita en las reivindicaciones 1 a 8.

Sin embargo, en lo que respecta a las reivindicaciones 10 a 18, nos permitimos señalar que en función de su dependencia, las mismas definen modalidades distintas a las mencionadas en dichas reivindicaciones 1 a 8 y por tanto no recaen en ninguna falta de claridad que justifique su eliminación del actual pliego reivindicatorio.

Debido a esto, solicitamos respetuosamente sea retirada la objeción que perjudica dichas reivindicaciones 10 a 18 puesto que las mismas constituyen una divulgación clara y por tanto válida de las diferentes modalidades de la presente invención.

Por último, notará el señor Examinador que la expresión *"aproximadamente"* fue completamente removida del actual pliego reivindicatorio, por lo cual damos por superada la falta de concisión señalada.

En vista de los anteriores comentarios y las modificaciones realizadas al actual pliego reivindicatorio, solicitamos respetuosamente sea reconocida la entera

claridad, concisión y validez del mismo, y que consecuentemente sean retiradas las objeciones que lo afectan.

Novedad

En opinión del señor Examinador, los documentos D1 (*"Composition For Local Anesthesia"*, US20110230534) y D3 (*"Pharmacokinetics of dexmedetomidine infusions for sedation of postoperative patients requiring intensive care"*, Venn R. M. Br. J. Anaesth. Vol. 88 (5): 669-675) anticipan todas y cada una de las características técnicas que dan lugar a la invención descrita en la reivindicación 1 y por tanto, esta carece de novedad.

En contraste con su apreciación, nos permitimos expresar que la materia reclamada en la actual reivindicación 1 es completamente distinguible del estado de la técnica y que este no logra desvirtuar su patentabilidad por cuanto falla en anticipar cada uno de los elementos que la conforman, hecho que procedemos a demostrar.

Teniendo en cuenta las modificaciones realizadas al pliego reivindicatorio, presentamos a continuación la nueva reivindicación 1 a fin de contextualizar el análisis que prosigue:

"Una composición farmacéutica líquida lista para el uso para la administración parenteral a un sujeto, que comprende dexmedetomidina o una sal farmacéuticamente aceptable de la misma en una concentración de 0.005 a 50 µg/mL, dispuesta dentro de un contenedor de vidrio sellado, en donde la composición farmacéutica líquida lista para el uso es administrable sin dilución a un sujeto."

De acuerdo con la anterior reivindicación, la presente invención debe ser entendida como una **composición farmacéutica líquida de administración parenteral lista para el uso** caracterizada según los siguientes elementos:

- (a) Ingrediente activo: Dexmedetomidina o una sal farmacéuticamente aceptable de la misma;

- (b) Concentración: De 0.005 a 50 µg/mL;
- (c) Recipiente: Contenedor de vidrio sellado;
- (d) Administración: Administrable sin dilución a un sujeto.

Tal y como se comentó previamente, la expresión "*en donde la composición farmacéutica líquida lista para el uso es administrable sin dilución a un sujeto*" fue incluida en dicha reivindicación 1 con el ánimo de indicar que la presente invención corresponde a una composición que se administra a un sujeto sin necesidad de llevar a cabo ninguna dilución; característica técnica que permite demostrar de mejor manera la total novedad de la misma.

Aclarada la caracterización de la presente invención, afirmamos que ninguno de los documentos citados por su Despacho anticipa exactamente la composición aquí divulgada, razón por la que no constituyen sustento documental suficiente a la objeción en mención y en base a lo cual solicitamos respetuosamente sea retirada.

Así pues, en términos generales encontramos que las referencias analizadas por el señor Examinador en lugar de sugerir o describir una composición como la reivindicada, se enfocan en divulgar composiciones concentradas de dexmedetomidina -estando dicho fármaco presente en cantidades de **100 µg/mL-**, las cuales deben ser diluidas antes de ser administradas a un sujeto, lo cual contrasta abiertamente con la presente invención, la cual como se ha venido mencionando, **no requiere ningún tipo de dilución o reconstitución previa a su administración.**

Más en detalle, encontramos que el documento D1 centra sus enseñanzas en un kit de anestesia local que incluye un agente anestésico local como lidocaína y una composición para anestesia local como dexmedetomidina, en donde una cantidad de la composición para anestesia local se mezcla con el agente anestésico local antes de ser usado.

Inclusive, dicho documento D1 menciona que la preparación de la composición comprende una etapa de **dilución** de la composición concentrada de dexmedetomidina, para luego **combinar** dicha composición diluida de

dexmedetomidina con el agente anestésico local, el cual resulta diluyéndose a su vez en tal composición diluida de dexmedetomidina, hecho que nos permite asegurar que la anterioridad descrita en el citado documento no es comparable de ninguna manera con la presente invención.

Dicho esto, y considerando que el documento D1 es completamente silencioso respecto a que la composición de dexmedetomidina se almacene en un contenedor de vidrio sellado (b) y constituya como tal una composición administrable sin dilución a un sujeto (c), concluimos que la referencia en mención no constituye soporte documental suficiente a la objeción por novedad que emite el señor Examinador, la cual respetuosamente solicitamos sea retirada.

Ahora bien, en lo que respecta al documento D3 encontramos un escenario similar puesto que este revela un estudio farmacocinético del fármaco dexmedetomidina, en donde se lleva a cabo la administración de una solución intravenosa de dicho fármaco que se obtiene tras **diluir** con solución salina normal una solución concentrada de 100 µg/mL para producir una concentración final de 8 µg/mL.

Partiendo de lo anterior, afirmamos que el citado documento D3 falla igualmente en anticipar una composición como la reivindicada, la cual se almacena en un contenedor de vidrio sellado (b) y constituye como tal una composición administrable sin dilución a un sujeto (c), razón por la que solicitamos respetuosamente sea reconocido que la presente invención cumple satisfactoriamente con el requisito de novedad a pesar de las enseñanzas del documento en mención.

Así las cosas, habiendo demostrado que ambos documentos D1 y D3 guardan total silencio en lo referente a los elementos (b) y (c) que caracterizan a la presente invención, afirmamos que la objeción emitida por su Despacho carece de todo fundamento y solicitamos, en consecuencia, sea reconsiderada.

En complemento de lo dicho, vale la pena destacar que tanto el documento D1 como el documento D3 fallan en divulgar una composición que comprenda **de 0.005 a 50 µg/mL de dexmedetomidina** puesto que, contrario a las afirmaciones del señor

Examinador, dichas referencias se enfocan en el análisis de diluciones de una composición concentrada de dexmedetomidina, lo cual difiere y se aleja rotundamente del objeto y alcance de la presente invención.

Es por tanto que consideramos que no hay punto de comparación entre las divulgaciones del estado de la técnica y la presente invención, la cual reiteramos se mantiene novedosa aun considerando las enseñanzas de los documentos D1 y D3 pertenecientes al estado de la técnica.

Adicionalmente, en esta instancia es oportuno mencionar que la reivindicación 10 (nueva reivindicación 9) cumple igualmente con el requisito de novedad a la luz de lo divulgado en los citados documentos D1 y D3 ya que estos no abordan en ningún momento el estudio de la **estabilidad y capacidad de almacenamiento** de las composiciones diluidas de dexmedetomidina, razón por la cual concluimos que la totalidad del nuevo pliego reivindicatorio cuenta con la debida novedad y por tanto, es meritoria del privilegio de patente que aquí se solicita.

Nivel inventivo

Adicionalmente, considera el señor Examinador que los documentos D1, D2 (*"Assessment report Dexdor dexmedetomidina"*, Committee for Medicinal Products for Human Use. European Medicines Agency) y D3 proporcionan todas las herramientas necesarias para que, partiendo de ellos, una persona normalmente versada en la materia sea completamente capaz de alcanzar la invención descrita en la reivindicación 4 de manera obvia o sin implicar el uso de la habilidad inventiva.

Teniendo en cuenta que la objetada reivindicación 4 depende directamente de la reivindicación 1, procedemos a elaborar nuestro análisis en torno a esta última.

Así pues, contrario a tal apreciación, insistimos en que las divulgaciones del estado de la técnica citado por su Despacho no son comparables con la materia reivindicada y tampoco proporcionan enseñanzas, motivación o instrucciones suficientes que motiven el desarrollo de la invención reclamada a lo largo del actual pliego reivindicatorio.

Retomando los argumentos previamente expuestos en favor de la novedad de la presente invención, es nuestra intención destacar que las enseñanzas de los documentos D1 y D3, en lugar de aproximar al versado en la materia a la presente invención, lo **alejan** de la misma toda vez que sugieren el desarrollo de composiciones completamente distintas al objeto de la presente invención, tal y como expondremos más adelante.

Similar es el caso del documento D2, el cual divulga una composición para administración parenteral que comprende dexmedetomidina a una concentración cercana a 100 µg/mL y que previo a su administración, debe ser **diluida** a una concentración final de 4 µg/mL, lo que como bien se ha comentado ya, no concuerda con el alcance y sentido de la presente invención.

Partiendo entonces de las manifiestas diferencias existentes entre las divulgaciones de los documentos D1, D2 y D3 y la presente invención, nos permitimos llamar la atención una vez más sobre el aspecto más relevante a considerar, el cual se relaciona con que la presente invención constituye una premezcla lista para el uso, lo que significa que esta **no requiere ningún tipo de dilución o reconstitución** previa a su administración parenteral a un paciente.

Según esto, es claro que la composición objeto de la presente invención puede ser administrada directamente al paciente tan pronto como se retira de su envase de vidrio sellado, contrario a lo que ocurre con las composiciones descritas en el estado de la técnica, las cuales **deben ser diluidas previo a su administración**.

Considerando que ninguna de las composiciones dadas a conocer por los documentos D1, D2 o D3 podría ser administrada de manera directa -tal y como provienen de su envase sellado- por vía parenteral a un sujeto, desconocemos los motivos que llevan al señor Examinador a suponer que tal materia podría inspirar el desarrollo de la presente invención, la cual **se opone** evidentemente a lo enseñado en el citado arte previo.

Debido a esto, afirmamos que en lugar de suscitar la concepción de las composiciones aquí reclamadas, las referencias analizadas por el señor Examinador a lo largo de su examen de patentabilidad **alejan** al versado en la materia de la presente invención por las siguientes razones:

- Todos los documentos citados hacen referencia a composiciones de dexmedetomidina de 100 µg/mL, lo cual motivaría al versado en la materia a formular composiciones de concentración similar, la cual excede notoriamente la dosificación indicada de dicho fármaco, por lo que resulta imposible considerar que la misma podría ser administrada directamente a un sujeto como ocurre con la presente invención.
- Partiendo de lo divulgado en los documentos D1, D2 y D3, el versado en la materia contaría con motivación suficiente para considerar el desarrollo de una composición concentrada de dexmedetomidina cuya dosis pueda ser ajustada mediante dilución previo a la administración parenteral, en lugar de considerar el desarrollo de una composición lista para ser administrada, como es el caso de la presente invención.
- Según lo divulgado en el documento D1, el versado en la materia podría fácilmente desarrollar una composición que combine un agente anestésico local como la lidocaína con una composición para anestesia como la dexmedetomidina, modalidad que no se encuentra cobijada de ninguna manera por el alcance de la presente invención.
- Ninguno de los documentos D1, D2 o D3 contempla el diseño y desarrollo de composiciones listas para ser administradas por la vía parenteral, por lo cual no proporcionan ninguna instrucción al versado en la materia respecto a tal atributo característico de la presente invención.
- De igual manera, ninguna de tales referencias aborda o estudia de algún modo los parámetros de estabilidad y capacidad de almacenamiento de las composiciones de dexmedetomidina allí divulgadas, por lo que es claro que el versado en la materia no cuenta con ninguna enseñanza que oriente o dirija

su atención a dichos aspectos, los cuales resultan además de esenciales en el desarrollo de la presente invención, ventajosos.

Con base en lo anterior, concluimos que no hay ningún motivo por el cual sea posible atribuirle obviedad a la presente invención en vista de las divulgaciones del estado de la técnica definido por los documentos D1, D2 y D3 de la mano con los conocimientos generales del versado en la materia, ya que tal materia falla en sugerir o motivar el desarrollo de una composición que comprenda todas y cada una de las características técnicas de la presente invención.

En vista de este hecho, solicitamos respetuosamente sea retirada la objeción que cuestiona el nivel inventivo de la presente invención debido a que contrario a lo expuesto en el Oficio técnico, los documentos D1, D2 y D3 carecen de información suficiente que permita alcanzar de manera obvia o evidente la invención descrita a lo largo del actual pliego reivindicatorio.

Ahora bien, en este punto nos permitimos expresar que, contrario a lo percibido por el señor Examinador al momento de ejecutar el debido examen de patentabilidad, la presente invención sí demuestra una clara ventaja derivada precisamente de las diferencias anteriormente expuestas, la cual se relaciona directamente con la **estabilidad y capacidad de almacenamiento** de las composiciones reivindicadas.

En este orden de ideas, es preciso mencionar que la presente invención, al representar una composición farmacéutica líquida de administración parenteral lista para el uso goza de **estabilidad superior** comparada con las composiciones diluidas descritas en el arte previo, las cuales son estables y aptas para ser usadas únicamente por un periodo limitado de tiempo de hasta 24 horas.

Dado que el uso y estabilidad de las composiciones diluidas resulta tan restringido, es evidente que la presente invención demuestra claras **ventajas y beneficios** al introducir al campo técnico una composición lista para ser usada que, como tal, puede ser almacenada por periodos de tiempo prolongados, superiores a los alcanzados por las composiciones descritas en los documentos D1, D2 y D3.

Adicionalmente, cualquier versado en la materia se encuentra en capacidad de reconocer que la presente invención, al ser dispuesta en recipientes de vidrio sellados favorece tal estabilidad superior y, más allá de eso, facilita todos los procesos involucrados en el **almacenamiento y manipulación** de la misma.

Como muestra de lo anterior, nos permitimos citar brevemente aquí un aparte del capítulo descriptivo de la presente solicitud, el cual hace mención de la estabilidad asociada con dicha característica técnica de la presente invención:

“Puede ser estable bajo las condiciones de manufactura y almacenamiento y se puede preservar contra la acción contaminante de microorganismos tales como bacterias y fungosidades.”

Por otra parte, llamamos la atención sobre el hecho que los ejemplos presentados a lo largo del capítulo descriptivo reportan igualmente la **ventajosa estabilidad** de la presente invención, hecho que resumimos a continuación:

Ejemplos 1 a 3: Demuestran que la composición lista para ser usada de 4 µg/mL de acuerdo con la presente invención fue estable por un periodo de hasta 9 meses cuando se almacena en un contenedor de vidrio.

Ejemplo 1: La composición lista para ser usada de 4 µg/mL almacenada en contenedores de vidrio mantuvo niveles de potencia superiores en comparación con la misma composición almacenada en contenedores de plástico, CR3 o PVC, tal y como es posible apreciar en la siguiente tabla:

Tabla 1. Estabilidad de la Formulación de la Composición de Dexmedetomidina Premezcladas de 4 µg/mL en Solución Salina Normal.

Adaptada del capítulo descriptivo de la presente solicitud

	2 Semanas/ 25°C		1 Mes/ 40°C		2 Meses/ 40°C	3 Meses/ 40°C	5 Meses/ 40°C
	Potencia Prom. (%)	PH	Potencia Prom. (%)	PH	Potencia Prom. (%)	Potencia Prom. (%)	Potencia Prom. (%)
Ampolla	99.0	5.0	99.0	5.6	97.7	98.3	98.7
Vial	98.2	6.7	99.4	6.3	98.0	98.3	98.6
Jeringa	95.0	5.5	94.6	5.7	92.2	89.5	90.8
CR3	80.2	4.7	79.5	4.8	NT	75.3	79.2
PVC	79.9	4.8	81.4	4.6	NT	79.0	76.7
Vis-IV™	95.8	5.9	92.8	5.8	NT	94.0	NT

NT - No probado

En este sentido, la Tabla 1 reporta que dicha composición lista para ser usada de 4 µg/mL y almacenada en contenedores de vidrio mantuvo una potencia de 98% tras 5 meses de almacenamiento; mientras que aquellas composiciones almacenadas en jeringas o bolsas plásticas presentaron una potencia reducida hasta en un 20% tras un periodo de almacenamiento de apenas dos semanas.

Ejemplo 3: La potencia de la composición lista para ser usada de 4 µg/mL permaneció relativamente inalterada tras ser almacenada en viales y ampollas de vidrio a 25 °C durante 9 meses.

A la luz de lo anterior, solicitamos sea reconocido que la presente invención goza de **estabilidad y capacidad de almacenamiento** superiores a las logradas por composiciones similares que han sido almacenadas en contenedores o envases distintos, las cuales son equiparables a las composiciones diluidas descritas a lo largo de los documentos D1, D2 y D3, ya que en nuestro concepto este hecho constituye evidencia de peso en favor de la patentabilidad de la misma.

Con el fin de demostrar de la mejor manera la superioridad de la presente invención frente al arte previo que cita su Despacho, adjuntamos en medios digitales los siguientes anexos:

Anexo 1: **FDA Memorandum** por Cynthia G. McCormick M.D. Noviembre 30, 1999; en referencia a la Solicitud No. 21-038 "*Medical Reviews of the Precedex (dexmedetomidine hydrochloride injection)*" presentada ante la FDA (siglas en inglés de *Food and Drugs Administration*) y disponible en su sitio web desde Julio 26, 2001.

Anexo 2: **Declaration under 37 C.F.R. §1.132** por Huailiang Wu Ph.D. Septiembre 17, 2012; presentada como sustento a los argumentos expuestos en favor de la patentabilidad de la Patente de Estados Unidos No. 8,338,470.

Anexo 3: "Trends in Pharmaceutical Primary Packaging for Injectables – Solutions for New Changes" por Claudia Petersen. *Drug Development and Delivery*, Septiembre, 2012.

Primeramente, es de notar que el Memorando de la FDA (Anexo 1) reporta que si bien la composición madre –aquella que no ha sido diluida– de dexmedetomidina es elaborada mediante un proceso de llenado aséptico y esterilización final en autoclave para garantizar que pueda ser almacenada; la estabilidad de la misma es de apenas 24 horas una vez diluida para su administración (Anexo 1, página 8).

Es por tanto que afirmamos que la estabilidad de las composiciones diluidas de dexmedetomidina descritas en los documentos D1, D2 y D3 se mantiene únicamente por un periodo de **24 horas** y, por tanto, no son aptas para ser sometidas a periodos prolongados de almacenamiento contrario a lo que ocurre en el caso de la presente invención, la cual puede ser almacenada por periodos de hasta **9 meses** manteniendo la debida integridad.

Así pues, mientras que el estado de la técnica enseña que la dilución de una composición concentrada que contiene 100 µg/mL de dexmedetomidina deriva en composiciones diluidas que sólo pueden ser usadas y/o almacenadas dentro de un periodo de tiempo de 24 horas, la presente invención constituye una evidente **ventaja** al constituir una composición lista para ser usada que puede almacenarse hasta por 9 meses en un contenedor de vidrio sellado sin incurrir en deterioro de la misma.

A raíz de este hecho, se hace notorio que la presente invención demuestra **ventajas sorprendentes e inesperadas** al constituir una composición de dexmedetomidina que, contrario a la expectativa derivada del estado de la técnica, logra mantener parámetros de estabilidad y potencia satisfactorios tras ser almacenada por periodos de tiempo considerables, lo cual no habría podido ser previsto de ninguna manera a partir de lo divulgado en los documentos D1, D2 y D3.

Asimismo, es claro que dicho Memorando demuestra que el estado de la técnica no enseña otra cosa distinta a la limitada estabilidad de dichas composiciones diluidas

de dexmedetomidina, razón por la cual afirmamos que el versado en la materia no habría podido concebir o prever la **estabilidad superior** de la que goza la presente invención y que, por tanto, no habría podido alcanzarla de manera obvia.

Más allá de lo ya comentado, vale la pena mencionar que el desarrollo de composiciones de baja concentración obtenidas por dilución a partir de una composición madre se acompaña de inconvenientes que deben ser tenidos en cuenta al momento de su preparación, tales como la **presencia de contaminantes e impurezas** derivadas tanto del proceso de dilución *per se*, como de los periodos y condiciones de almacenamiento.

