Regulatory Challenges of Brain Delivered Therapies: A Combination Product Perspective

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Abstract

Delivery of therapeutic agents directly to the central nervous system can be critical to address a number of diseases. Intraventricular administration of drugs has been used for over 50 years. Despite a substantial number of drugs routinely administered to the central nervous system in the course of medical practice, very few medical devices are appropriately cleared in the US for this route of administration. This review explores the regulatory challenges, the supplementary testing and more stringent acceptance criteria required for combination products and medical devices intended for CNS therapies. A case study of the recent Brineura® combination product approval is also presented.

Keywords: Intracerebroventricular; Intraventricular; FDA; Combination product; Drug administration; Central nervous system; Regulatory; Brineura

Abbreviations: CFR: Code of Federal Regulations; CNS: Central Nervous System; CSF: Cerebrospinal Fluid; Intrathecal: Administration within the Cerebrospinal Fluid at any Level of the Cerebrospinal Axis, Including Injection into the Cerebral Ventricles; Intraventricular: Administration within a Ventricles; ICV: Intracerebroventricular; FDA: U.S. Food and Drug Administration; FD&C Act: Food, Drug, and Cosmetics Act.

Introduction

Delivery of therapeutic agents directly to the Central Nervous System (CNS) can be critical to address a haemorrhage, CNS lymphoma, glioblastoma and refractory pain. The two principal routes of administration to the Cerebrospinal Fluid (CSF) are via intrathecal lumbar puncture, or directly in a lateral ventricle of the brain.

Intraventricular, or intracerebroventricular (ICV) administration of drugs has been used for over 50 years, and delivery of therapeutic agents to the brain can be accomplished by a variety of means [1]. The most direct access requires subcutaneous implantation of an ICV access device or ventriculostomy port, such as an Ommaya reservoir [2]. Excellent comprehensive reviews on this subject have already been written [1,3]. Despite a long history of successful outcomes, there is only one drug specifically approved for this route of administration (per the FDA Drug Labeling Database [4]). A few therapeutic agents are approved for intrathecal administration, and depending on the drug, this may or may not include “intraventricular” administration based on the approved labeling found in Table 1. For example, in the case of DepoCyt® (cytarabine), which has an official FDA-approved route of administration of “intrathecal”, the Dosage and Administration section of the labeling text instructs the user to administer the drug by “intraventricular or lumbar puncture”. Conversely, other drugs approved for intrathecal delivery are not explicitly approved for intraventricular delivery, although many are used off-label via this route of administration.

Despite the lack of approved drugs specifically intended for intraventricular delivery, many therapies are administered to the brain in the course of routine medical practice. Drugs commonly delivered intraventricularly include: chemotherapy agents (methotrexate, mafosfamide, cytarabine, etoposide), radioisotopes, contrast agents, antimicrobials, and pain modulating agents (morphine, lidocaine, baclofen, bupivacaine, ziconotide) [1,3,5-22]. While there is an increasing number of drugs being administered off-label via the intraventricular route, pharmaceutical companies wishing to develop drugs for intraventricular delivery face greater challenges than drugs developed for other, more common routes of administration.

Challenges with the Development of Drugs for Intraventricular Delivery

Administration of drugs via the intraventricular route poses numerous challenges. Firstly, surgical implantation of an ICV access device (also known as Ommaya-type reservoir and catheter, or ventriculostomy port) is required for administration. Complications associated with the procedure are described in other comprehensive reviews [3,23]. Secondly, very few disposable medical devices are appropriately cleared in the US for intraventricular administration of drugs. The vast majority of medical devices used for therapeutic drug delivery are cleared for the intravascular route only, although these devices are commonly used off-label for intrathecal and intraventricular administration. Additionally, the regulatory framework surrounding devices intended for intraventricular administration is lacking (see “regulatory considerations” below) and there are few incentives for medical device developers to enter the market (smaller market, greater risks, etc.). Consequently, drug developers find themselves responsible for finding or developing devices appropriate for intraventricular delivery of their drugs. Finally, differences exist between the testing requirements to obtain approval or clearance for drugs and medical devices intended for intraventricular administration versus intrathecal administration. Supplementary testing, including biocompatibility and endotoxin, and more stringent acceptance criteria have been established for drugs and devices intended for delivery to the CNS. The regulatory considerations and testing requirements for devices intended for intraventricular drug administration are discussed in the following sections.