Dada tal limitación, consideramos que la persona versada en la materia se vería motivada más bien a usar tales composiciones diluidas inmediatamente o lo más pronto posible después de su preparación, en lugar de concebir almacenarlas por periodos elevados de tiempo, lo cual evidentemente aumentaría el riesgo de contaminación.

En concordancia con este hecho, afirmamos que el estado de la técnica no hace otra cosa que **alejar** al versado en la materia del objeto y alcance de la presente invención, situación que solicitamos sea reconocida mediante el retiro de las objeciones que cuestionan el nivel inventivo de la misma.

Por otro lado, en complemento de los argumentos ya expuestos, remitimos a su Despacho la Declaración de Huailiang Wu Ph.D. (Anexo 2) en donde se expone abiertamente la ventaja inesperada derivada de almacenar composiciones listas para ser usada de dexmedetomidina de 1, 10, 15 y 50 µg/mL en **contenedores de vidrio**, comparada con una serie de composiciones similares almenadas en **bolsas plásticas de PVC**.

Más puntualmente, dicha Declaración reporta los siguientes resultados relativos a las composiciones almacenadas en bolsas plásticas de PVC:

- La potencia de la composición de 1 µg/mL **disminuyó** (i) en **1.82%** tras 12 horas de ser empacada en dichas bolsas de PVC, y (ii) en **7.81%** en comparación con el control autoclavado.
- La potencia de la composición de 1 µg/mL **disminuyó en 8.05% y 8.33%** tras ser almacenada en bolsas plásticas de PVC por 3 días a 25 °C y 40 °C respectivamente, tomando como referencia dicho control.
- De manera similar, la potencia de las composiciones de 10, 15 y 50 µg/mL almacenadas en bolsas plásticas de PVC **disminuyó en 5.84%, 5.54% y 4.32%** respectivamente, comparadas frente a cada uno de los controles autoclavados.
- Igualmente, la potencia de las composiciones de 10, 15 y 50 µg/mL **disminuyó en 6.24%, 6.17% y 5.26%** respectivamente tras ser almacenadas en bolsas plásticas de PVC por tres 3 días a 25 °C, tomando como referencia las composiciones control.

En contraste con los resultados de estabilidad alcanzados por tales composiciones, la presente invención –la cual es almacenada en contenedores sellados de vidrio– **no demostró pérdidas de potencia considerables** al ser sometida a las mismas condiciones de temperatura y tiempo, teniendo en cuenta los siguientes datos:

Tabla 2. Evaluación de la pérdida de potencia de composiciones de dexmedetomidina listas para ser usadas, almacenadas en viales de vidrio por un periodo de 3 días.

Concentración	Pérdida de potencia* (T = 25 °C)	Pérdida de potencia* (T = 40 °C)
1 µg/mL	0%	0.42%
10 µg/mL	0%	0%
15 µg/mL	0.39%	0.27%
50 µg/mL	0.44%	0.51%

*Comparada frente a soluciones control que fueron tratadas en autoclave.

Tal y como revelan los anteriores resultados, las composiciones de dexmedetomidina de 1, 10, 15 y 50 µg/mL de acuerdo con la presente invención demostraron **mantener la potencia** del dicho fármaco al ser sometidas a las mismas condiciones, lo cual constituye como tal un *efecto inesperado* teniendo en cuenta que el estado de la técnica reporta ampliamente los problemas de estabilidad asociados con este tipo de composiciones.

Igualmente, cabe anotar que al comparar los resultados alcanzados por las composiciones almacenadas bajo las dos condiciones de ensayo, la máxima pérdida de potencia detectable tras 3 días de almacenamiento para el caso de la presente invención fue de apenas **0.51%**, lo cual contrasta fuertemente con el **8.83%** observado para las composiciones de dexmedetomidina almacenadas en bolsas plásticas de PVC, demostrando una vez más la **superioridad** de las composiciones que aquí se reivindican.

Similar es el comportamiento de las mismas muestras, analizadas esta vez tras un periodo de almacenamiento de 24 horas a temperatura ambiente y cuyos resultados se resumen en la siguiente tabla:

Tabla 3. Evaluación de la pérdida de potencia composiciones de dexmedetomidina almacenadas por 24 horas a temperatura ambiente.

Concentración	Pérdida de potencia* de las composiciones almacenadas en bolsas plásticas de PVC	Pérdida de potencia* de las composiciones almacenadas en viales de vidrio
1 µg/mL	1.48%	0%
10 µg/mL	1.22%	0.56%
15 µg/mL	1.06%	0.24%
50 µg/mL	1.78%	0%

*Comparada frente a soluciones control que fueron tratadas en autoclave.

Con base en la totalidad de los resultados mencionados previamente y expuestos a profundidad en la Declaración adjunta, es posible afirmar que el mantenimiento de la potencia de una composición de dexmedetomidina lista para ser usada depende directamente de tipo de contenedor o envase en el cual se almacena la misma.

En este orden de ideas, dada la evidente **ventaja de la presente invención** – entendida como la incidencia de pérdidas de potencia prácticamente imperceptibles bajo diversas condiciones de almacenamiento –, solicitamos sea retirada la objeción emitida por su Despacho considerando que la presente invención no sólo es novedosa e inventiva frente al arte previo, sino que demuestra ventajas que como tal, simbolizan un aporte valioso al campo técnico en el que esta se desarrolla.

Aclarado lo anterior, nos permitimos ahora hacer especial énfasis en un aspecto que, a nuestro parecer, constituye la diferencia más relevante entre la presente invención y el estado de la técnica.

Tal y como se comentó previamente, las composiciones de dexmedetomidina ya conocidas son elaboradas mediante un procedimiento aséptico (que incluye llenado aséptico de los respectivos envases seguido de esterilización en autoclave) que garantiza (i) la adecuabilidad de las mismas para ser almacenadas y (ii) la seguridad para ser diluidas y administradas a pacientes.

Muy por el contrario, la composición descrita a lo largo del actual pliego reivindicatorio proporciona una alternativa que, además de ser igualmente **apta para ser almacenada** –atributo que hemos demostrado supera enormemente los estándares de estabilidad y capacidad de almacenamiento asociados a las composiciones diluidas del arte previo–, **está lista para ser usada**, es decir, no requiere de ninguna etapa de dilución o adecuación previa a su administración a pacientes, hecho que la cataloga como una **alternativa sin precedentes en el arte previo** completamente meritoria del privilegio de patente aquí solicitado.

Inclusive, es nuestra intención destacar que el hecho de que la presente invención constituya una composición lista para ser usada resulta de por sí ventajoso puesto que **elimina la necesidad de llevar a cabo una etapa de dilución previa a la administración a un paciente**, lo cual es evidentemente favorable por cuanto:

- No requiere de tiempo, locaciones y personal capacitado para llevar a cabo dicho proceso de dilución;

- Evita someter la composición a una situación en donde es susceptible de adquirir impurezas o incluso contaminación microbiana y por tanto, garantiza la **seguridad e inocuidad** de la misma;
- Evita someter la composición a una situación en donde es susceptible de presentar errores de formulación o dosificación asociados con la **manipulación** de la misma;

A la luz de las anteriores consideraciones, reiteramos que la presente invención constituye una alternativa terapéutica **ventajosa y beneficiosa** dado el contexto técnico en el que se desarrolla, el cual carece de composiciones que alcancen resultados de **estabilidad y capacidad de almacenamiento** similares o al menos comparables a los que implica la presente invención.

Asimismo, es oportuno agregar que de acuerdo con lo expuesto en los Ejemplos 1 y 2 del capítulo descriptivo, el aumento en la estabilidad de la presente invención fue detectable al compararla tanto con composiciones que fueron sometidas a esterilización en autoclave –como por ejemplo aquellas manufacturadas para ser administradas por la vía parenteral– como con aquellas que no lo fueron; hecho que indiscutiblemente respalda aún más la superioridad de la presente invención frente al estado de la técnica.

En consecuencia, tomando como punto de partida los argumentos elaborados en torno de los Anexos 1 y 2, es posible concluir que la presente invención, además de cumplir satisfactoriamente con los requisitos de novedad y nivel inventivo, demuestra una clara superioridad en términos de **estabilidad y capacidad de almacenamiento** que no podría haber sido anticipada por el versado en la materia en vista de las divulgaciones de las referencias citadas.

En este orden de ideas, solicitamos respetuosamente sea tenido en cuenta que la presente invención demuestra **ventajas y efectos técnicos superiores e inesperados** que constituyen como tal indicios adicionales de la existencia de nivel inventivo, lo cual ratifica nuestra posición en favor de la patentabilidad de la materia contenida en el actual pliego reivindicatorio.

Por si fuera poco, y contemplando el caso en el que el señor Examinador insista en que la caracterización de la presente invención podría haber sido alcanzada de manera obvia, acudimos al documento *"Trends in Pharmaceutical Primary Packaging for Injectables - Solutions for New Changes"* de Claudia Petersen (Anexo 3), el cual brinda una visión general de las consideraciones a tener en cuenta al momento de elegir el envase indicado para una composición farmacéutica.

Según Petersen, la elección de un envase para una composición farmacéutica se debe acompañar de un riguroso análisis que abarque una serie de factores, entre ellos las propiedades de la formulación, la dosificación, el tipo de aplicación o uso al cual se orienta, la favorabilidad para el usuario, costos, etcétera, los cuales definen atributos particulares de cada posible material y que en definitiva, representan criterios de preferencia entre uno y otro.

Teniendo en cuenta lo anterior, encontramos que ninguna de las referencias citadas por el señor Examinador proporciona sugerencias o instrucciones que motiven la elección de un **contenedor de vidrio** de entre el sinnúmero de posibles materiales que un versado en la materia podría considerar para el fin de almacenar la composición de dexmedetomidina reivindicada, y mucho menos anticipan las ventajas derivadas de tal elección, las cuales ya han sido comentadas en profundidad a lo largo del presente memorial.

En este sentido, es preciso señalar que dentro de los posibles materiales que el versado en la materia podría considerar se encuentran precisamente los materiales plásticos, los cuales además de ser ampliamente usados en la industria farmacéutica, cuentan con propiedades deseables tales como flexibilidad de diseño, facilitan tolerancias dimensionales más estrechas y presentan una resistencia a la ruptura superior a la del vidrio, a partir de lo cual su elección sería completamente factible aún antes de considerar la utilización de un contenedor de vidrio como el de la presente invención (Anexo 3, página 5).

Es así como nos permitimos manifestar que dada la amplia gama de opciones a las que se enfrentaba el versado en la materia, e incluso considerando la favorabilidad de otros materiales como el plástico en comparación con el contenedor de vidrio



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reivindicado, no hay ningún motivo por el cual la elección de dicho envase haya podido resultar de manera obvia.

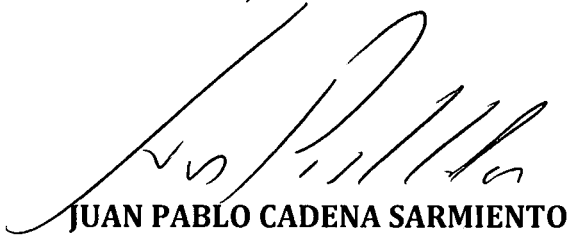
De hecho, consideramos que el vidrio como material presenta ciertas desventajas que, a simple vista, guiarían la elección del versado en la materia más hacia la preferencia de materiales plásticos, ya que los envases de vidrio son altamente susceptibles de ruptura, baja flexibilidad, tienen un peso comparativamente alto respecto a otros materiales, implican cierta dificultad de transporte y manipulación, muchas veces requieren de la aplicación de tratamientos superficiales para evitar la interacción con el fármaco o composición allí contenido, entre otros; siendo tales condiciones hecho suficiente que respalda una vez más la no obviedad de la presente invención en vista del arte previo y los conocimientos generales del campo técnico.

En definitiva, habiendo demostrado que el versado en la materia no contaba con motivación o instrucción alguna para seleccionar un **contenedor de vidrio** para almacenar la composición reivindicada, y que de este modo se hubiera enfrentado a un elevado número de posibilidades –dentro de las cuales el uso de materiales plásticos juega un rol importante dada su alta favorabilidad como envase versus la ya comentada incidencia negativa en la estabilidad de las composiciones–; afirmamos que las referencias citadas por el señor Examinador no constituyen soporte documental suficiente a sus objeciones, las cuales solicitamos respetuosamente sean retiradas.

De igual modo, insistimos en que las divulgaciones del estado de la técnica fallan completamente en aproximar al versado en la materia al objeto de la presente invención debido a que no proporcionan instrucciones o motivación que anticipe tanto la caracterización precisa que da origen a las composiciones reivindicadas, como las ventajas y beneficios derivadas de la misma.

En vista de lo anteriormente expuesto, respetuosamente solicitamos el retiro de las objeciones de la presente solicitud y la concesión del privilegio solicitado, ya que en opinión del solicitante cumple con todos los requisitos establecidos en la Decisión 486.

Atentamente,



JUAN PABLO CADENA SARMIENTO

T.P. No. 57.492 del C.S.J.

C.C. 80.410.337 de Usaquén

Calle 70 A No. 4 - 41

REIVINDICACIONES

1. Una composición farmacéutica líquida lista para el uso para la administración parenteral a un sujeto, que comprende dexmedetomidina o una sal farmacéuticamente aceptable de la misma en una concentración de 0.005 a 50 $\mu\text{g/mL}$, dispuesta dentro de un contenedor de vidrio sellado, en donde la composición farmacéutica líquida lista para el uso es administrable sin dilución a un sujeto.

2. La composición farmacéutica líquida lista para el uso de la reivindicación 1, en donde la dexmedetomidina o la sal farmacéuticamente aceptable de la misma está en una concentración de 0.05 a 15 $\mu\text{g/mL}$.

3. La composición farmacéutica líquida lista para el uso de la reivindicación 1, en donde la dexmedetomidina o la sal farmacéuticamente aceptable de la misma está en una concentración de 0.5 a 10 $\mu\text{g/mL}$.

4. La composición farmacéutica líquida lista para el uso de la reivindicación 1, en donde la dexmedetomidina o la sal farmacéuticamente aceptable de la misma está en una concentración de 1 a 7 $\mu\text{g/mL}$.

5. La composición farmacéutica líquida lista para el uso de la reivindicación 1, en donde la dexmedetomidina o la sal farmacéuticamente aceptable de la misma está en una concentración de 4 $\mu\text{g/mL}$.

6. La composición farmacéutica líquida lista para el uso de la reivindicación 1, la cual además comprende cloruro de sodio en una concentración de entre 0.01 y 2.0 por ciento en peso.

7. La composición farmacéutica líquida lista para el uso de la reivindicación 6, en donde el cloruro de sodio está presente en una concentración de 0.9 por ciento en peso.

8. La composición farmacéutica líquida lista para el uso de la reivindicación 1, en donde la composición se formula como un volumen total seleccionado a partir del grupo que consiste de 20 mL, 50 mL y 100 mL.

9. Una composición farmacéutica líquida lista para el uso para la administración parenteral a un sujeto, que comprende dexmedetomidina o una sal farmacéuticamente aceptable de la misma dispuesta dentro de un contenedor de vidrio sellado, en donde cuando la composición farmacéutica líquida se almacena en el contenedor de vidrio por al menos cinco meses exhibe no más de 2% de disminución de la concentración de dexmedetomidina, en donde la composición farmacéutica líquida lista para el uso es administrable sin dilución a un sujeto.

10. La composición farmacéutica líquida lista para el uso de la reivindicación 9, en donde la dexmedetomidina o la sal farmacéuticamente aceptable de la misma está en una concentración de 0.005 a 50 $\mu\text{g/mL}$.

11. La composición farmacéutica líquida lista para el uso de la reivindicación 9, en donde la dexmedetomidina o la sal farmacéuticamente aceptable de la misma está en una concentración de 0.05 a 15 $\mu\text{g/mL}$.

12. La composición farmacéutica líquida lista para el uso de la reivindicación 9, en donde la dexmedetomidina o la sal farmacéuticamente aceptable de la misma está en una concentración de 0.5 a 10 $\mu\text{g/mL}$.

13. La composición farmacéutica líquida lista para el uso de la reivindicación 9, en donde la dexmedetomidina o la sal farmacéuticamente aceptable de la misma está en una concentración de 1 a 7 $\mu\text{g/mL}$.

14. La composición farmacéutica líquida lista para el uso de la reivindicación 9, en donde la dexmedetomidina o la sal farmacéuticamente aceptable de la misma está en una concentración de 4 $\mu\text{g/mL}$.

15. La composición farmacéutica líquida lista para el uso de la reivindicación 9, la cual además comprende cloruro de sodio en una concentración de entre 0.01 y 2.0 por ciento en peso.

16. La composición farmacéutica líquida lista para el uso de la reivindicación 15, en donde el cloruro de sodio está presente en una concentración de 0.9 por ciento en peso.

17. La composición farmacéutica líquida lista para el uso de la reivindicación 9, en donde la composición se formula como un volumen total seleccionado a partir del grupo que consiste de 20 mL, 50 mL y 100 mL.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

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SUPERINTENDENCIA

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*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr. UNDITARIO	Vr. CONCEPTO
7	50005-01-01 SOLICITUDES	1607 REIVINDICACION PATENTE UNITARIA ADICIONAL A LAS 10 INIC	31.000.00	217.000.00
				\$217.000.00
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Marzo 4 de 2014 - 16:43:28

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Dependencia: 2020	Fecha: ____/____/____ AAAA MM DD 2014 9 24		Recorrido: 4
Tipo de Radicación: Entrada: ☐ Salida: ☐ Traslado: ☐ Convenio: ☐			
Radicador:			Planilla:

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Item	Unidad de Conservación
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5	Tomo
6	Otro
Item	Soporte Documental
7	CD X
8	Disquete
9	DVD
10	Folleto
11	Foto
12	Periódico
13	Plano
14	Publicación Periódica
15	USB
16	Otro

Observaciones: El cd anexo contiene: 3 archivos en formato PDF, los cuales son procesados y subidos al sistema Claudia

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number **21-038**

MEDICAL REVIEW(S)

N21038

n #21-038

HFD-170

K1.2



N21038



K1.2

DRUG NAME: Precedex (dexmedetomidine nci injection)

REC.
12/28/99

APPLICANT: ABBOTT LABORATORIES

CHEMICAL & THERAPEUTIC CLASS:1S

Review Cycles

Review Cycle: 1 Submission Date:12-18-98 Receipt Date:12-18-98 Goal Date:12-18-99 Action:AP	Review Cycle: 2 Submission Date: Receipt Date: Goal Date: Action:
Review Cycle: 3 Submission Date: Receipt Date: Goal Date: Action:	Review Cycle: 4 Submission Date: Receipt Date: Goal Date: Action:

CORE REVIEW TEAM MEMBERS

PROJECT MANAGER/ CSO :Susmita Samanta Phone # & Office Room #:301-827-7410, 9B-45
MEDICAL:Patricia Hartwell, M.D., M.B.A.
CHEMISTRY:Michael Theodorakis, Ph.D.
PHARM/TOX:Harry Geyer, Ph.D.
BIOPHARMACEUTICS:Suresh Doddapaneni, Ph.D.
BIOMETRICS: Z.Jonathan Ma, Ph.D.
ABUSE LIABILITY: BeLinda A. Hayes, Ph.D.
MICROBIOLOGIST: Patricia Hughes, Ph.D.

Volume 2 of 4

Administrative volume #(s): 1

Clinical volume #(s): 2

CMC volume #(s): 3

Pharmacology/Toxicology volume #(s): 4

ODE II ACTION PACKAGE TABLE OF CONTENTS

Application #21-038

Drug Name: Precedex (dexmedetomidine Hydrochloride injection), 2 mL ampule/2 mL vial, 100 mcg/mL

Applicant: Abbott Laboratories

Chem./Ther. Type: IS

CSO/PM: Susmita Samanta

Phone: 301-827-7410

HFD-170

Original Application Date: December 18, 1998 Original Receipt Date: December 18, 1998

CURRENT USER FEE GOAL DATE: December 18, 1999 Date Table of Contents Completed: 9/13/99

Section A:

Administrative Information

X (completed).
N/A (not applicable).
or Comment

Tab A-1	Action Letter(s)	Current Action: AP	X
Tab A-2	Phase 4 Commitments:		
	a. Copy of applicants communication committing to Phase 4		NA
	b. Agency Correspondence requesting Phase 4 Commitments		NA
Tab A-3	FDA revised Labels & Labeling and Reviews: (Separate each version/cycle with a colored sheet)		
	a. Package Insert		X
	b. Immediate Container and Carton Labels		NA
Tab A-4	Original Proposed Labeling		X
Tab A-5	Foreign Labeling:		
	a. Foreign Marketing History		NA
	b. Foreign Labeling and Review(s)		NA
Tab A-6	Labeling and Nomenclature Committee's Tradename Review		X
Tab A-7	Summary Memoranda (e.g., Division Director, Group Leader, Office)		X
Tab A-8	Copy of Patent Statement		X
	Exclusivity Checklist (and any requests for exclusivity)		X
	Debarment Statements		X
Tab A-9	Correspondences, Faxes, & Telecons		X
Tab A-10	Minutes of Meetings:		
	a. End-of-Phase II meeting		NA
	b. Pre-NDA meeting(s)		NA
	c. Filing meeting		X
	d. Other meetings		X
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Application #21-038 Drug Name: Dexmedetomidine HCL

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N/A (not applicable),
or Comment

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N/A (not applicable),
or Comment

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Pharmacology/Toxicology Information

X (completed),
N/A (not applicable),
or Comment

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ADDITIONAL NOTES:



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETICS, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS**

HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857

Tel: (301) 827-7410

MEMORANDUM

to: John K. Jenkins, MD
Director,
Office of Drug Evaluation II

Division File: NDA # 21-038

from: Cynthia G. McCormick, MD
Director, Division of Anesthetics, Critical Care and Addiction Drug
Products

subject: Dexmedetomidine NDA

date: November 30, 1999

This memorandum summarizes for the file the basis for the approval action recommended by the Division of Anesthetics, Critical Care, and Addiction Drug Products for NDA #21-038, Dexmedetomidine HCl for Injection, a sedative/hypnotic agent intended for use in the intensive care setting.

Background

Dexmedetomidine is the dextro-enantiomer of the racemic mixture, medetomidine¹ and a selective α -2-adrenoreceptor agonist. It has been shown in standard animal models of efficacy to have anxiolytic activity (0.3-2.0 μ g/kg IV), analgesic activity (3-6 μ g/kg IV), and sedative properties (10-30 μ g/kg IV) in a dose-related manner in mice, rats and dogs. Dexmedetomidine was developed in humans primarily for its sedative properties and was studied as a sedative in the intensive care setting, delivered by continuous intravenous infusion.

It was anticipated that dexmedetomidine would provide effects similar to those of clonidine, also an α -2-adrenergic agonist which has been used as an anesthetic adjuvant producing analgesia and sedation, and purported to decrease anesthetic requirements and

¹ Medetomidine is a veterinary sedative widely available in Europe and approved in the US in 1997.

improve hemodynamic stability. The theoretical basis for the use of the α -2-adrenergic agonists as adjunctive medications is that they are thought to act as neuromodulators, regulating central (medullary) cardiovascular or peripheral vasomotor responses such as those to anesthetics, thus producing an anesthetic-sparing effect. These effects were not specifically characterized for approval purposes, although some exploratory studies were undertaken during early development.

A unique feature of dexmedetomidine as a sedative which was observed in phase I studies was its property of providing adequate sedation but with ease of alerting and without persisting central effects, once the patient is aroused.

Efficacy

The Sponsor submitted two adequate and well-controlled studies of similar design in support of the proposed indication for sedation. The studies were randomized, double blind, double-dummy parallel group multicenter trials comparing the effects of dexmedetomidine infusion with placebo. The trials evaluated the sedative properties of dexmedetomidine and control by inference, that is, they compared the amount of rescue medication (midazolam in one trial and propofol in the second) required to achieve a specified level of sedation (by the standardized Ramsay sedation scale) between the placebo and treatment group from onset to extubation. There were a number of potentially confounding variables that were assessed as secondary outcome measures, particularly time to extubation and amount of morphine used for analgesia.

In study W97-245, 175 patients were randomized to the placebo arm and 178 patients were randomized to receive dexmedetomidine by intravenous infusion at doses of 0.4 μ g/kg/hr (with allowed adjustment between 0.2 and 0.7 μ g/kg/hr) following an initial bolus of 6 μ g/kg IV. Patients were allowed to receive midazolam as needed to maintain a Ramsay sedation score of ≥ 3 . In addition, morphine sulfate could be administered as an analgesic as needed. The primary outcome measure for this study was the total amount of rescue medication (midazolam) needed to maintain sedation as specified while intubated. There was a statistically significantly greater use of midazolam in patients randomized to placebo than to dexmedetomidine during treatment.

A second prospective primary analysis was undertaken at the request of the division to obtain a direct assessment of the sedative effects of dexmedetomidine, that is, a comparison of the percentage of patients who were able to achieve a Ramsay sedation score of ≥ 3 during intubation, without the use of additional rescue medication, between the dexmedetomidine and the placebo groups. It can be seen from the results reported in the table on the following page that a significantly greater number of patients in the dexmedetomidine group (61%) compared to the placebo group (25%) maintained a Ramsay sedation score of ≥ 3 without any additional midazolam rescue.

Midazolam use as rescue medication during intubation (ITT)			
Study W97-245			
	PBO	Dexmedetomidine	p-value
	N=175	N=178	
Mean total dose (mg) of midazolam	18.6 mg	4.8 mg	0.0011*
Categorized midazolam use			
# pts used			
0mg	43(25%)	108 (61%)	<0.001**
0-4 mg	34 (19%)	36(20%)	
>4 mg	98 (56%)	34 (19%)	

* ANOVA model with rx and ctr. **Chi-square (after J.Ma's table 3.2, review, p.5)

In study W97-246, 198 patients were randomized to the placebo arm and 203 patients were randomized to receive dexmedetomidine by intravenous infusion at doses of 0.4 µg/kg/hr (with allowed adjustment between 0.2 and 0.7 µg/kg/hr) following an initial bolus of 6 µg/kg IV. Patients were allowed to receive propofol as needed to maintain a Ramsay sedation score of ≥3. In addition, morphine sulfate could be administered as an analgesic as needed. The primary outcome measure for this study was the total amount of rescue medication (propofol) needed to maintain sedation as specified while intubated. There was a statistically significantly greater use of propofol in patients randomized to placebo than to dexmedetomidine during treatment.

The same prospective primary analysis that was performed in study W97-245 was also performed in this study. It can be seen from the results reported in the table below that a significantly greater number of patients in the dexmedetomidine group (60%) compared to the placebo group (24%) maintained a Ramsay sedation score of ≥3 without any additional propofol rescue.

Midazolam use as rescue medication during intubation (ITT)			
Study W97-246			
	PBO	Dexmedetomidine	p-value
	N=198	N=203	
Mean total dose (mg) of propofol	513 mg	72 mg	<0.0001*
Categorized propofol use			
# pts used			
0mg	47(24%)	122 (60%)	<0.001**
0-50 mg	30 (15%)	43 (21%)	
>50 mg	121 (61%)	38 (19%)	

* ANOVA model with rx and ctr. **Chi-square (after J.Ma's table 3.5, review, p.9)

For both studies, the time to extubation was measured and analyzed, and found to be, based on a very conservative approach, not significantly different between groups. For more detail, Dr. Jonathan Ma's analysis p.10-11 should be referenced. In addition the

amount of morphine used for analgesia in both studies was found to be significantly greater in the control group. These are both important findings combined with the primary analysis, since they establish that the treatment group did not succeed based on the sedation afforded by morphine sulfate or because of a longer time and therefore greater access to more medication.

Dexmedetomidine is said to have been studied as adjunctive therapy insofar as rescue with a second agent was required in many cases to achieve the specified sedation, rather than increasing the infusion (and thus the dose) of dexmedetomidine as needed. Clearly it was the primary agent. The sponsor compared between the two randomized groups in both studies, the percentage of patients who received only dexmedetomidine and who required no rescue medication, confirming its efficacy as monotherapy in two trials:

The primary review team and Dr. Rappaport have carefully reviewed these trials. There is nothing to add to the Medical and Statistical analyses and I concur with their conclusions that these studies, while somewhat unique in their design, clearly establish that dexmedetomidine is an effective sedative when administered by intravenous infusion at doses of 0.4 $\mu\text{g/kg/hr}$ (with allowed adjustment between 0.2 and 0.7 $\mu\text{g/kg/hr}$) following an initial bolus of 6 $\mu\text{g/kg IV}$.

Safety

Nonclinical

No significant animal toxicity was described in acute studies in rats or dogs. However, chronic dosing of up to 28 days in dogs and rats was associated with hepatic toxicity, specifically enlarged livers, eosinophilic inclusions in hepatocytes, and elevated LFTs. These changes were not observed in the acute studies. The genesis of the hepatotoxicity has not been characterized as to whether it is correlated with parent compound or any specific metabolite. While there appears to be an adequate safety margin in dosing, the contribution of a different human metabolic profile may theoretically alter the toxicity of this compound with chronic dosing in humans. This bears further evaluation.

Dexmedetomidine had no effect on ACTH-stimulated cortisol release in dogs given just a single dose of 80 $\mu\text{g/kg/dose S.C.}$, but after one week of treatment with 3 $\mu\text{g/kg/hr}$, the ACTH-stimulated release of cortisol was reduced by 40%. This has implications on the hypothalamic-pituitary-adrenal axis with prolonged ICU treatment with this agent, and should be further elaborated concurrently with human trials evaluating the safety of long-term infusion.

The nonclinical pharmacokinetics of dexmedetomidine are similar to humans with the exception of metabolism, which differs by two major metabolites. The two major metabolites found in human (the 2 glucuronides of imidazole nitrogen) and absent in the rat and dog, were never studied in animals. Because it is projected that this product will be used in ICU for longer than 24 hrs of infusion, the potential toxicity of these human metabolites should be evaluated. This should be done as a Phase 4 study of long-term

infusion in an appropriate animal species, either indirectly by administration to an animal species that does not produce these metabolites or in an animal species which produces the same metabolites.

Dexmedetomidine was not shown to be teratogenic in rats or rabbits. However fetal toxicity was observed in rats, evidenced by increased postimplantation losses and reduced number of live pups per litter. Prenatal and postnatal effects included reduced pup body weights during and after nursing and delayed motor development. Placental transfer of dexmedetomidine was observed in rats.

Dexmedetomidine was not mutagenic in the Ames test or the mouse lymphoma assay. It was shown to be clastogenic in both the *in vitro* human lymphocytes chromosomal aberration assay in the presence of metabolic activation and in *in vivo* mouse micronucleus assay.

Carcinogenicity testing was considered unnecessary due to the projected short-term use of this product.

Clinical

The safety data for this NDA was combined from two sources, the Japanese original development program, and subsequent Abbott Laboratories data from the more recent development. The safety database of dexmedetomidine exposure includes 3038 subjects, of whom 1473 were ICU patients who received the drug by continuous infusion. The bulk of exposure was in the range of 4-6 mg/kg and less than 16 hours. The dose and duration of exposure provide sufficient experience to be able to assess the safety of this product for the proposed duration of up to 24 hours infusion.

There was also limited exposure (78 patients) who received infusion longer than 24 hours with the longest infusion lasting between 30-40 hours in 2 patients.

The deaths and serious adverse events reported were not unexpected for the ICU population under study in this NDA either in quality or in quantity.

In the placebo-controlled infusion studies in Phase 2-3, the only commonly reported adverse events observed in more than 1% of patients treated with dexmedetomidine and occurring with a frequency more than 2-fold that of the placebo were predictably hypotension (22%), hypertension (12%), and bradycardia (5%).

Summary of Treatment-Emergent Adverse Events Occurring in >1% of Dexmedetomidine patients in Phase II/III Continuous Infusion ICU Sedation Studies²

Adverse Event	Randomized dexmedetomidine (N=387)	Placebo N=379
Hypotension	84 (22%)*	16 (4%)
Hypertension	47 (12%)*	24 (6%)
Bradycardia	20 (5%)*	6 (2%)
Mouth Dry	13 (3%)	4 (1%)
Nausea	16 (4%)	20 (5%)

*Statistically significant difference between randomized dexmedetomidine and placebo patients $p \leq 0.05$
Data source 2.2.5.5

Abnormal laboratory findings, which might have been anticipated from the preclinical studies, such as elevated LFTs and glycosuria, were not borne out in laboratory testing.

There are no safety data in pediatric patients. The sponsor will be required to study this product in children from birth to 16 years of age as a Phase 4 commitment.

Approximately 500 patients over 65 years of age have been studied in this NDA. An additional analysis of patients over 75 years has been requested of the sponsor with comparison of adverse events by age, separating the elderly by >65 to 75 and >75 years of age. This will be undertaken in an effort to assess whether dosage adjustment may be needed in the very elderly patients based on anticipated PD differences associated with sedative agents.

Abuse Potential

Dexmedetomidine might be expected, based on its clinical pharmacological effects and its similarity to clonidine³, to have some abuse liability. Indeed animal studies indicate that there are some reinforcing properties. Reinforcing behavior in primates was elicited by dexmedetomidine 1.0 µg/kg/dose >saline and equivalent to saline at 0.0625 µg/kg/dose. At a dose of 0.25 µg/kg/dose dexmedetomidine produced reinforcing behavior comparable to pentazocine (CIV). Dexmedetomidine also has been shown to attenuate morphine withdrawal; suggestive but not conclusive evidence for dependence liability. A mild withdrawal syndrome has been described in rodents after 7 days of treatment.

Extensive receptor binding studies using standard radioligands were presented in the NDA, demonstrating very high affinity for the α-adrenergic receptors and moderate affinity for the serotonergic receptors. Binding at the opiate receptors was negligible. Comparative binding to relevant controlled substances was not provided.

² After Sponsor's Table 21 ISS 8/10-239-65

³ Clonidine is not currently controlled in the CSA. There have been reports of abuse with clonidine, mostly of reports of opiate addicts using clonidine to suppress withdrawal symptoms rather than for its psychotropic effects.

On balance, the available studies suggest an abuse potential lower than some products controlled in schedule IV or as low as some not controlled at all. I do not agree with the controlled substances evaluation team that this product should not be scheduled due to lack of information, but rather that the available information suggests a rather low potential for abuse. Furthermore the clinical setting in which it will be used, limited to hospital intensive care units, reduces that potential. Continued vigilance is indicated, nevertheless, for any actual diversion and abuse that might occur in the post approval setting, so that appropriate measures can be taken to control this substance if needed. There have been to date no reports of diversion or abuse of medetomidine approved in 1997.

Biopharmaceutics

The ADME of dexmedetomidine has been fairly well studied, but some unanswered questions remain that may be very relevant to long term infusion. For example, it has been demonstrated that there is almost no accumulation of parent drug, following IV bolus administration, and that there is nearly complete biotransformation. The fate of the metabolites, however, has not been well characterized. Biotransformation includes direct N-glucuronidation (two major metabolites, total of 34%) and CYP 2A6-mediated metabolism (three additional metabolites, 14%), and N-methylation (three metabolites, 18%). There are additional urinary metabolites that have not been identified yet. Dexmedetomidine is about 94% protein-bound.

Evaluation of dexmedetomidine in patients with renal failure demonstrated no change in dexmedetomidine PK with severe renal failure following a single dose, but there is no information about the possible accumulation of metabolites when dexmedetomidine is infused continuously, particularly for long periods of time. The bulk of elimination of metabolites is thought to be renal. Therefore, this information should be obtained in Phase 4 in anticipation of more prolonged infusion in patients with renal insufficiency.

Hepatic impairment affected the PK of dexmedetomidine as expected, and the appropriate adjustments for patients with mild, moderate and severe hepatic impairment will be included in the package insert.

There was no effect of age on the pharmacokinetics of dexmedetomidine, although only 20 elderly volunteers, ranging from 66 to 83 years (mean, 72) were evaluated. The possibility of pharmacodynamic differences increasing with increasing age were not examined, but should be looked at more closely in Phase 4, as sedative/hypnotics have a tendency to result in more significant safety problems (hypotension, confusion, respiratory depression) in the elderly. Dexmedetomidine has not been evaluated in the pediatric population.

Interaction studies with a spectrum of anesthetics *in vivo* such as alfentanil, midazolam, propofol and isoflurane did not indicate interactions when added to dexmedetomidine or to alfentanil, midazolam, propofol or rocuronium when dexmedetomidine was added.

Chemistry and Manufacturing

Dexmedetomidine is the dextro-enantiomer of medetomidine (4-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole hydrochloride) and it is manufactured by separation of the isomers from the racemic mixture. Preparation and characterization of the drug substance, levels of impurities including optical purity (levo-enantiomer limited to $\leq 1\%$) have all been judged acceptable. Stability data on the bulk drug substance and regulatory specifications were also deemed acceptable.

The drug product is a sterile aqueous solution of dexmedetomidine for intravenous infusion upon further dilution. The formulation consists of dexmedetomidine HCl (the active ingredient) and sodium chloride and water for injection. The drug product is prepared using standard methods, has undergone stability testing (undiluted) under ICH storage conditions generating data to support a 2-year shelf life, and has been shown to be stable in light. Sterility of the drug product is achieved through aseptic fill and terminal sterilization by autoclave. The process and data have been reviewed by microbiology and found to be acceptable.

The drug product is prepared for use by diluting it with sterile 0.9% sodium chloride solution for injection after which it is stable for 24 hours.

Compatibility data are provided with commonly used IV solutions, drugs (vasoactive agents, muscle relaxants, sedatives, narcotics and plasma substitute), tubing, and syringes commonly used for administration of IV drugs. It was observed that dexmedetomidine has the potential for adsorption onto certain types of natural rubber. This will be noted in the package insert, advising use with synthetic components or coated natural rubber components.

A suitable trade name has not yet been selected for the drug product to which the Agency agrees.

Data Integrity

All questions related to data integrity were resolved during the course of review and inspection, including questions about some unreported deaths, randomization errors and protocol violations that were not reported. DSI inspections were conducted, and aside from some reports of careless errors in recordkeeping there was no evidence to suggest

that the data on which the conclusions and recommendations for this NDA will be based have significant problems.

Comments:

There is adequate evidence to support the efficacy and safety of dexmedetomidine to approve it for ICU sedation by continuous infusion for 24 hours. It is anticipated that there will be increasing demand for more prolonged use of this product once it is approved. In addition to collecting additional safety data on prolonged use, there should be a better characterization of the activity, toxicity and fate of the metabolites.

Additional data should be obtained for safe use at the extremes of age—pediatric dosing, pharmacokinetics and safety should be obtained. Geriatric pharmacodynamic/safety data in the very elderly >75 years should also be generated or existing data analyzed.

Once the metabolic profile is better established with multiple dosing, its safety should be evaluated in patients with renal failure.

Surveillance for possible diversion and abuse can be done through the existing mechanisms such as Medwatch, SAMHSA's DAWN database, and DEA reports.

Phase 4 Commitments

The focus of the dexmedetomidine development plan was short-term ICU sedation in adults. It is quite clear that this product will not have use limited to this population, and therefore the following phase 4 commitments will be requested of the sponsor in an effort to obtain safety data in more extended ICU infusion, in pediatric patients and in the elderly.

Nonclinical studies

1. A two-week study in dogs with a 2-week recovery phase should evaluate general toxicology of prolonged infusion of dexmedetomidine and the effect of chronic infusion on HPA axis.
2. A second study should evaluate changes in drug metabolism following two weeks of infusion.
3. A third study should evaluate the potential toxicity of human major metabolites which are absent in rats and dogs.

Clinical Studies

1. **Pediatrics:** Studies to obtain an indication for sedation in pediatric patients from birth to 16 years of age in the ICU setting. The development plan should include pharmacokinetics and safety in pediatric patients from birth to 16 years, and efficacy data designed at determining appropriate dosage regimens.
2. **Geriatrics:** Further studies are needed to evaluate the safety v. differential toxicity of dexmedetomidine in very elderly patients, as has been described with other sedative/hypnotic drug products.
3. **Longer-term infusion studies** should include safety and pharmacokinetics.

4. **Renal Impairment:** Additional data are needed to examine the potential accumulation of dexmedetomidine metabolites upon continuous infusion in patients with renal impairment.

It is expected that a reasonable timeline for submission of the protocols might be approximately 6 months from approval; and completion of these studies, approximately 2 years.

Recommended Action: Approval of dexmedetomidine HCl as an adjunctive medication for ICU sedation.

**APPEARS THIS WAY
ON ORIGINAL**



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)443-3741

MEMORANDUM

DATE: November 5, 1999
TO: File, NDA 21-038
FROM: Bob A. Rappaport, M.D.
Deputy Director, DACCADP
Team Leader, Anesthetic Drug Group
RE: Supervisory Review of NDA 21-038, Dexmedetomidine HCl

BACKGROUND:

NDA 21-038, Dexmedetomidine HCl, was submitted by Abbott Laboratories Inc. on December 18, 1998. Dexmedetomidine is a potent and highly selective α -2-adrenoreceptor agonist. The sponsor claims that their product produces titratable, predictable sedation in an ICU setting, from which patients are easily arousable and cooperative. The sponsor also claims that their product provides improved analgesia in the postoperative ICU setting. The α -2-adrenoreceptor agonist detomidine was developed for use as a sedative/analgesic in horses and cattle and was registered for marketing in Finland in 1983. Medetomidine, launched in 1987 in Scandinavia, was a more selective α -2-adrenoreceptor agonist used as a sedative/analgesic in cats and dogs. It was approved for veterinary use in the US in 1997. The sedative and analgesic activity of medetomidine are believed to reside predominantly in its dextroenantiomer dexmedetomidine. The enantiomer was first synthesized by Farnos Group in Finland in 1986. Numerous perioperative indications have been evaluated since that time. Farnos merged with Orion Corp. in 1990, and Orion licensed the injectable dosage form of dexmedetomidine for clinical use to Abbott Laboratories in 1994.

Orion conducted 56 clinical trials of dexmedetomidine with various modes of administration including rapid intravenous infusion, continuous intravenous infusion,

intramuscular injection, as well as transdermal and oral administration. Abbott initiated its own clinical development program and completed 21 studies (13 Phase I and 8 Phase II/III) in the US, Canada and Europe. They also completed 2 studies in Japan: a Phase I safety and pharmacokinetic study of rapid infusion in 9 healthy males, and a Phase II safety and dose response study of rapid infusion in 109 patients. The sponsor reported that the case report forms for these 2 studies were unavailable and they did not include the data in the ISS database.

The clinical studies of the effectiveness and safety of this new formulation have been reviewed [submitted August 29, 1999] by Charles Cortinovis, M.D. Dr. Patricia Hartwell contributed two addenda [submitted September 13, 1999 and October 27, 1999] reviewing safety data in the original application, a supplementary safety package, and the 120-Day Safety Update. The application has also been reviewed by Jonathan Ma, Ph.D. (biostatistics), Suresh Doddapaneni, Ph.D. (clinical pharmacology and biopharmaceutics), Harry Geyer, Ph.D. (pharmacology/toxicology), Michael Theodorakis, Ph.D. (chemistry), and BeLinda A. Hayes, Ph.D. (abuse liability). In this memo, I will briefly review the effectiveness and safety data summarized in the primary clinical review, as well as any relevant information found in the primary reviews from the other disciplines, and make appropriate recommendations for action on the NDA.

EFFECTIVENESS:

Evidence of efficacy has been submitted in two clinical studies W97-245 and W97-246.

Study W97-245:

This was a randomized, double blind, placebo-controlled, parallel group study conducted at 33 centers in Canada and Europe. The Study consisted of two parts. Part I was an open-label evaluation of dexmedetomidine in up to 4 patients per site. This portion of the study was designed to allow the investigators to become familiar with the observed clinical effects of dexmedetomidine prior to starting the double-blind portion of the study. Patient data from Part I was not included in the efficacy analyses.

In Part II of the study, adult postoperative patients who required a minimum of 6 hours of ventilation and sedation in the ICU setting were randomized to either dexmedetomidine or placebo for sedation. Within one hour of admission to the ICU, patients were

administered a loading dose 6.0 µg/kg/hour over a 10 minute period, followed by a maintenance infusion of 0.4 µg/kg/hour. The infusion rate could be adjusted by increments of 0.1 µg/kg/hour in order to maintain a Ramsay Sedation Score¹ of 3 or higher. However, it was required that the rate be maintained between 0.2 and 0.7 µg/kg/hour. Following extubation, the infusion rate was adjusted to achieve a Ramsay Sedation Score of 2 or above. Study drug infusion was continued for at least 6 hours after extubation and, at the discretion of the investigator, up to a maximum of 24 hours total study drug infusion.

Rescue medications were limited to midazolam for sedation and morphine for pain. After extubation, paracetamol was administered when clinically indicated. When the investigators judged that there was need for an increase in sedative medication, they were to first adjust the maintenance dose of dexmedetomidine. Midazolam was administered as bolus doses of 0.02 mg/kg. Using the Ramsay Sedation Score, the patient was assessed prior to and 10 minutes after every rate change in study drug or administration of midazolam. If the patient required 3 bolus doses of midazolam within any 2 hour period, after appropriate adjustments of the study drug infusion rate, further midazolam was administered as a continuous infusion at 0.01 to 0.02 mg/kg/hour.

The need for analgesic administration was assessed either by direct communication with the patient regarding pain, or by the presence of abnormal autonomic signs such as sweating, tachycardia and hypertension. Morphine was administered for pain as 2-mg intravenous boluses.

The protocol specified primary efficacy parameter was the total dose of midazolam in milligrams administered during the period that the patient was intubated. The efficacy analysis was based on the Intent to Treat (ITT) population and analysis on the Evaluable population was also performed. A second primary efficacy endpoint was analyzed based on a recommendation made by the Division biostatistician, Dr. Permutt, at a development meeting with the sponsor. This endpoint was a comparison of the numbers of patients who fell into one of the following three categories of midazolam use:

1. No dose (0 mg)
2. Subtherapeutic dose (0-4 mg)
3. Therapeutic dose (>4 mg)

This outcome measure was not specified in any amendment to the protocol. However, the analysis was undertaken prior to breaking the study blind.

¹ 6 = asleep, no response

5 = asleep, sluggish response to light glabellar tap or loud auditory stimulus

4 = asleep but with brisk response to light glabellar tap or loud auditory stimulus

3 = patient responds to commands

2 = patient cooperative, oriented, and tranquil

1 = patient anxious, agitated, or restless

Secondary efficacy parameters listed in the protocol for this study included²:

1. Use of morphine for pain – as assessed by total dose used with dexmedetomidine as compared to placebo (mg/hr)
2. Use of paracetamol for pain after extubation – as assessed by total dose used with dexmedetomidine compared to placebo (mg/hr)
3. Time to extubation – measured as time of arrival in ICU until time of extubation

However, the secondary efficacy parameters listed in the study report were:

1. Total dose of midazolam during study drug administration
2. Total dose of morphine during study drug administration
3. Total dose of morphine by time period
4. Ramsay Sedation Score
5. Ratio³ of Ramsay Sedation Score of "1" during study drug administration
6. Time to extubation and weaning duration
7. Nurses' and patients' assessment

These changes in secondary outcome measures were not specified in any amendment to the protocol.

Results:

Eighty-six patients were enrolled and 85 treated in Part I of the study.

In Part II of the study, 178 patients were randomized to dexmedetomidine and 175 to placebo. All patients were administered study drug and comprised the ITT population. Two dexmedetomidine treated and 6 placebo patients were excluded from the Evaluable patient set.

Dr. Cortinovis' Table 4 [page 22 of his review], reproduced below, summarizes the patient disposition:

² This information differs from that documented by Dr. Cortinovis in the medical officer's review and by Dr. Ma in the Statistician's review. It is based on documentation provided by Dr. Patricia Hartwell who examined the original documents at my request.

³ The ratio is the proportion of assessments that equal 1 divided by the total number of assessments for the patient.

Table 1.

	Placebo	Dexmedetomidine
Intent to Treat Patients (All Treated)	175	178
Non-Evaluable patients	6	2
Evaluable Patients	169	176
Reasons for Non-Evaluability (Patient Numbers)*		
Insufficient Study drug therapy	1001,4104	1806
Insufficient Intubation	1001,11705	1806
Received disallowed medication	1303,6004, 7601	6106

* Patients could have had more than one reason for non-evaluability
Modified Sponsor's Table 8.1a Vol. 8/10-62-73

Nine patients in the dexmedetomidine group and 10 in the placebo group were discontinued from the study prematurely. Each of these patients discontinued due to adverse events.

Primary Efficacy Analyses:

1. Dexmedetomidine patients required statistically significantly less midazolam compared to the placebo treated patients in both the ITT and Evaluable patient analyses. Dr. Cortinovis' Table 8, page 25 of his review, summarizes these results and is reproduced below:

**APPEARS THIS WAY
ON ORIGINAL**

Table 2. Total Dose of Midazolam (mg) During Intubation

	Placebo	Dexmedetomidine	Treatment Effect p-Value*
Intent to Treat Patients (N)	175	178	
Mean $\pm$ SEM	18.61 $\pm$ 4.02	4.83 $\pm$ 1.43	0.0011
Evaluable Patients (N)	169	176	
Mean $\pm$ SEM	18.46 $\pm$ 4.14	4.56 $\pm$ 1.42	0.0014

* p-value from ANOVA

SEM = Standard Error of Mean

Modified Sponsor's Table 8.2a Vol. 8/10-62-74

2. Statistically significant differences were observed between the treatment groups in both the ITT and Evaluable analyses, with the majority of the dexmedetomidine treated patients requiring no midazolam compared to the majority of placebo patients who required greater than 4 mg of midazolam. Dr. Cortinovis' Table 9, page 25 of his review, summarizes these results and is reproduced below:

Table 3. Total Dose Categories of Midazolam During Intubation

	Placebo	Dexmedetomidine	Treatment Effect p-Value*
Intent-to-Treat Patients (N)	175	178	<0.001
0 mg	43(25%)	108(61%)	
>0mg to 4 mg	34(19%)	36(20%)	
>4 mg	98(56%)	34(19%)	
Evaluable Patients (N)	169	176	<0.001
0 mg	43(25%)	107(61%)	
>0 mg to 4 mg	32(19%)	36(20%)	
> 4 mg	94(56%)	33(19%)	

* p-value from chi-square

Modified Sponsor's Table 8.2b Vol. 8/10-62-75

Secondary Efficacy Analyses:

There were no differences in any of the analyses when performed on either the ITT or Evaluable patient data sets. The following table, based on Dr. Ma's Table 3.3, page 6 of his review, summarizes the results for six of these analyses:

Table 4.

	Placebo N = 175 Mean $\pm$ SEM*	Dexmedetomidine N = 178 Mean $\pm$ SEM	p-value Treatment Effect
Total dose of midazolam during drug administration (mg/hour)	1.19 (0.23)	0.29 (0.07)	0.0001
Total dose of morphine during drug administration (mg/hour)	0.83 (0.07)	0.47 (0.06)	<0.0001
Total dose of morphine during 0 to 6.5 hours (mg)	8.5 (0.79)	4.9 (0.56)	<0.0001
Total dose of morphine during 6.5 to end (mg/hour)	0.42 (0.08)	0.24 (0.05)	0.042
Ramsay Sedation Score AUC during drug administration	3.3 (0.05)	3.6 (0.05)	<0.0001
Ratio of Ramsay Sedation Score of 1 during drug administration (%)	7 (0.8)	3 (0.5)	<0.0001

*SEM = Standard Error of Mean

As noted by Dr. Ma in his review, the Ramsay Sedation Score itself (AUC) was not a useful endpoint to consider as, for both groups, dose titration and rescue medication were used to maintain the patients at a specified level of sedation indicated by the Ramsay Score. However, a smaller ratio of Ramsay score of 1, for any particular patient, might indicate less anxiety during the treatment period. Statistically significant center effects were noted for most secondary endpoints indicating that patients in different countries either required and/or were administered differing amounts of sedative and analgesic medications.

The following additional secondary endpoints were discussed by Dr. Cortinovis in his review:

Time to extubation and weaning duration:

No statistically significant differences were noted in time to readiness for extubation or actual extubation, when that time was measured either from ICU arrival or start of study drug. No statistically significant differences were found between the treatment groups for median duration of weaning.

Nurses' and patients' assessment

Dexmedetomidine treated patients had a statistically significantly lower patient management index [defined on page 30 of Dr. Cortinovis' review] score compared with

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placebo treated patients. However, the actual numerical differences were not likely to be clinically relevant, according to Dr. Cortinovis.

Patient satisfaction survey

The dexmedetomidine treated and placebo patients rated similarly their present experience with sedation compared to prior experiences, their comfort during the ICU sedation, their remembrance of pain, discomfort from breathing tube, people and noise, and whether or not they would have the same sedative treatment in the future. However, 61% of dexmedetomidine treated patients compared to 52% of placebo patients rated their overall experience as "better than expected."

Data Integrity:

The Division of Scientific Investigations' (DSI) Clinical Inspection Summary for this application notes that one of the two pivotal study sites inspected by DSI was found to have protocol violations which may compromise some of the data arising out of that site. That site in Study W97-245 enrolled 5 out of 45 patients out of sequence; and one of those five subjects appeared to be a seven year old child who did not meet the inclusion criterion for age. DSI has requested clarification of the discrepancies and recommends that, until the matters are clarified and found to be satisfactory, we not use the data from those five subjects in support of the application.

Dr. Thomas Permutt, biostatistics teamleader, has reviewed the data and the DSI recommendations and has concluded that removal of the data from those five patients would not affect the outcome of the efficacy analyses.

Study W97-246:

This was a randomized, double blind, placebo-controlled, parallel group study conducted at 36 centers in Canada and Europe. The Study consisted of two parts. Part I was an open-label evaluation of dexmedetomidine in up to 4 patients per site. This portion of the study was designed to allow the investigators to become familiar with the observed clinical effects of dexmedetomidine prior to starting the double-blind portion of the study. Patient data from Part I was not included in the efficacy analyses.

In Part II of the study, adult postoperative patients who required a minimum of 6 hours of ventilation and sedation in the ICU setting were randomized to either dexmedetomidine or placebo for sedation. Within one hour of admission to the ICU, patients were administered a loading dose 6.0 µg/kg/hour over a 10 minute period, followed by a

maintenance infusion of 0.4 µg/kg/hour. The infusion rate could be adjusted by increments of 0.1 µg/kg/hour in order to maintain a Ramsay Sedation Score⁴ of 3 or higher. However, it was required that the rate be maintained between 0.2 and 0.7 µg/kg/hour. Following extubation, the infusion rate was adjusted to achieve a Ramsay Sedation Score of 2 or above. Study drug infusion was continued for at least 6 hours after extubation and, at the discretion of the investigator, up to maximum of 24 hours total study drug infusion.

Rescue medications were limited to propofol for sedation and morphine for pain. After extubation, paracetamol was administered when clinically indicated. When the investigators judged that there was need for an increase in sedative medication, they were to first adjust the maintenance dose of dexmedetomidine. Propofol was administered as bolus doses of 0.02 mg/kg. Using the Ramsay Sedation Score, the patient was assessed prior to and 10 minutes after every rate change in study drug or administration of propofol. If the patient required 3 bolus doses of propofol within any 2 hour period, after appropriate adjustments of the study drug infusion rate, further propofol was administered as a continuous infusion at 0.5 to 4.0 mg/kg/hour.

The need for analgesic administration was assessed either by direct communication with the patient regarding pain, or by the presence of abnormal autonomic signs such as sweating, tachycardia and hypertension. Morphine was administered for pain as 2-mg intravenous boluses.

The protocol specified primary efficacy parameter was the total dose of propofol in milligrams administered during the period that the patient was intubated. The efficacy analysis was based on the Intent to Treat (ITT) population and analysis on the Evaluable population was also performed. A second primary efficacy endpoint was analyzed based on a recommendation made by the Division biostatistician, Dr. Permutt, at a development meeting with the sponsor. This endpoint was a comparison of the numbers of patients who fell into one of the following three categories of propofol use:

- | | |
|------------------------|-----------|
| 1. No dose | (0 mg) |
| 2. Subtherapeutic dose | (0-50 mg) |
| 3. Therapeutic dose | (>50 mg) |

This outcome measure was not specified in any amendment to the protocol. However, the analysis was undertaken prior to breaking the study blind.

⁴ 6 = asleep, no response

5 = asleep, sluggish response to light glabellar tap or loud auditory stimulus

4 = asleep but with brisk response to light glabellar tap or loud auditory stimulus

3 = patient responds to commands

2 = patient cooperative, oriented, and tranquil

1 = patient anxious, agitated, or restless

Secondary efficacy parameters listed in the protocol for this study included⁵:

1. Use of morphine for pain – as assessed by total dose used with dexmedetomidine as compared to placebo (mg/hr)
2. Use of paracetamol for pain after extubation – as assessed by total dose used with dexmedetomidine compared to placebo (mg/hr)
3. Time to extubation – measured as time of arrival in ICU until time of extubation

However, the secondary efficacy parameters listed in the study report were:

1. Total dose of propofol during study drug administration
2. Total dose of morphine during study drug administration
3. Total dose of morphine by time period
4. Ramsay Sedation Score
5. Ratio⁶ of Ramsay Sedation Score of "1" during study drug administration
6. Time to extubation and weaning duration
7. Nurses' and patients' assessment

These changes in secondary outcome measures were not specified in any amendment to the protocol.

Results:

Ninety-three patients were enrolled and 92 treated in Part I of the study.

In Part II of the study, 203 patients were randomized to dexmedetomidine and 198 to placebo. All patients were administered study drug and comprised the ITT population. Three dexmedetomidine treated and 7 placebo patients were excluded from the Evaluable patient set.

Dr. Cortinovis' Table 18 [page 44 of his review], reproduced below, summarizes the patient disposition:

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⁵ This information differs from that documented by Dr. Cortinovis in the medical officer's review and by Dr. Ma in the Statistician's review. It is based on documentation provided by Dr. Patricia Hartwell who examined the original documents at my request.

⁶ The ratio is the proportion of assessments that equal 1 divided by the total number of assessments for the patient.

Table 5.

	Placebo	Dexmedetomidine
Intent to Treat Patients (All Treated)	198	203
Non-Evaluable patients	7	3
Evaluable Patients	191	200
Reasons for Non-Evaluability (Patient Numbers)		
Insufficient Intubation	1	N/A
Received disallowed medication	5	3
Enrolled twice	1	N/A

Modified Sponsor's Table 8.1a Vol. 8/10-86-73

Fourteen patients in the dexmedetomidine group and 8 in the placebo group were discontinued from the study prematurely. Most of these patients discontinued due to adverse events.

Primary Efficacy Analyses:

1. Dexmedetomidine patients required statistically significantly less propofol compared to the placebo treated patients in both the ITT and Evaluable patient analyses. Dr. Cortinovis' Table 22, page 47 of his review, summarizes these results and is reproduced, with modifications, below:

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Table 6. Total Dose of Propofol (mg) During Intubation

	Placebo	Dexmedetomidine	Treatment Effect p-Value*
Intent to Treat Patients (N)	198	203	
Mean $\pm$ SEM	513 $\pm$ 55.58	72 $\pm$ 17.51	<0.0001
Evaluable Patients (N)	191	200	
Mean $\pm$ SEM	505 $\pm$ 56.40	73 $\pm$ 17.76	<0.0001

* p-value from ANOVA

SEM = Standard Error of Mean

Modified Sponsor's Table 8.2a Vol. 8/10-86-73

2. Statistically significant differences were observed between the treatment groups in both the ITT and Evaluable analyses, with the majority of the dexmedetomidine treated patients requiring no propofol compared to the majority of placebo patients who required greater than 50 mg of propofol. Dr. Cortinovis' Table 24, page 48 of his review, summarizes these results and is reproduced, with modifications, below:

Table 7. Total Dose Categories of Propofol During Intubation

	Placebo	Dexmedetomidine	Treatment Effect p-Value*
Intent-to-Treat Patients (N)	198	203	<0.001
0 mg	47(24%)	122(60%)	
> 0mg to 50 mg	30(15%)	43(21%)	
> 50 mg	121(61%)	38(19%)	
Evaluable Patients (N)	191	200	<0.001
0 mg	46(24%)	120(60%)	
>0 mg to 50 mg	30(16%)	42(21%)	
> 50 mg	115(60%)	38(19%)	

* p-value from chi-square

Modified Sponsor's Table 8.2b Vol. 8/10-86-74

Secondary Efficacy Analyses:

Their were no differences in any of the analyses when performed on either the ITT or Evaluable patient data sets. The following table, based on Dr. Ma's Table 3.6, page 10 of his review, summarizes the results for six of these analyses:

Table 8.

	Placebo N = 198 Mean $\pm$ SEM*	Dexmedetomidine N = 203 Mean $\pm$ SEM	p-value Treatment Effect
Total dose of midazolam during drug administration (mg/hour)	39 (4.1)	5.3 (1.2)	<0.0001
Total dose of morphine during drug administration (mg/hour)	0.89 (0.07)	0.43 (0.05)	<0.0001
Total dose of morphine during 0 to 6.5 hours (mg)	8.5 (0.64)	4.1 (0.47)	<0.0001
Total dose of morphine during 6.5 to end (mg/hour)	0.55 (0.07)	0.16 (0.03)	<0.0001
Ramsay Sedation Score AUC during drug administration	3.1 (0.04)	3.4 (0.04)	<0.0001
Ratio of Ramsay Sedation Score of 1 during drug administration (%)	7 (0.7)	4 (0.5)	0.0008

*SEM = Standard Error of Mean

As noted by Dr. Ma in his review, the Ramsay Sedation Score itself (AUC) was not a useful endpoint to consider as, for both groups, dose titration and rescue medication were used to maintain the patients at a specified level of sedation indicated by the Ramsay Score. However, a smaller ratio of Ramsay score of 1, for any particular patient, might indicate less anxiety during the treatment period. Statistically significant center effects were noted for most secondary endpoints indicating that patients in different countries either required and/or were administered differing amounts of sedative and analgesic medications.

The following additional secondary endpoints were discussed by Dr. Cortinovis in his review:

Time to extubation and weaning duration:

No statistically significant differences were noted in time to readiness for extubation or actual extubation, when that time was measured either from ICU arrival or start of study drug. No statistically significant differences were found between the treatment groups for median duration of weaning.

Nurses' and patients' assessment

Dexmedetomidine treated patients had a statistically significantly lower patient management index [defined on page 52 of Dr. Cortinovis' review] score compared with

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placebo treated patients. However, the actual numerical differences were not likely to be clinically relevant, according to Dr. Cortinovis.

Patient satisfaction survey

The dexmedetomidine treated and placebo patients rated similarly their present experience with sedation compared to prior experiences, their comfort during the ICU sedation, their remembrance of pain, discomfort from breathing-tube, people and noise, and whether or not they would have the same sedative treatment in the future. However, 70% of dexmedetomidine treated patients compared to 60% of placebo patients rated their overall experience as "better than expected."

Subgroup Analyses of Efficacy:

Dr. Ma has reviewed the sponsor's subgroup analyses and reports a few exceptions to the overall findings of significant efficacy of dexmedetomidine. These include:

1. Of the 43 patients in both groups at the five German centers in Study 245, only 1 (5%) in the treated group required 0 mg of midazolam during the intubation period. At the other centers more than 50% of the treated patients required no midazolam.
2. For the 20 patients at the single Austrian center in Studies 245 and 246, similar amounts of midazolam and propofol were required by the placebo and dexmedetomidine treated groups.
3. When analyzed by type of surgery, similar amounts of midazolam were required by the 34 patients undergoing head and neck surgery in Study 245 ($p=0.96$). Statistically significant differences were found for the two treatment groups for patients undergoing cardiac surgery, laparotomy and other surgeries in that study and all types of surgery in Study 246. However, the p -value for head and neck surgery for Study 246 was 0.052.

SAFETY:

The original NDA submission excluded the _____ data from the ISS database. This fact was discovered by Dr. Cortinovis after the submission had been filed. In a teleconference in late May of 1999, the sponsor claimed that they had not included this data because it came from studies performed to assess different indications than the one that is the subject of this application. The sponsor was informed that it would be necessary for them to compile, analyze and submit this missing data. The sponsor informed us that it would take a minimum of two months to complete the assignment and an early August submission was agreed upon. The new data was submitted on August 16, 1999. This submission was found to be incomplete, with missing case report forms [CRF's], CRF's from the _____ which had not been translated, and missing

case report form tabulations. During a follow-up teleconference, the sponsor acknowledged the missing data and stated that they had determined some of the data to be not useful due to unavailability of CRF's or the omission of data from CRF's. They were told to immediately provide as much of the data as possible and written explanations for any data which would not be submitted. These final portions of the safety database have been submitted piecemeal since that time. In her first addendum to the medical review, Dr. Hartwell has evaluated this late data in full and carefully delineates the various parts, based on GCP suitability, availability of primary documentation, and overall importance to the safety profile of dexmedetomidine.

In an attempt to incorporate the recently submitted data into the exposure database, Dr. Hartwell created two tables [see pages 5 and 6 of her first addendum] which summarize the number of studies and the number of patients included in the supplemental ISS, broken down by GCP suitability and by those with 'available CRF's. She then incorporated the patients from the supplemental submissions into a table [page 6 of her first addendum] of all exposed patients, updating Dr. Cortinovis' Table 32 [page 57 of his review]. At this time, based on the information available from the sponsor, it appears that a total of 3338 subjects have been exposed to dexmedetomidine in clinical studies. However, the sponsor has categorized 11 Phase I studies (109 subjects) and 4 Phase II/III studies (146 subjects) as containing inadequate information; and this data was not included in the supplemental ISS. Thus, the overall ISS database includes 3083 subjects exposed to dexmedetomidine.

Extent of exposure by dose is summarized in the table below, based on Dr. Cortinovis' Tables 7 and 22 [pages 24 and 47, respectively, of his review] and Dr. Hartwell's Tables 4 and 5 [page 7 of her first addendum]:

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Table 9.

	Continuous Infusion	Rapid Infusion	IM Administration
Phase I Studies:			
Mean Total Dose			
N	174	184	36
($\mu\text{g/kg}$) $\pm$ SD	3.52 ± 3.97	0.90 ± 0.63	3.86 ± 3.33
Mean Total Duration			
N	174	167	10
(hr) $\pm$ SD	7.65 ± 8.26	0.13 ± 0.05	0.02 ± 0.00
Minimum	0.72	0.02	0.02
Maximum	24.02	0.18	0.02
Phase II Studies:			
Mean Total Dose			
N	1518	267	662
($\mu\text{g/kg}$) $\pm$ SD	4.29 ± 3.09	1.00 ± 0.67	1.91 ± 0.75
Mean Total Duration			
N	1475	106	N/A
(hr) $\pm$ SD	10.10 ± 6.54	0.05 ± 0.03	N/A
Minimum	0.02	0.02	
Maximum	39.58	0.17	
Phase III Study 245:			
Mean Total Dose			
N	178	N/A	N/A
($\mu\text{g/kg}$) $\pm$ SD	7.0 ± 2.95		
Mean Total Duration			
N	16.6 $\pm$ 5.0	N/A	N/A
(hr) $\pm$ SD			
Phase III Study 246:			
Mean Total Dose			
N	203	N/A	N/A
($\mu\text{g/kg}$) $\pm$ SD	7.1 ± 2.81		
Mean Total Duration			
N	14.7 $\pm$ 4.51	N/A	N/A
(hr) $\pm$ SD			

N.B. The total N for all patient/subject listings in this table does not equal the total N for the safety database. The total N here falls between the total N for patients exposed and the total N for patients in the database (those with adequate and available data), based on availability of dose and duration information from the different study sites.

During her review of the safety data, Dr. Hartwell requested more specific information on exposure by dose and duration from the sponsor. Dose by duration exposure data for all treated patients in the Phase II/III continuous infusion studies is summarized in Dr. Hartwell's Table 1 from page 2 of her second addendum:

From Sponsor's Table of Duration by Dose, Supplement to NDA, 10-27-99, Exhibit 4
N.B. The total N corresponds to the total number of patients with available total duration data as in my Table 9, above. However, there was a discrepancy in the total N between the sponsor's ISS Supplement (submitted August 16, 1999), Appendix C, Table 2.1.2, p. 68 and Supplemental Information submitted on October 27, 1999 (p. 7). This discrepancy of 2 patients appears to be a simple error in addition.

Dose by duration exposure data for all treated patients in the Phase I continuous infusion studies is summarized in Dr. Hartwell's Table 1 from page 1 of her second addendum:

**Table 11. Extent of Exposure – Frequency of Duration by Dose
Phase I Continuous Infusion Studies – All-Treated Patients**

N.B. The total N corresponds to the total number of patients with available total duration data as in my Table 9, above.

Amongst the 3083 dexmedetomidine treated patients, there were 12 deaths in the Abbott sponsored clinical studies and 1 death in unpublished reported to the

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original NDA [total deaths equals 16 with the additional deaths reported during the review period; see below]. In all of the studies combined, there were 8 deaths in the placebo groups (N = 1495) and none in the comparator groups (N = 407) reported to the original NDA.

Dr. Cortinovis has summarized the 12 Abbott deaths in his review and Dr. Hartwell has summarized _____ in her addendum. While there were no deaths that could clearly be attributed directly to dexmedetomidine, a few of the cases raise concerns regarding intraoperative or postoperative cardiovascular events which may have, ultimately, contributed to the patients' deaths.

Patient 1115, Study 95-002, was an elderly male who underwent a low anterior colon resection. The patient experienced intermittent hypotension and the dexmedetomidine infusion was discontinued after only two hours. The patient experienced a cardiac arrest two days later. An autopsy did document severe atherosclerotic cardiac disease. Dr. Cortinovis assessed this case as unrelated to study drug. However, if the episodic hypotension was exacerbated by the dexmedetomidine infusion, it is possible that significant damage was done to the myocardium, allowing an already diseased organ system to deteriorate and fail over the next two days.

Patient 0622, Study 95-004, was a 59 year old male who underwent coronary artery bypass surgery and developed acute renal failure postoperatively. Dr. Cortinovis determined this case to be unrelated to study drug. The exact postoperative course leading to death is not clear, but the renal failure could certainly have been directly or indirectly related to dexmedetomidine, a drug with an established adverse event profile that includes hypotension. However, it is important to note that the patient's preoperative medical problems included hypertension, hypercholesterolemia, paroxysmal atrial fibrillation, and chronic renal insufficiency.

Patient 10202, Study W97-246, was a 74 year old male who underwent coronary artery bypass surgery and developed hypotension postoperatively, soon after the dexmedetomidine infusion was started. Episodes of hypotension continued and the study drug was discontinued 9 hours after initiation. The patient then developed renal insufficiency, but was reportedly stable over the next 3 days. He then suffered an acute myocardial infarction and died. Dr. Cortinovis assessed the relationship of study drug to this patient's death to be "doubtful." Again, the postoperative hypotension may have been a complication of, or have been complicated by, the dexmedetomidine infusion. Over time, this may have resulted in a deterioration in cardiac function and contributed to the patient's terminal events.

Patient 109, Study 97-249, was 47 year old who underwent coronary bypass surgery. Approximately 14 hours following initiation of the dexmedetomidine infusion, the patient developed circulatory collapse, hypotension and an acute myocardial infarction. The infusion was discontinued and the patient returned to the operating room for repair of an incomplete coronary revascularization. The patient died of multiorgan failure following that procedure. Dr. Cortinovis determined that the proximate cause of death is not clear, but "...is of the opinion that the cause of death was the direct result of the surgical repair." [page 63 of his review] As with the above cases, this patient's postoperative cardiovascular collapse may have been directly or indirectly related to the dexmedetomidine infusion.

Patient 211, Study 3005006, was a 73 year old male who underwent coronary artery bypass surgery and received infusions of dexmedetomidine both intraoperatively and postoperatively. His postoperative course was complicated by hyperglycemia, acidosis, hemodynamic instability, and decreased urine output. Following extubation he became agitated and confused, requiring sedation and supplemental oxygen to maintain his saturation. Three days after surgery the patient's intravenous line became disconnected and he died of massive blood loss. The investigators concluded that the death was not due to study drug. Dr. Hartwell states that "...if dexmedetomidine was a contributor or initiator of the patient's confusional state and if the patient's ongoing confusion and agitation was the cause of an inadvertent intravenous disconnection, the study agent must be secondarily implicated in this patient's death. From the data provided, it is not possible to completely discount dexmedetomidine as a factor in the initial agitation/confusion episode." [page 9 of her addendum] As Dr. Hartwell notes, the patient's change in mental status may have been due to multiple factors. Certainly, the documented hemodynamic instability and decreased urine output may both have been the result of dexmedetomidine induced hypotension and hypoperfusion, and have resulted in hypoxic-ischemic encephalopathy.

At Dr. Hartwell's request, the sponsor provided information on two additional deaths reported with minimal information in the 120-Day Safety Update from ongoing, blinded Phase II studies.

Patient 104, Study W98-263, was a 79 year old female with multiple medical problems was treated with a continuous infusion of dexmedetomidine in the ICU following myocardial infarction and cardiac arrest and resuscitation. During treatment she experienced recurrent hypotension and bradycardia. All treatments were discontinued after 18 hours and the patient died of multiorgan failure. Dr. Hartwell's conclusion

that the sponsor cannot rule out that study drug contributed to the patient's demise is appropriate.

Patient 101, Study W98-264, was a 58 year old male with multiple medical problems treated with a continuous infusion of dexmedetomidine in the ICU. The patient experienced two episodes of transient hypotension which responded readily to reduction in the dexmedetomidine infusion rate. The patient received dexmedetomidine for a total of 50 hours, at which time all supportive care was withdrawn. The patient died of multiorgan failure soon after. Once again, Dr. Hartwell's conclusion that the sponsor cannot rule out that study drug contributed to the patient's demise is appropriate.

Dr. Hartwell next compared data on deaths submitted to the sponsor's IND for dexmedetomidine, [Annual Report dated 3-24-99] and that submitted to the original NDA and the Safety Update. Nine deaths not reported to the NDA or Safety Update were documented in the Annual Report. One death occurred in a patient exposed to dexmedetomidine, 3 in placebo treated patients, and five in patients without documentation of treatment group. Clarification of this data was requested of the sponsor in September 1999 and received on October 1, 1999. In that communication, the sponsor explains that serious adverse events [SAE's], presumably incorporating deaths, occurring greater than 24 hours after discontinuation of treatment were included in a special company database, but not necessarily in the NDA database.

Clarification of the discrepancies was requested of the sponsor. On pages 6 and 7 of her second addendum, Dr. Hartwell summarizes the information received from the sponsor. Only 1 of the patients in this group of deaths was exposed to dexmedetomidine.

Patient 11601, Study 97-246, was a 73 year old male who underwent pneumonectomy for lung cancer. He received a continuous infusion of dexmedetomidine for 7 hours at constantly decreasing doses. His course was complicated by severe hypotension requiring treatment with dopamine, followed by cardiac arrest from which the patient was resuscitated. He died five days later. The investigator attributed the death to "poor cardiac function - myocardial hypersensitivity to dopamine", and determined it to be "unrelated" to study drug. As per Dr. Hartwell's discussion, it remains possible that dexmedetomidine exposure contributed to the patient's death.

Discontinuations:

Dr. Cortinovis has summarized the narratives of all 41 patients who discontinued due to adverse events in his review. No clearcut trends or conclusions may be drawn from those summaries.

My review of the sponsor's Table 2.1.5.11, "Summary of Discontinuation Due to Adverse Events; All Treated Patients in Phase II/III Continuous Infusion Studies", pages 166-168, Volume 1.302, revealed no events resulting in patient discontinuation that occurred with a frequency greater than 1%. In particular, circulatory failure, hypotension, cardiac arrhythmias, myocardial infarction and hypoxia each occurred in less than 1% of both dexmedetomidine treated and placebo patients. My review of the sponsor's Table 2.2.5.11, "Summary of Discontinuation Due to Adverse Events; All Treated Patients in Phase II/III Continuous Infusion ICU Sedation Studies", pages 275-277, Volume 1.303, revealed similar findings.

In the 120-Day Safety Update, the sponsor reported on 1 treated subject who discontinued due to an adverse event. That subject suffered a seizure after receiving study drug and discussed below under Serious Adverse Events.

It is worth noting here that there are discrepancies in the numbers of patients listed as discontinuations in the sponsor's initial ISS documents and the follow-up documents. There are also discrepancies internally within the original ISS. However, with all available data regarding this patient subset having been reviewed by either Dr. Cortinovis, Dr. Hartwell, or myself, there is no evidence that the adverse event profile was unusual or unexpected. Thus, it is unlikely that a full accounting of discontinued patients would provide new information that would significantly affect our decision regarding approvability.

Serious Adverse Events:

Dr. Cortinovis' review of SAE's consisted of copies of modified sponsor's tables which summarized the incidence of all SAE's in all clinical trials. Therefore, I requested that Dr. Hartwell undertake a more thorough analysis of this data.

In her first addendum, Dr. Hartwell reports that 5 subjects in the Phase I trials experienced SAE's. The events that Dr. Hartwell concludes are possibly related to study drug exposure are sinus arrest (2), bradycardia, hypotension, convulsions, and allergic reaction after transdermal application.

In the Phase II/III trials, Dr. Hartwell reports that 9% of patients in the Abbott sponsored continuous infusion studies and 11% of patients in the non-Abbott sponsored continuous infusion studies experienced SAE's. The overall incidence was similar to the randomized placebo population for these studies (9% and 10%, respectively). In the Abbott continuous infusion studies, the only SAE's occurring more frequently in the dexmedetomidine treated patients compared to the placebo treated patients were: hypotension (4% vs. 2%), hypertension (2% vs. 1%), and bradycardia (2% vs. 0%). All other SAE's occurred in less than 1% of dexmedetomidine treated patients. Similar data is unavailable for the non-Abbott studies.

As summarized in Dr. Hartwell's Table 3, page 4 of her second addendum, the incidences of the treatment emergent SAE's myocardial infarction and cardiac arrest were less than 1% in both the dexmedetomidine treated and placebo treated patients. In her Table 4 on page 4 of the addendum, Dr. Hartwell summarizes the treatment emergent respiratory adverse events in the Phase II/III continuous infusion studies. The incidences of all events were similar between the dexmedetomidine and the placebo treated patients.

In her first addendum, Dr. Hartwell summarizes the SAE's reported to the 120-Day Safety Update. Most of these events appeared to be unrelated to study drug exposure. Three patients [two of whom have already been discussed in the section of Deaths] experienced hemodynamic instability which might have been directly or indirectly related to dexmedetomidine exposure. One subject in a Phase I study experienced a single seizure after receiving an infusion of 1.25 ng/mL dexmedetomidine for approximately 18.5 hours. Although he had no history of seizure disorder, he did have a history of head trauma. Nevertheless, the dexmedetomidine may have directly or indirectly contributed to this event. Dr. Hartwell concludes that the overall incidence of SAE's in the 120-Day Safety Update is consistent with what has been reported in the original and in the supplementary NDA submissions.

Once again, as with the reporting of Deaths, the sponsor explained that SAE's reportedly occurring greater than 24 hours after discontinuation of treatment were included in a special company database, but not necessarily in the NDA database. Consequently, as Dr. Hartwell notes on page 5 of the second addendum: "...inaccuracies in both the identification of serious adverse events and the total number of events reported for each study are a possibility."

Other Adverse Events:

Dr. Cortinovis' Table 42, page 99 of his review [reproduced below], summarizes the incidence and dose association of the most common adverse events seen in the Phase I continuous infusion studies. Dry mouth and somnolence were extremely common in some target concentration groups (up to 73% and 85%, respectively), with some non-dose relatedness possibly explained by incomplete reporting.

Table 12. Most Common* Treatment Emergent Adverse Events By Target Dexmedetomidine Plasma Concentration: All Dexmedetomidine Treated Subjects Phase I Continuous Infusion Studies

Adverse Event ^b	Target Dexmedetomidine Plasma Concentration (ng/mL)					
	0.1-0.2 (N=25)	0.3 (N=59)	0.4-0.5 (N=34)	0.6 (N=61)	1.25 (N=12)	Increasing Dex Conc (N=22)
Subjects with at least one treatment-emergent adverse event	24(96%)	39(66%)	27(79%)	39(64%)	12(100%)	10(45%)
Mouth dry	5(20%)	16(27%)	9(26%)	12(20%)	9(75%)	1(5%)
Somnolence	17(68%)	10(17%)	20(59%)	8(13%)	10(83%)	0
Headache	2(8%)	15 (25%)	5(15%)	11(18%)	4(33%)	2 (9%)
Hypotension	14(56%)	9(15%)	16(47%)	9(15%)	0	1(5%)
Nausea	1(4%)	9(15%)	2(6%)	2(3%)	0	5 (23%)
Hypoxia	0	1(2%)	0	1(2%)	0	0
Dizziness	3 (12%)	3 (5%)	1(3%)	1(2%)	1(8%)	2(9%)
Bradycardia	1(4%)	4(7%)	0	3 (5%)	1(8%)	4(18%)
Muscle contractions involuntary	0	3 (5%)	1(3%)	5 (8%)	0	2(9%)
Palto	0	8(14%)	0	5(8%)	0	0
Apnea	0	4(7%)	0	4(7%)	0	0
Stupor	1(4%)	3 (5%)	2(6%)	1(2%)	1(8%)	1(5%)
Hyperkinesia	0	3 (5%)	1(3%)	5 (8%)	0	0
Pain	0	4(7%)	1(3%)	2(3%)	0	1(5%)
Pharyngitis	1(4%)	4(7%)	1(3%)	4(7%)	0	0
Paresthesia	0	0	0	4(7%)	1(8%)	0
Xerophthalmia	1(4%)	5 (8%)	3 (9%)	0	0	0
Fatigue	0	3 (5%)	0	3 (5%)	1(8%)	0
Hallucination	0	0	0	3 (5%)	4 (33%)	0
Vomiting	0	5(8%)	0	0	0	0
Agitation	2(8%)	0	4(12%)	0	0	1(5%)
Pruritus	1(4%)	4(7%)	1(3%)	1(2%)	0	0
Rhinitis	1(4%)	2 (3%)	1(3%)	0	1(8%)	0
Back pain	1(4%)	2 (3%)	0	0	1(8%)	1(5%)
Vision abnormal	0	4(7%)	0	2 (3%)	0	0
Abdominal pain	0	1(2%)	2(6%)	1(2%)	0	1(5%)
Conjunctivitis	0	0	0	1(2%)	3 (25%)	1(5%)

Sponsor's Table 43, ISS Vol. 8/10-238-135

a: Experienced by ≥22% of all dexmedetomidine-treated subjects in the Phase I studies.

b: Subjects may have been counted in more than one column if they received treatment in more than one treatment period, but a subject was counted only once in a given column.

Dex = Dexmedetomidine Concs = concentrations

The most common adverse events occurring in the Phase II/III continuous infusion studies are summarized in Dr. Cortinovis' Table 43 [page 100 of his review], reproduced below:

Table 13. Most Common* Treatment Emergent Adverse Events by Total Dose of Dexmedetomidine: All Treated Patients in Phase II/III Continuous Infusion Studies

Adverse Event	Total Dexmedetomidine Dose (mcg/kg)					
	0-1 (N=88)	>1-3 (N=455)	>3-5 (N=300)	>5-7 (N=226)	>7-10 (N=173)	>10 (N=92)
Patients with at least one treatment-emergent adverse event	66(75%)	255 (56%)	183 (61%)	147(65%)	104(60%)	56(61%)
Hypotension	29(33%)	145(32%)	92(31%)	65(29%)	36(21%)	25 (27%)
Hypertension	5(6%)	47(10%)	39(13%)	45(20%)	28(16%)	12(13%)
Nausea	24(27%)	53 (12%)	38(13%)	28(12%)	14(8%)	5 (5%)
Bradycardia	8(9%)	28(6%)	21(7%)	12(5%)	15(9%)	10(11%)
Tachycardia	4(5%)	25 (5%)	12(4%)	14(6%)	4(2%)	5 (5%)
Fever	3 (3%)	20(4%)	13(5%)	9(4%)	10(6%)	4(4%)
Hypoxia	19(22%)	14(3%)	9(3%)	8(4%)	4(2%)	4(4%)
Anemia	1 (1%)	15(3%)	17(6%)	14(6%)	4(2%)	1 (1%)
Vomiting	2(2%)	14(3%)	12(4%)	11(5%)	6(3%)	3 (3%)
Hemorrhage NOS	2(2%)	13 (3%)	9(3%)	4(2%)	5 (3%)	3 (3%)
Pain	5 (6%)	10(2%)	7(2%)	7(3%)	4(2%)	1 (1%)
Rigors	0	13 (3%)	8(3%)	5(2%)	4(2%)	3 (3%)
Atrial fibrillation	0	10(2%)	9(3%)	6(3%)	6(3%)	2(2%)
Mouth dry	0	3 (<1%)	4(1%)	6(3%)	11(6%)	6(7%)
Agitation	1 (1%)	9(2%)	9(3%)	3 (1%)	4(2%)	4(4%)

Sponsor's Table 44 ISS Vol. 8/10-239-137

NOS = not otherwise specified

*: Experienced by $\geq 2\%$ of all Dexmedetomidine treated patients in Phase II/III continuous infusion studies

No apparent dose relationship can be seen for these adverse events, except for dry mouth. The high incidence of hypoxia in the 0-1 $\mu\text{g/kg}$ group is attributable to a single study [dexmedetomidine-96-012] in which hypoxia was reported by $\geq 75\%$ of patients in all treatment groups, including the placebo group.

A comparison of the adverse events occurring in the Phase II/III continuous infusion studies between the dexmedetomidine treated and placebo treated patients can be seen in the table below:

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Table 14. Events Experienced by $\geq 2\%$ of All Dexmedetomidine Treated Patients in Phase II/III Continuous Infusion ICU Sedation Studies

Adverse Event	Randomized Dexmedetomidine		
	Dexmedetomidine Only (N = 158)	Dexmedetomidine and Midazolam (N = 104)	Dexmedetomidine and Propofol (N = 125)
Patients with at least one treatment-emergent adverse event:	100 (63%)	79 (76%)	80 (64%)
Hypotension	47 (30%)	25 (24%)	36 (29%)
Hypertension	23 (15%)	25 (24%)	15 (12%)
Nausea	11 (7%)	15 (14%)	16 (13%)
Bradycardia	8 (5%)	5 (5%)	14 (11%)
Dry Mouth	4 (3%)	3 (3%)	6 (5%)
Fever	1 (<1%)	11 (11%)	6 (5%)
Vomiting	5 (3%)	3 (3%)	8 (6%)
Atrial Fibrillation	11 (7%)	5 (5%)	0
Hypoxia	6 (4%)	5 (5%)	5 (4%)
Anemia	4 (3%)	4 (4%)	3 (2%)
Pain	6 (4%)	1 (<1%)	2 (2%)
Tachycardia	2 (1%)	6 (6%)	4 (3%)
Hemorrhage	5 (3%)	5 (5%)	2 (2%)
Pleural Effusion	1 (<1%)	5 (5%)	2 (2%)
Hypovolemia	0	3 (3%)	2 (2%)
Thirst	3 (2%)	2 (2%)	3 (2%)
Rigors	2 (1%)	5 (5%)	1 (<1%)
Hyperpyrexia	3 (2%)	3 (3%)	1 (<1%)
Agitation	1 (<1%)	5 (5%)	2 (2%)
Somnolence	4 (3%)	0	0
Atelectasis	3 (2%)	1 (<1%)	1 (<1%)
Oliguria	2 (1%)	4 (4%)	0
Adverse Event	Placebo		
	Placebo Only (N = 71)	Placebo and Midazolam (N = 150)	Placebo and Propofol (N = 158)
Patients with at least one treatment-emergent adverse event:	46 (65%)	104 (69%)	88 (56%)
Hypotension	10 (14%)	24 (16%)	14 (9%)
Hypertension	6 (8%)	23 (15%)	39 (25%)
Nausea	6 (8%)	12 (8%)	18 (11%)
Bradycardia	4 (6%)	4 (3%)	2 (1%)
Dry Mouth	1 (1%)	2 (1%)	1 (<1%)
Fever	2 (3%)	9 (6%)	6 (4%)
Vomiting	3 (4%)	9 (6%)	9 (6%)
Atrial Fibrillation	2 (3%)	7 (5%)	4 (3%)
Hypoxia	3 (4%)	8 (5%)	3 (2%)
Anemia	0	7 (5%)	2 (1%)
Pain	1 (1%)	5 (3%)	1 (<1%)
Tachycardia	1 (1%)	11 (7%)	6 (4%)
Hemorrhage	2 (3%)	9 (6%)	6 (4%)
Pleural Effusion	1 (1%)	0	3 (2%)
Hypovolemia	2 (3%)	5 (3%)	3 (2%)
Thirst	0	1 (<1%)	0
Rigors	1 (1%)	4 (3%)	8 (5%)
Hyperpyrexia	2 (3%)	6 (4%)	2 (1%)
Agitation	2 (3%)	5 (3%)	4 (3%)
Somnolence	2 (3%)	2 (1%)	2 (1%)
Atelectasis	4 (6%)	2 (1%)	7 (4%)
Oliguria	0	2 (1%)	1 (<1%)

Modified sponsor's Table 48, ISS Vol. 9/10-239-143

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As noted by Dr. Cortinovis on page 102 of his review, there was an increased incidence of both hypotension and hypertension in the dexmedetomidine treated patients compared to any of the placebo groups. Patients in the dexmedetomidine/propofol group had a higher incidence of bradycardia compared with patients in the other groups. The sponsor has speculated that dexmedetomidine may exacerbate the bradycardia known to occur with propofol.

Dr. Cortinovis includes in his review discussion of the adverse event profile for different age categories, by gender, by disease (specifically renal and hepatic impairment), and by type of surgical procedure that the patient underwent. The only clinically significant result of these analyses is the finding of an increased incidence of hypertension, fever, tachycardia, rigors, agitation and atelectasis in patients who underwent head and neck surgery compared to patients who underwent cardiac surgery, laparotomy, or "other" surgery [see Dr. Cortinovis' Table 47, page 106 of his review]. This occurred in both the dexmedetomidine treated and the placebo treated patients, though with a slightly lower incidence in the latter group. This finding may be explained by the fact that many of the patients undergoing head and neck surgery would have been cancer victims with compromised immune systems and a resultant increased incidence of infection. In fact, when reviewed by Dr. Hartwell, 100% of the patients in W97-246 underwent surgery for cancer related complications.

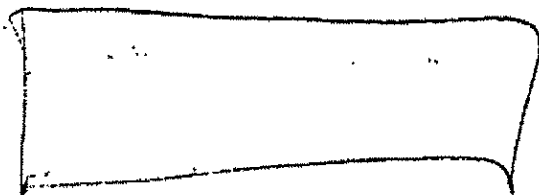
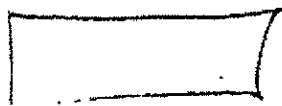
Laboratory Values:

Although statistically significant differences were noted between the dexmedetomidine treated and placebo treated patients in the mean change from baseline for hematocrit, hemoglobin, red blood cells, and serum glucose level, these changes were not clinically significant. Dr. Cortinovis' Table 41, page 95 of his review, summarizes the laboratory data and these specific findings.

Vital Signs:

The vital sign data presented in the ISS was from the Phase II/III ICU sedation studies only (N = 576). This was explained to be due to failure of a novel monitoring system used in the other studies to provide accurate data.

Although there was a statistically significantly greater degree of hypotension in the dexmedetomidine treated patients compared to the placebo patients, this difference was not clinically significant. Bradycardia also occurred significantly more frequently in the dexmedetomidine group. The mean heart rate appeared to be approximately 10 bpm slower for those patients compared to the placebo patients, though still within a clinically acceptable range. Small, statistically, but not clinically significant differences in central venous pressure were found between the groups; with the dexmedetomidine group having the lower values.

CHEMISTRY, MANUFACTURING AND CONTROLS:**PHARMACOLOGY AND TOXICOLOGY:**

Dr. Geyer found no animal toxicity that would raise concerns regarding the approvability of this product. However, long term continuous intravenous administration is only now being studied, at our request. After subcutaneous infusion of 10 $\mu\text{g/kg/hr}$ dexmedetomidine to dogs for one week, the cortisol response to ACTH stimulation was diminished by about 40%. In light of the clinical findings of adrenal suppression in patients treated with the related compound etomidate, further investigation during long term administration may be warranted.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS:

Dr. Doddapaneni notes that the pharmacokinetics of dexmedetomidine were affected by hepatic impairment. The mean clearance values for subjects with mild, moderate and severe hepatic impairment were 74%, 64% and 53%, respectively, of those observed in normal healthy subjects. Dosage adjustment for patients with hepatic impairment is recommended.

ABUSE LIABILITY:

Dr. Hayes has recommended that dexmedetomidine not be scheduled under the Controlled Substances Act as there is a lack of evidence to support such a regulatory action. However, if other dosage forms of dexmedetomidine are approved, the abuse liability of those new formulations would have to be reassessed.

Careful postmarketing surveillance for evidence of trafficking of the drug out of the hospital environment and for community abuse and dependence problems will be necessary for this sedative product.

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COMMENTS:

The sponsor has provided evidence of effectiveness from two adequate and well-controlled trials for dexmedetomidine when administered as a continuous intravenous infusion for postoperative sedation over a 24 hour period. On subgroup analysis, there was a suggestion that dexmedetomidine may be less effective in patient's undergoing head and neck surgery compared to other types of major surgery. Of interest, this same group of patients, all suffering from significant malignancies, appeared to have an adverse event profile suggestive of infection.

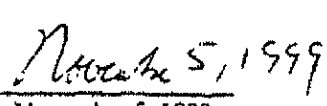
While there appears to be evidence of some analgesic effect from treatment with dexmedetomidine, the studies were not designed to assess whether this is intrinsic analgesic activity or potentiation of morphine induced analgesia. The measures used to assess the anxiolytic activity of dexmedetomidine were not adequate to determine whether a patient was anxious or not anxious, in light of the fact that patients can appear calm while experiencing dysphoria. Finally, the measures used to assess patient manageability have not been validated for this use. In addition, the so-called "Patient Management Index" was not prospectively defined and while the difference between the placebo and dexmedetomidine groups was statistically significant, these differences were not clinically significant.

The safety profile of this new molecular entity is as expected for an α -2-adrenoreceptor agonist with clinically significant hypotension and bradycardia being the most prominent adverse events. Concerns regarding the effect of long-term continuous infusion of dexmedetomidine on the adrenal-pituitary axis will require further investigation. There is currently no information on the use of this product in pediatric subjects or patients.

RECOMMENDATIONS:

I recommend that this application be approved with appropriate labeling. In addition, Phase IV commitments from the sponsor to perform studies to evaluate pediatric pharmacokinetics and clinical use, as well as preclinical and clinical safety evaluations of adrenal suppression, should be required. Prior to recommending administration of dexmedetomidine for greater than 24 hours, the sponsor should also undertake appropriate studies to assure persistent effectiveness and that there are no new safety concerns that arise when the drug is administered as a long-term continuous infusion.


Bob A. Rappaport, M.D.


November 5, 1999

Dexmedetomidine
NDA 21-038

Cc: Original NDA 21-038
HFD-170: Division File
HFD-170:

McCormick
Rappaport
Hartwell
Ma
Doddapaneni
Geyer
Theodorakis
Hayes
Samanta

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Drug Delivery

Issue Date: September 2012, Posted On: 9/5/2012

Trends in Pharmaceutical Primary Packaging for Injectables - Solutions for New Challenges

INTRODUCTION

With a share of approximately 27%, injectables were No. 2 in the \$860-billion dollar drug delivery market in 2010, preceded only by oral medication. Double-digit growth rates, mainly triggered by biotech-derived products, and the rise of injectable generics show that the importance of this segment is still on the rise. Still, prefilled glass syringes and vials are still the most common primary packaging containers for modern injectables.

However, end user requirements and even marketing related reasons have led to a growing market for innovative devices, such as safety syringes, pen systems, and needle-free or intradermal injectors.

Various glass container systems are traditionally used for the storage of parenterals. All of them are standardized to facilitate processing on automated filling lines (eg, ISO 11040-4 for prefilled syringes).

With the exception of ampoules, all glass containers have pharmaceutical rubber closures. The so-called container closure systems (c/c system) are designed to protect the drug product from qualitydiminishing environmental influences (eg, light, moisture, microbial contamination). However, the c/c system is not just a container. Throughout the product shelflife, it also has to ensure that functionality and drug delivery accuracy always comply with the specifications.

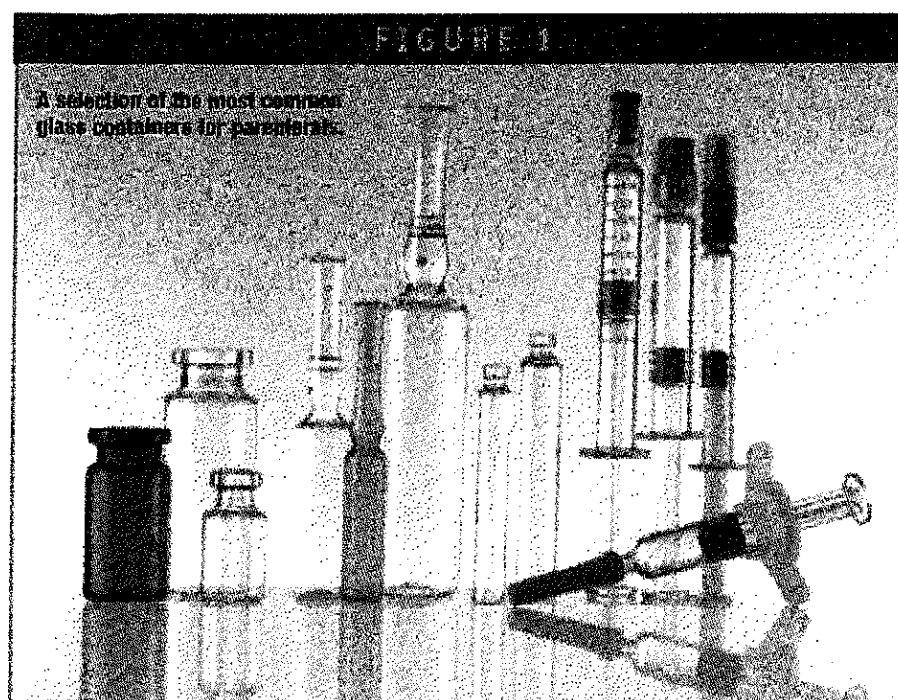
Available container closure systems/devices include vials, reconstitution kits, disposable or prefilled syringes, ampoules and autoinjectors or pen systems. Several factors have to be considered when choosing the right c/c system, such as drug product formulation properties, dosage, type of application, and end-user friendliness. Examples of drug product formulationrelated factors observed especially with prefilled syringes are high metal ion sensitivity and viscosity. A high sensitivity to metal ions may necessitate the use of new alternative primary packaging materials. In the case of highviscosity drug products, syringe features such as needle inner diameter, have to be considered.

Furthermore, the dosage regime can influence device decisions, driven by the type of application, frequency and volume, and fixed or variable dose. In connection with end-user friendliness factors, such as the place of application (clinic, home, or emergency setting), the length of therapy, the target patient group and the dexterity of the operator have to be considered. It may be necessary to develop different packaging solutions for one product to satisfy different patient group needs.

BIOGRAPHY



Claudia Petersen completed her education from 1990 to 1996 in Bioprocess Engineering at the Technical University of Berlin. Following 2 years post-graduate work in the field of Oncology Research, she joined in 1998 Life Sciences Meissner & Wurst working finally as a Lead Validation Engineer mainly on projects for biopharma customers. From 2000 to 2007, she held different positions at West Pharmaceutical Services, including European Technical Support and Marketing finally as Senior Manager Biotechnology. Since 2007, she has been working as Director, Business Development for the Tubular Glass Division at Gerresheimer Bünde. Ms. Petersen is a member of several pharmaceutical organizations, including the PDA and APV. She is a frequent speaker at international congresses and



seminars related to primary packaging and drug delivery devices for injectable drug products.

TREND 1: OUTSOURCING OF CLOSURE PRODUCTION STEPS

A dominant trend in primary packaging is the evolution from simple bulk packaging materials toward ready-to-sterilize (RTS) or even ready-to-use (RTU) primary packaging components and systems. Process steps in the pharmaceutical production process, such as washing, siliconization, and sterilization of container system components, are outsourced to suppliers that have to ensure these processes are qualified and validated in accordance with current global regulatory requirements. When pharmaceutical manufacturers opt for ready-to-sterilize products, they have a significantly lower investment in machinery and qualification/validation. Because the requirement of washing and siliconizing equipment is eliminated, and products are supplied with a certified endotoxin, bioburden, and particle load. For rubber components and prefillable syringe systems, this also includes the necessary siliconization process.

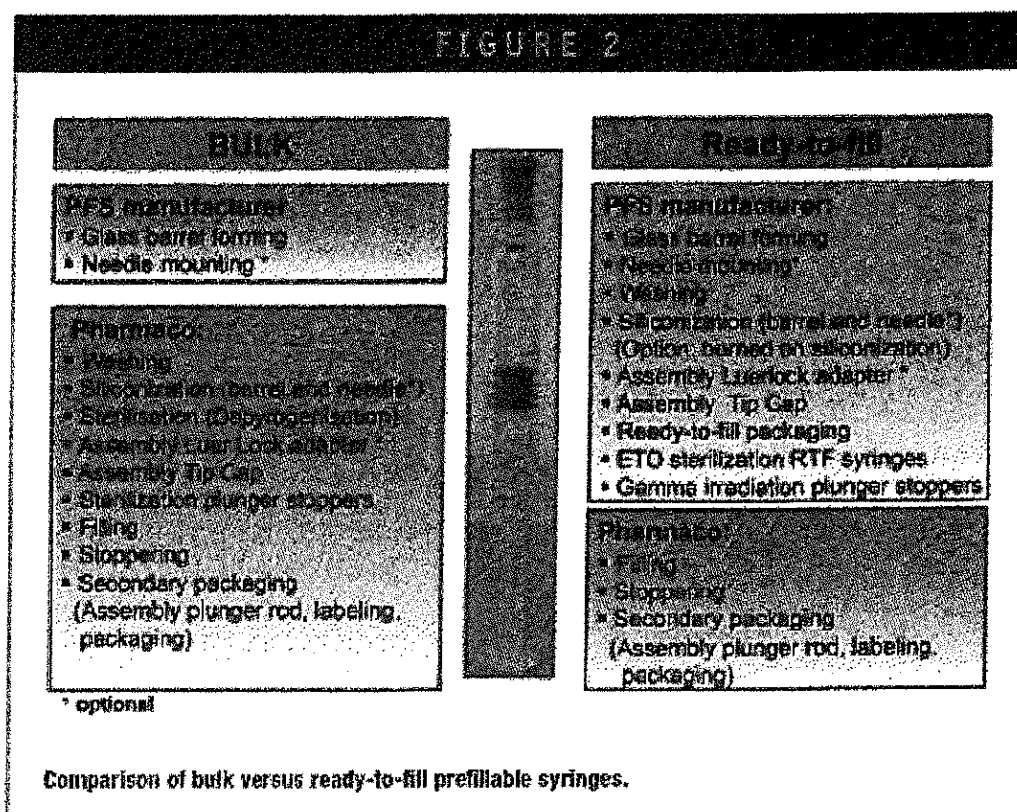
RTU quality is the next logical step. Pharmaceutical manufacturers outsourcing RTU components can thereby also eliminate the need to invest in sterilization equipment and the regular revalidation of this process. The sterility and shelf-life of the products are certified by the primary packaging supplier. While prefillable syringe systems are always ETO-sterilized, plunger stoppers undergo mainly gamma irradiation. A validated gamma sterilization process has to provide a minimum sterility assurance of 10. Dose mapping and setting have to conform to ISO 111337-2. In general, a package transport simulation and integrity validation should be performed on the sterilized goods, and an expiration date has to be stated (Figure 2).

RTF syringe systems, including sterile plunger stoppers, have already been available for many years. In recent years, pharmaceutical rubber suppliers have recognized this trend and now offer a broad range of RTU (either gamma or steam-sterilized) rubber components on their own. Glass suppliers have now begun working on RTU glass vials. Also in recent years, customer interest regarding RTU glass vials did increase. The first glass suppliers did address this developing RTU glass vial offerings.

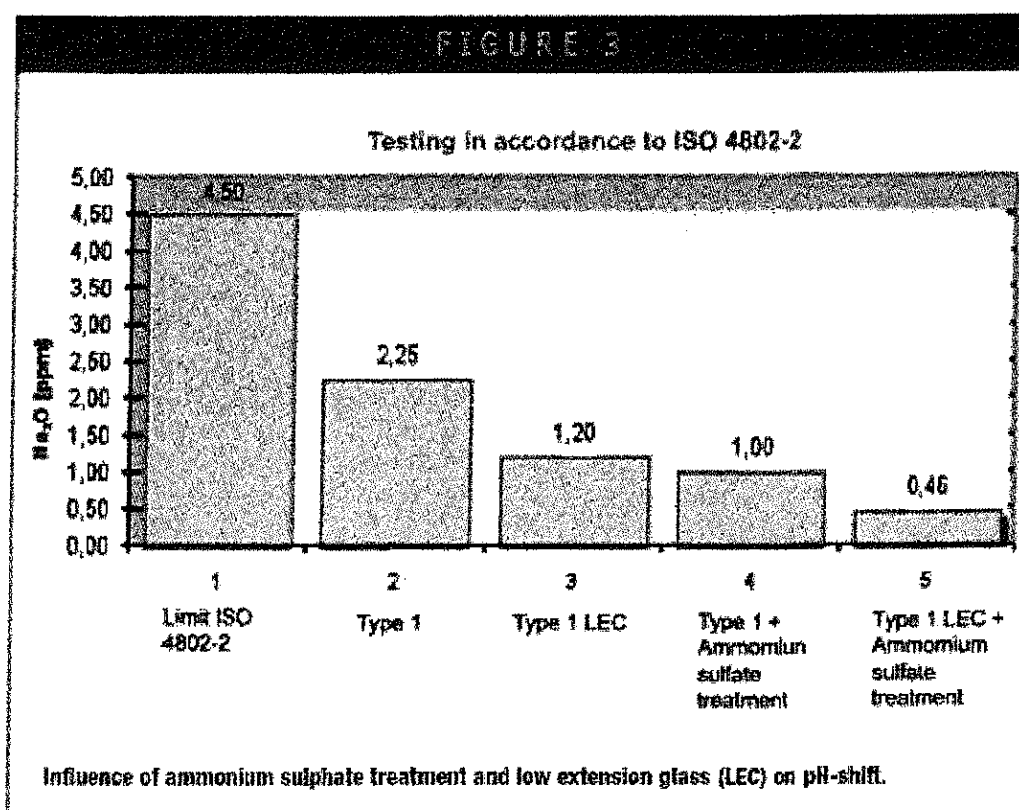
TREND 2: INCREASINGLY STRINGENT QUALITY REQUIREMENTS

Regulatory authorities all over the world are paying greater attention to the use of appropriate primary packaging materials with the consequence that standards have become very comprehensive and detailed. In 1997, the European pharmacopeia included 19 pages on primary packaging materials. Eight years later, the number of pages had nearly

tripled to 53. Within the same time frame, regulatory authorities around the globe issued new guidelines dedicated to primary packaging materials, such as the Container Closure Guideline published by the FDA in 1999 and the EMA Guideline on Plastic Immediate Packaging Materials dated 2005.^{1,2} Another example is the DIN ISO standard 15378 "Primary packaging materials for medicinal products – Particular requirements for the application of ISO 9001:2000, with reference to Good Manufacturing Practice (GMP)" dated 2006. The primary packaging industry has coped with these increasingly tough regulatory requirements by enlarging quality departments, installing dedicated regulatory affairs functions and intensifying technical support. ISO 15378-compliant production is nowadays standard practice in the European and US primary packaging industry.



Quality requirements for glass containers, which are likely to be tightened up, include specifications regarding the particle load, lower rates of cracks or cosmetic defects, and smaller dimensional tolerances. Prefillable syringes are associated with specific requirements, such as low hold-up volumes and reduced tungsten or siliconization levels. The tungsten oxide contamination resulting from the forming process of the bore inside the syringe cone can, for example, be avoided using pins made from other metals in the forming process. No official tungsten limit exists as yet. An upper limit of 500 ppb is under discussion. Superior quality requirements on the cosmetic and dimensional side can be met by improved manufacturing processes, the introduction of comprehensive process control with camera systems, and packaging inside clean rooms. Automated visual inspections to check for dimensional and cosmetic defects allow constant sorting performance with high reliability and output. Inevitable negative side effects are the cost of the equipment and a proper sorting process qualification to avoid an excessive scrap rate due to false rejects. Rubber component suppliers have developed similar visual inspection procedures.



TREND 3: GROWING SYSTEM COMPLEXITY

Relentless progress in medical technology, the cost pressure of increasingly expensive healthcare systems, and the necessity to operate profitably in a globalized economy all contribute to the complexity of decisions in the primary packaging market. Medical factors that have to be taken into consideration are demands for simpler and safer administration and increased dosage accuracy. Economic factors include the total cost of a system and the retail price of drugs. It is also necessary to consider that developed nations face an aging population that will double the percentage of people aged 60 and older by 2050. Other factors are demands for optimized production processes or enhanced product value, specific regulatory frameworks, or a company's IP position. Currently, four major drug delivery market trends can be observed, which in some respects are controversial:

- More standardized, simpler, and more robust packaging solutions to address the increasing cost pressure.
- Modern drug delivery systems as a means of differentiation from competitors.
- Modern drug delivery systems as a reflection of modern lifestyle.
- New regulatory and legislative requirements, such as dose counting for metered dry powder inhalers and needle stick legislation to be considered during device development.

In this complex situation, the requirements of the drug product, syringe/container, and device are all interlinked, which necessitates the close collaboration of all project participants. Pharmaceutical and primary packaging/drug delivery device manufacturers should share their expertise to specify system requirements and achieve a common understanding.

TREND 4: NEW MATERIALS

There are a number of reasons why packaging and device suppliers should develop enhanced primary packaging solutions or even use new materials. New, complex devices may require primary packaging that cannot be made from glass due to the limitations of its technical and material properties. As mentioned previously, modern biopharmaceuticals that are mostly based on large proteins are more likely to interact with traditional c/c system components. Also, biopharmaceuticals are often quite expensive, so low overfills and excellent container drainability are essential.

Primary packaging manufacturers are responding to these challenges with new or modified materials. For example, elastomeric components, such as plunger or injection stoppers can be coated with fluoropolymers. The FluroTec® system manufactured by West/Daikyo is partially coated, while Omniflex® by Daetwyler has a completely coated closure surface. Acting as a barrier, the coating improves compatibility with drugs and minimizes extractables/leachables. This eliminates or significantly reduces the need for additional siliconization of plunger stoppers for lubrication purposes while maintaining the functionality of the syringe system.

In cases where the technical limitations of glass prevent its use, modern plastics, such as cyclic olefins, can be a solution. They offer far greater design flexibility, facilitate tighter dimensional tolerances, and are more breakresistant than glass.

Surface treatments, such as ammonium sulfate treatment, can be applied to glass containers to minimize sodium ion leaching and a subsequent pH shift. The use of low alkali glass, called low extension glass, has the same effect (Figure 3).

Another approach is based on thin film technology. Pure silica (SiO₂) coatings are applied to the inner surfaces of glass containers. The silica layer acts as a diffusion barrier, preventing interaction of the glass matrix with the drug without impairing compatibility with standard filling lines and sterilizing procedures.

In the past, the high cost and complexity of meeting regulatory requirements discouraged manufacturers from considering other materials than the well-established combination of borosilicate glass and pharmaceutical elastomers. Now that new types of drugs with unique properties are entering the market, innovative materials are being scrutinized more closely. The polymers of choice are cyclic olefin polymers/copolymers (COP/COC), which have some properties comparable to those of glass. Both materials are transparent, durable, and solvent-resistant. Cyclic olefins also have some properties, which are superior to glass, such as higher break-resistance, broader pH range tolerance, and no leakage of metal ions. One particularly important feature relating to the storage of biotechnological drugs is the excellent drainability of cyclic olefin containers, which limits the need for excess overfill. However, cyclic olefins also have some downsides. Compared to glass, they are more susceptible to scratching and, with few exceptions, compendia standardization does not exist. Another parameter to consider during primary packaging material selection is the gas and water vapor permeability of cyclic olefins. Compared to other plastics, such as polyethylene or polypropylene, they have much lower permeation values, though glass is gas impermeable.

Prefillable plastic syringes, such as ClearJect™ by Taisei Kako Co. Ltd, are manufactured in "lights out" factories. Specifically, the entire production process, providing highest injection molding accuracy, is fully automated and takes place inside clean rooms. Camera inspection systems are used for 100% quality control of dimensions, cosmetic defects, and other product parameters, such as the siliconization. These syringe systems are gamma-sterilized. They offer the advantage over glass prefillable syringe systems that the tip cap and plunger stopper are made of the same modern latexfree, chlorobutyl-based pharmaceutical elastomer.

OUTLOOK

Current trends indicate the future of pharmaceutical primary packaging will be characterized by continuous change. Although traditional disposable syringes with vials or ampoules will remain in use, the trend in biopharmaceuticals toward prefillable syringes, auto-injectors, and pen systems as well as customized delivery systems will continue. Primary packaging containers will be made from either glass or plastic. Alternative coatings to standard siliconization are being developed and will gain in importance.

For the primary packaging industry, this means an expanding market for more convenient and easier-to-use injectable products. This trend is closely related to rising demand for complex services that cover more stages in the supply chain. Primary packaging suppliers will assume an increasing number of production steps relating to closure preparation for the fill & finish process. As a result, they will evolve from component providers to system suppliers and product development project partners.

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1. Guideline on plastic immediate packaging materials of May 2005, CPMP/QWP/4359/03, EMEA/CVMP/205/04.
2. Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics of May 1999, U.S. Department of Health and Human Services Food and Drug Administration.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Roychowdhury *et al.* Customer No. : 62965
Appln. No. : 13/541,524 Confirmation No. : 8238
Filed : July 3, 2012 Art Unit : 1629
Examiner : Polansky, Gregg
For : DEXMEDETOMIDINE PREMIX FORMULATION

DECLARATION UNDER 37 C.F.R. §1.132

I, Huailiang Wu, Ph.D., hereby declare the following:

1. I am currently employed as a Group Leader, Global Pharma Research & Development, by HOSPIRA, INC., (hereafter "Hospira") having its principal place of business at 275 North Field Drive, Lake Forest, IL 60045. My curriculum vitae is attached as Exhibit A.
2. HOSPIRA, INC. is the sole Assignee of United States Patent Application Serial No. 13/541,524 (hereafter "the '524 application") pursuant to the Assignment recorded at Reel/Frame: 027480/0592 which was recorded with the United States Patent and Trademark Office (hereafter, "USPTO") on January 4, 2012.
3. I, along with other scientists employed by, and under the direction of, Hospira, designed and conducted assays relating to a ready to use liquid pharmaceutical composition for parenteral administration to a subject, comprising dexmedetomidine

or a pharmaceutically acceptable salt thereof at a concentration of about 0.005 to about 50 µg/mL disposed within a sealed glass container. Ready to use parenteral pharmaceutical compositions, such as the claimed dexmedetomidine composition, are manufactured to be sterile so that the compositions are safe to be administered to patients upon removal from their storage container. Sterility can be achieved, for example, by autoclaving the ready to use composition.

4. A first assay (Assay 1) measured the potency of various concentrations of a ready to use dexmedetomidine composition stored in Polyvinyl chloride (PVC) bags and glass vials over a three-day period following autoclave. A second assay (Assay 2) was conducted to measure the potency of various concentrations of a ready to use dexmedetomidine composition without autoclave following storage at ambient temperature over a 24 hour period.
5. As described in greater detail below, Exhibit B (describing the results of Assay 1) demonstrates an unexpected maintenance of potency of 1, 10, 15 and 50 µg/mL dexmedetomidine compositions following autoclave and storage over a three-day period in glass containers compared to storage in PVC plastic containers.
6. Exhibit C (describing the results of Assay 2) demonstrates an unexpected maintenance of potency of 1, 10, 15 and 50 µg/mL dexmedetomidine compositions when stored at ambient temperature over a 24-hour storage period without autoclave in glass containers compared to storage in PVC plastic containers.

7. For Assay 1, ready to use dexmedetomidine solutions were prepared at concentrations of 1 µg/mL, 10 µg/mL, 15 µg/mL and 50 µg/mL by dissolving dexmedetomidine and sodium chloride in water to achieve the target dexmedetomidine concentration and a 0.9% sodium chloride concentration. The solutions were then filtered through a 0.22 µm filter. A sample of the filtered solution was collected and used as the control. The filtered solution was then disposed into 100-mL PVC bags and 50-mL glass vials. The solutions from two PVC bags or two glass vials were tested for dexmedetomidine potency as the "preTS" (pre terminal sterilization) sample about 12 hours after the solutions were disposed into the PVC bags or glass vials. The remaining filled PVC bags and glass vials were autoclaved (terminal sterilization) about 12 hours after the solutions were disposed into the PVC bags or glass vials. The solutions from two PVC bags or two glass vials immediately after autoclave were tested for dexmedetomidine potency as the "T=0" samples. The autoclaved PVC bags and glass vials were stored in stability chambers under conditions of 25°C/60%RH (relative humidity) and 40°C/75%RH for up to two weeks. Samples from the PVC bags and glass vials were tested after storage times of 3 days, 1 week and 2 weeks (for PVC samples only). Testing to determine dexmedetomidine potency in the samples was conducted using HPLC.
8. As shown in Exhibit B, the potency of the 1 µg/mL dexmedetomidine formulation decreased by 1.82% about 12 hours after being disposed in a PVC storage bag

(preTS), and by 7.81% following autoclave (T=0) compared to control. After storage for three days in the PVC bag at 25°C and 40°C, the potency of the 1 µg/mL formulation decreased by 8.05% and 8.83%, respectively, compared to control. Similarly, the potency of the 10, 15 and 50 µg/mL formulations disposed in PVC bags decreased by 5.84%, 5.54% and 4.32% following autoclave, respectively, compared to control. After storage for three days in PVC bags at 25°C, the potency of the three concentrations decreased by 6.24%, 6.17% and 5.26%, respectively, compared to control. After storage for three days in PVC bags at 40°C, the potency of the three concentrations decreased by 6.28%, 6.62% and 5.36%, respectively, compared to control.

9. As described by Exhibit B, in contrast to storing the dexmedetomidine compositions in PVC bags, when the dexmedetomidine compositions were stored in glass vials, the potency of the dexmedetomidine was maintained. When stored in glass vials, none of the four concentrations of dexmedetomidine experienced any loss in potency after disposing the formulations in glass vials or after autoclave, compared to control. After storage for three days in glass vials at 25°C, the decrease in potency of the 1, 10, 15 and 50 µg/mL dexmedetomidine compositions were 0%, 0%, 0.39% and 0.44%, respectively, compared to control. After storage for three days in glass vials at 40°C, the decrease in potency of the 1, 10, 15 and 50 µg/mL dexmedetomidine compositions were 0.42%, 0%, 0.27% and 0.51%, respectively, compared to control.

10. As described by Exhibit B, storing a ready to use formulation of dexmedetomidine at concentrations recited by the claims of the '524 application in glass containers resulted in an unexpected reduction in potency loss of the composition compared to storage in plastic PVC containers. Storing the formulations in PVC containers resulted in a decrease in dexmedetomidine potency after disposition within the containers, after autoclave, and after a three-day storage period at 25°C or 40°C. The maximum detectable loss in potency of the samples stored in PVC containers after the three-day storage period was 8.83%, whereas the glass containers showed a maximum loss of only 0.51%.
11. For Assay 2, dexmedetomidine solutions were prepared as described for Assay 1 at concentrations of 1, 10, 15 and 50 µg/mL. A sample of the filtered solution was collected and used as the control. Prior to storage, the solutions from PVC bags and glass vials were tested for dexmedetomidine potency as the "T=0" sample. PVC bags and glass vials were stored at ambient temperature on a laboratory bench for 24 hours. Samples from the PVC bags and glass vials were tested after storage times of 12 hours and 24 hours. Testing to determine dexmedetomidine potency in the samples was conducted using HPLC.
12. As shown in Exhibit C, when stored in PVC bags, the potency of the 1, 10, 15 and 50 µg/mL dexmedetomidine compositions decreased by 1.48%, 1.22%, 1.06% and 1.78%, respectively, compared to control following the 24-hour storage period. In

contrast, when stored in glass vials, the potency of the 1, 10, 15 and 50 µg/mL dexmedetomidine compositions decreased by only 0%, 0.56%, 0.24% and 0%, respectively, compared to control following the 24-hour storage period.

13. As described above, and as shown in Exhibits B and C, storing a ready to use formulation of dexmedetomidine at concentrations recited by the claims of the '524 application in glass containers resulted in an unexpected reduction in potency loss of the composition compared to storage in plastic PVC containers. Specifically, storing the formulations in PVC containers resulted in a decrease in dexmedetomidine potency after disposition within the containers, after autoclave, and after a three-day storage period at 25°C or 40°C. The maximum detectable loss in potency of the samples stored in PVC containers after the three-day storage period was 8.83%, whereas the glass containers showed a maximum loss of only 0.51%. Similarly, when the dexmedetomidine formulations were stored in glass containers and PVC bags for 24 hours without autoclave, the dexmedetomidine stored in the glass vials maintained greater dexmedetomidine potency than the samples stored in PVC containers. Such a reduction in potency loss of a dexmedetomidine composition after autoclave and storage would not have been expected when stored in a glass container, and as such, is a surprising and unexpected result of practicing the claims of the '524 application.

14. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patent issuing therefrom.

By:  Date: 9/17/12
Huailiang Wu

Title: Group Leader, Global Pharma Research & Development, HOSPIRA, INC.

EXHIBIT A

Huailiang (Leon) Wu, Ph.D.

(224) 212-5262 (O); Email: huailiang.wu@hospira.com

PROFESSIONAL EXPERIENCE

2/11 – Present: Generic, Global Pharma R&D, Hospira, Lake Forest, IL

9/10 – 1/11: Project Manager I (contractor), Global Formulation Sciences, Abbott, Abbott Park, IL

- ✓ Investigation of root cause for unexpected bioperformance of a spray drying dispersion (SDD) tablet product
- ✓ Initiation and evaluation of feasibility of developing a pediatric oral suspension ER
- ✓ Improvement of a SDD tablet product's manufacturability and scale up

5/10 – 9/10: General Manager, Alpharmaca Inc., Shanghai, P.R. China

- ✓ Responsible for setting overall business strategy and managing daily operation for achieving company objectives
- ✓ Applied formulation expertise and innovation to pharmaceutical product design and development without infringing patents of innovators on branded products.
- ✓ Led and oversaw R&D activities with following specific objectives
 - Achieve bioequivalent version of branded products
 - Improve performance and patient compliance for extending lifecycle of branded pharmaceutical products
 - Collaborate with Big Pharma companies in China to co-develop products and to put them through SFDA approval process.

5/10 Principal Scientist and Group leader

10/06 – 5/10: Senior Research Scientist III and Group leader

8/02 – 9/06: Senior Research Scientist I

8/00 – 8/02: Research Scientist

Global Formulation Sciences, GPRD, Abbott Laboratories, North Chicago, IL

- ✓ Lead formulator for formulation design and development of multiple compounds, from early development through various stages of clinical studies (FIM to Phase III).
- ✓ Led independent research activities for bioavailability improvement for insoluble molecules. Supported life cycle management projects and patent filing. Participated in regularly evaluation of external drug delivery technologies.
- ✓ Designed and developed oral formulations, including both immediate and extended release solid dosage form, lipid based systems, solid dispersion formulations and suspension formulation for clinical studies.
 - Developed spray drying dispersion (SDD) tablet formulations at various scales
 - Defined a procedure to effectively screen and optimize SDD formulations
 - Worked with a Third Party Manufacturer to manufacture SDD materials at scale of up to ~4000L/batch
 - Scaled up post-dried SDD tablet formulations at a scale of up to 300kg/batch
 - Defined and developed one lipid formulation for clinical study
 - Developed two controlled release formulations (either matrix tablets or multiparticulate beads)
 - Developed an oral suspension formulation (Phase III)
- ✓ Led, coordinated and managed manufacturing of clinical supplies (tablets or capsules) for many clinical phase studies ranging from Phase I, II to III internally as well as at third party manufacturers (TPM) at scales up to 300kg/batch
- ✓ Authored formulation development and/or CMC section for IND, CTA and IMPD regulatory filings
- ✓ Hands-on experience with manufacture of various oral formulations at lab and pilot plant scales
- ✓ Knowledgeable and experienced in biopharmaceutic and pharmacokinetic evaluations
- ✓ Knowledgeable and skilled in physical pharmacy (mass transport, dissolution, solubility, stability, solid state, etc)

12/99 – 7/00 Postdoctoral Scientist, Exploratory Formulation, Pharmaceutical Development, Pharmacia, MI

- ✓ Developed good understanding of mechanisms by which lipid-based formulations enhance oral absorption/bioavailability
 - Investigated effect of physicochemical properties of formulations on permeability, absorption and bioavailability of insoluble model compounds in animal model.
 - Evaluated effect of bile (salt), surfactants and lipids on bioavailability of the model compounds in animals
 - Hands-on experience with animal studies on oral drug absorption, *in situ* rat intestine perfusion.
 - Experience in analytical chemistry and bioanalysis (HPLC, UV, fluorescence and LC/MS/MS etc)

8/95 – 11/99 Research Assistant, College of Pharmacy, University of Michigan, MI

- ✓ Designed and developed topical delivery systems including microemulsion and liposomal formulations for hydrophilic macromolecules such as protein and DNA
- ✓ Characterized DNA delivery systems and evaluated in *in vivo* animal models

2/94 - 8/95 Visiting Research Investigator II, College of Pharmacy, University of Michigan, MI

Designed and characterized nonionic liposome and emulsion formulations for topical delivery systems

8/87 - 12/93 Assistant Researcher, Nanjing Institute of Materia Medica, Nanjing, China

- ✓ Designed and developed solid and parenteral formulations including analytical method development, pharmacokinetic evaluation and regulatory filing with SFDA
 - Amphotericin B liposomal injectable formulation (Phase II)
 - Famotidine powder/granule for oral suspension (commercial production approved by SFDA)
 - FDC ibuprofen tablet (commercial production approved by SFDA)
 - FeSO₄ CR tablets (commercial production approved by SFDA)
 - Developed Yunzhi polysaccharide injection (lyophilized)

9/84 – 7/87 Research Assistant, Pharmaceutical Department, Nanjing Institute of Materia Medica, China

- ✓ Investigated feasibility of increasing efficacy and reducing toxicity of Harringtonine via liposomal iv formulations
 - Isolated and purified the phospholipid from the egg yolk
 - Evaluated impact of formulation factors and preparation methods etc on efficiency of incorporation, stability
 - Develop analytical method
 - Performed PK and in vivo distribution study in rat and rabbit models

2/82 - 8/84 Assistant Engineer/Head of Central Research Lab/Manager

Dongfeng Pharmaceutical Co., Lianyungang, China

- ✓ Developed and manufactured allicin (garlic oil) products
 - Synthesized garlic oil and scaled up
 - Applied microencapsulation techniques to develop allicin (garlic oil) capsule formulation (commercial production approved by SFDA)
 - Developed garlic oil injection (commercial production approved by SFDA)
- ✓ Developed generic products including solid dosage form and parenteral formulations
- ✓ Worked with colleagues from different function areas to solve problems which might happen during production of various products including solid and parenteral formulations

EDUCATION

Ph.D. in Pharmaceutics, College of Pharmacy, University of Michigan, 1999

MS. in Pharmaceutics, China Pharmaceutical University, Nanjing, China, 1987

BS. in Pharmacy, China Pharmaceutical University, Nanjing, China, 1982

PATENT APPLICATIONS

1. Solid Dispersions Containing An Apoptosis-Promoting Agent (Filed application in 6/10)
2. New Pharmaceutical Formulation for ABT-072/ABT-333 (MOI submitted, 2010)
3. Solid Dispersions Containing An Anti-HCV Agent (MOI submitted, 2009)
4. Extended release formulation for ABT-894 (MOI submitted, 2009)
5. Pharmaceutical Formulation for Feno Acid: Wu, H., Lee, D., Ju, T. and Gao, Y. (Filed application in 9/06)
6. 7852US02 (Dissolution criteria for Feno Acid Formulations (NFE)): Ju, T., Davila, C., Engh, E., Gao, Y., Gustavson, L., Jayaraman, S., LeBlond, D., Lee, D., Zhu, T., Wu, H. Filed in 10/06.
7. Pharmaceutical Composition Having Improved Dissolution Profiles For Poorly Soluble Drugs (Provisional application, Case No. 7858.US.L1. Filed 4/05), Wu, H., Lee, D., Zhang, G.
8. Nanoemulsion Formulations (United States Patent Application, 20020155084). Roessler, B., Baker, J., Chandrasekharan, R., Weiner, N. and Wu, H.

INVITED SPEECHES

1. "NCE Based (Oral) Drug Product Development" The 1st International Innovate and Generic Drug Research &

- Development Forum, Canton, China 2010
2. "Modified Release Formulation Development" College of Pharmacy, University of Michigan, MI, 2009
 3. "Dissolution Enhancement For Formulations Containing Salt of Poorly Soluble Compounds" AAPS 2005 Annual Meeting, Nashville, TN
 4. "Oral Drug Absorption vs. Formulation Design" College of Pharmacy, University of Michigan, MI, 2005
 5. "Dissolution Enhancement For Formulations Containing Salt Of Poorly Soluble Compounds" Pharmaceutical Education Associates Conference: Improving Delivery of Poorly Soluble Compounds: Formulation and Preformulation Approaches, Philadelphia, PA, 2005
 6. "Principle of Oral Controlled-Release Formulation Design" College of Pharmacy, University of Michigan, MI, 2004
 7. "Topical Delivery Of Hydrophilic Macromolecules With Formulations" AAPS/FIP/SFDA Joint Symposium: Drug Development, Clinical Research and Registration, Nanjing, China, 2004

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2. Wu, H. et al. "Topical transport of hydrophilic compounds using water-in-oil nanoemulsions" *Int. J. Pharm.* 220 (2001) 63-75
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8. Ze, Q. and Wu, H. Industrial production of Allicin microcapsule. *J. Chinese Traditional Medicine*, (1): 7-9, 1984.

ABSTRACTS AND PRESENTATIONS

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2. Wu, H. et al. Understanding Dissolution Behavior of the Salt of a Poorly Soluble Acid Compound In Dual Ph Media. AAPS 2005 Annual Meeting, Nashville, TN
3. Wu, H. et al. Effect of Polymers on Dissolution of the Salt of a Poorly Soluble Acid Compound In Dual Ph Media. AAPS 2005 Annual Meeting, Nashville, TN
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5. Zhang, G., Cao, Y., Gao, Y., Han, J. and Wu, H. In Situ Precipitation of Weak Acid In Aqueous Media: Considerations Beyond Salt Selection, *AAPS PharmSci*, 4(4), 2002
6. Wu, H. et al. Dissolution Testing Using Multi-Medium In The Development Of Formulations For An Acidic Salt Compound, *AAPS PharmSci*, 4(4) 2002
7. Wu, H. et al. Influence of Bile Salt Micelles And Mixed Micelles on the Absorption of PNU-96988 in the Rat Small Intestine, *AAPS Annual Meeting, Indianapolis, 2000*
8. Wu, H. et al. Evaluation of Water-in-Oil DNA Microemulsions as Topical Vehicles for Skin Transfection. *AAPS Annual Meeting, New Orleans, LA, 1999.*
9. Wu, H. et al Topical Delivery of Expression Plasmid DNA and Transfection *In Vivo* Using A Novel Nonionic Microemulsion System, *American Society of Gene Therapy national meeting, Washington, D.C, 1999*
10. Wu, H. et al. A Simple Method to Estimate the Contribution of the Transfollicular Pathway to Transport of Minoxidil into and Across Skin from Various Vehicles. *AAPS Annual Meeting, San Francisco, CA, 1998.*
11. Wu, H. et al. Topical Delivery of Tranexamic Acid from Nonionic Liposomal and Emulsion Formulations *Pharm. Res*, 14: S-314, 1997
12. Wu, H. et al. Deposition of Taxol from Nonionic Liposomal Systems: An *In Vitro-In Vivo* Study Using Hairless Mouse Skin. *Pharm. Res.*, 11:S-187, 1994.
13. Hu, Z., Niemiec, S.M., Wu, H. et al. Topical Delivery of Alpha-Interferon from Nonionic Liposomal Formulations *Pharm. Res*, 11:S-186, 1994
14. Wu, H. et al. Pharmacokinetics of Harringtonine Liposomes in Rabbits. *Chemical Abstracts*, 120:24, 1994

15. **Wu, H.** et al. Distribution of Harringtonine in Positively and Negatively Charged Liposomes in Rat Tissues.
Chemical Abstracts, 118:417, 1993
16. **Wu, H.** et al. Quantitation of Liposome Encapsulated Harringtonine and Harringtonine in Tissues of Rat by HPLC.
Chemical Abstracts, 112:6,1990.

PROFESSIONAL ACTIVITIES

A member of 2001 and 2002 AAPS New Investigator Grant in Oral Lipid-based Drug Delivery Systems Selection Committee

EXHIBIT B

Exhibit B
Storage in PVC Bags

Time	Sample	Concentration (ug/ml)	Potency (%) of control	Potency (%) of T0
Initial	1ug/mL-control	1.0176	100.00	N/A
	1ug/mL-preTS	0.9991	98.18	N/A
	1ug/mL-T=0	0.9361	92.19	100.00
	10ug/mL-control	10.0337	100.00	N/A
	10ug/mL-preTS	9.9222	98.89	N/A
	10ug/mL-T=0	9.4481	94.16	100.00
	15ug/mL-control	15.0155	100.00	N/A
	15ug/mL-preTS	14.9035	99.25	N/A
	15ug/mL-T=0	14.1842	94.46	100.00
	50ug/mL-control	49.8850	100.00	N/A
3 days	50ug/mL-preTS	49.7035	99.64	N/A
	50ug/mL-T=0	47.7288	95.68	100.00
	1ug/mL-40C	0.9277	91.17	98.89
	1ug/mL-25C	0.9356	91.95	99.73
	10ug/mL-40C	9.4037	93.72	99.53
	10ug/mL-25C	9.4078	93.76	99.57
	15ug/mL-40C	14.0222	93.38	98.86
	15ug/mL-25C	14.0887	93.83	99.33
	50ug/mL-40C	47.2099	94.64	98.91
	50ug/mL-25C	47.2602	94.74	99.02
1 wk	1ug/mL-40C	0.9433	92.70	100.55
	1ug/mL-25C	0.9444	92.81	100.67
	10ug/mL-40C	9.4544	94.23	100.07
	10ug/mL-25C	9.5342	95.02	100.91
	15ug/mL-40C	14.2671	95.02	100.58
	15ug/mL-25C	14.2765	95.09	100.66
	50ug/mL-40C	47.9910	96.20	100.55
	50ug/mL-25C	48.1394	96.50	100.88
	1ug/mL-40C	0.9380	92.18	99.99
	1ug/mL-25C	0.9481	93.17	101.06
2 wk	10ug/mL-40C	9.4631	94.31	100.16
	10ug/mL-25C	9.5210	94.89	100.77
	15ug/mL-40C	14.1631	94.32	99.85
	15ug/mL-25C	14.2959	95.21	100.79
	50ug/mL-40C	47.5557	95.33	99.64
	50ug/mL-25C	48.2287	96.68	101.05

Note:

Control: Formulations before filling into PVC bags and glass vials;

PreTS: Formulations filled in PVC bags and glass vials without autoclave;

T0: Formulations filled in PVC bags and glass vials immediately after autoclave

Variability of the analytical method is not greater than 2%

Exhibit B
Storage in Glass Vials

Time	Sample	Concentration (ug/ml)	Potency (%) of control	Potency (%) of T0
Initial	1ug/mL-control	1.0323	100.00	N/A
	1ug/mL-preTS	1.0392	100.67	N/A
	1ug/mL-T=0	1.0357	100.33	100
	10ug/mL-control	10.1482	101.14	N/A
	10ug/mL-preTS	10.1855	101.51	N/A
	10ug/mL-T=0	10.1771	101.43	100
	15ug/mL-control	15.2373	101.48	N/A
	15ug/mL-preTS	15.2542	101.59	N/A
	15ug/mL-T=0	15.2453	101.53	100
	50ug/mL-control	51.1483	102.53	N/A
3 days	50ug/mL-preTS	51.2673	102.77	N/A
	50ug/mL-T=0	51.3839	103.00	100
	1ug/mL-40C	1.0280	98.58	99.26
	1ug/mL-25C	1.0330	100.07	99.74
	10ug/mL-40C	10.1550	100.07	99.78
	10ug/mL-25C	10.1528	100.04	99.76
	15ug/mL-40C	15.1969	98.73	99.68
	15ug/mL-25C	15.1782	98.61	99.56
	50ug/mL-40C	50.8683	95.49	99.04
	50ug/mL-25C	50.9256	95.58	99.11
1wk	1ug/mL-40C	1.0252	95.31	98.99
	1ug/mL-25C	1.0214	95.94	98.62
	10ug/mL-40C	10.0452	98.98	98.70
	10ug/mL-25C	10.0631	98.16	98.88
	15ug/mL-40C	15.1969	95.73	99.68
	15ug/mL-25C	15.1782	95.61	99.56
	50ug/mL-40C	50.7608	95.24	98.79
	50ug/mL-25C	50.9493	95.61	99.15

EXHIBIT C

Exhibit C

PVC bags

Time	Sample	Concentration (ug/ml)	Potency (%) of control	Potency (%) of T0
Initial	1ug/mL-control	1.0274	100.00	N/A
	1ug/mL-T=0	1.0326	100.51	100.00
	10ug/mL-control	10.2784	100.00	N/A
	10ug/mL-T=0	10.2380	99.61	100.00
	15ug/mL-control	15.1541	100.00	N/A
	15ug/mL-T=0	15.1725	100.12	100.00
12h	50ug/mL-control	50.7557	100.00	100.00
	50ug/mL-T=0	50.5099	99.52	N/A
	1ug/mL	1.0157	98.86	98.36
	10ug/mL	10.1602	98.85	99.24
	15ug/mL	15.0347	99.21	99.09
	50ug/mL	50.0469	98.60	99.08
24h	1ug/mL	1.0122	98.52	98.02
	10ug/mL	10.1532	98.78	99.17
	15ug/mL	14.9934	98.94	98.82
	50ug/mL	49.8515	98.22	98.70

Note:

Control: Formulations before filling into PVC bags and glass vials;

Glass vials

Time	Sample	Concentration (ug/ml)	Potency (%) of control	Potency (%) of T0
Initial	1ug/mL-control	1.0274	100.00	N/A
	1ug/mL-T=0	1.0337	100.61	100.00
	10ug/mL-control	10.2784	100.00	N/A
	10ug/mL-T=0	10.2390	99.62	100.00
	15ug/mL-control	15.1541	100.00	N/A
	15ug/mL-T=0	15.1478	99.96	100.00
12h	50ug/mL-control	50.7557	100.00	N/A
	50ug/mL-T=0	50.5308	99.56	100.00
	1ug/mL	1.0405	101.28	100.66
	10ug/mL	10.2327	99.56	99.94
	15ug/mL	15.1351	99.87	99.92
	50ug/mL	50.7833	100.05	100.50
24h	1ug/mL	1.0374	100.97	100.36
	10ug/mL	10.2204	99.44	99.82
	15ug/mL	15.1177	98.76	99.80
	50ug/mL	50.8899	100.26	100.71