Regulatory considerations

The FDA has established a classification system for medical devices, shortly after the 1976 Medical Device Amendments to Section 201(h) of thedevice (also known as Ommaya-type reservoir and catheter, or ventriculostomy port) is required for administration. Complications associated with the procedure are described in other comprehensive reviews [3,23]. Secondly, very few disposable medical devices are appropriately cleared in the US for intraventricular administration of drugs. The vast majority of medical devices used for therapeutic drug delivery are cleared for the intravascular route only, although these devices are commonly used off-label for intrathecal and intraventricular administration. Additionally, the regulatory framework surrounding devices intended for intraventricular administration is lacking (see “regulatory considerations” below) and there are few incentives for medical device developers to enter the market (smaller market, greater risks, etc.). Consequently, drug developers find themselves responsible for finding or developing devices appropriate for intraventricular delivery of their drugs. Finally, differences exist between the testing requirements to obtain approval or clearance for drugs and medical devices intended for intraventricular administration versus intrathecal administration. Supplementary testing, including biocompatibility and endotoxin, and more stringent acceptance criteria have been established for drugs and devices intended for delivery to the CNS. The regulatory considerations and testing requirements for devices intended for intraventricular drug administration are discussed in the following sections.

Regulatory considerations

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Interestingly, multi-purpose syringes, needles and port needles are cleared under the General Hospital specialty panel (21 CFR Part 880). This means that these devices have a broad 510(k) clearance with no restrictions to routes of administration. From a regulatory perspective, these devices are appropriately cleared or approved for intraventricular administration of medications. However, from a testing perspective, syringes and needles may not meet present day criteria for devices intended for intraventricular administration. Details of additional testing required for neuraxial devices are discussed further below.

Implanted ICV access devices, or ventriculostomy ports, are classified under the Neurological Devices specialty panel (882.5550: Central nervous system fluid shunt and components, Product Code: [XJG]) [31]. Despite being commercially available for over 40 years, only a handful of ports are actually cleared by the FDA for administration of medications [31]. Table 2 below illustrates the clearances of a few ICV devices: while the Codman and Integra Life Sciences devices have broad clearance for administration of any therapeutic drug, the Medtronic ICV access devices are only cleared for injection of chemotherapy agents or radioisotopes. Other types and brands of ventricular reservoirs and catheters exist; however, they are not appropriately cleared for drug administration.

The regulatory requirements for expanding the clearance or intended use of a currently marketed medical device are very extensive. Device manufacturers wishing to modify the indication for use would have to submit new premarket notification (510(k)) or premarket approval (PMA). And for many devices that were cleared or approved a long time ago, this would require complying with today’s testing standards, which are more stringent than they were decades ago. Additional testing, tighter limits and the requirement to submit a new 510(k) or PMA are significant obstacles to regulatory approvals, especially considering that the market size for devices used in intraventricular administration may be extremely small. Hence, there are very few medical devices appropriately cleared for intraventricular drug administration.

| Product Brand Name | Product Generic Name | Originator | Initial Approval Date | Routes of Administration | Reference / BLA / NDA # |
|--------------------|---------------------|------------|-----------------------|--------------------------|-------------------------|
| Briniva             | Cerliponase alfa    | BioMarin Pharmaceutical Inc. | 04/27/2017 | Intraventricular | 761052 |
| Spinraza            | Nuinsersen          | Biogen     | 12/23/2016 | Intrathecal        | 209531 |
| Prialt              | Ziconotide          | Jazz Pharmaceuticals Inc | 12/28/2014 | Intrathecal        | 021060 |
| Gablofen            | Baclofen            | Mallinckrodt Inc, Brand Pharmaceuticals | 11/19/2010 | Intrathecal        | 022462 |
| Depocyt             | Cytarabine          | Sigma Tau Pharmaceuticals Inc | 04/01/1999 | Intrathecal        | 021041 |
| Lioresal            | Baclofen            | Sol Therapecies Inc. | 06/17/1992 | Intrathecal        | 020075 |
| Isovue-M            | Iopamidol           | Bracco Diagnostics Inc | 12/31/1985 | Intrathecal        | 018735 |
| Omnipaque           | Iohexol             | Ge Healthcare Inc | 12/26/1985 | Intrathecal; Intravascular; Intravenous; Oral | 018956 |
| Infumorph 200       | Morphine Sulfate    | West Ward Pharmaceuticals Corp | 09/18/1984 | Epidural; Intrathecal | 018565 |
| Indium DTPA In 111  | Pentetate indium Disodium In 111 | GE Healthcare Inc | 02/18/1982 | Intrathecal | 017707 |
| Elliotts B          | Sodium Chloride, Sodium Bicarbonate, Anhydrous Dextror, Magnesium Sulfate, Potassium Chloride, Calcium Chloride, Sodium Phosphate | Lukare Medical Llc | 09/27/1966 | Intrathecal | 020577 |
| Methotrexate        | Methotrexate        | Hospira Worldwide Inc | 08/10/1959 | Intra-arterial; Intramuscular; Intrathecal; Intravenous | 011719 |

1 Generic values of the RLD are not included in this table for simplicity.

Data retrieved from FDA Label Database, 6 Apr 2017 [4]. List of drugs approved prior to 1980 may be incomplete.

Table 1. List of Reference Listed Drugs Approved for Intrathecal and Intraventricular Delivery

the Federal Food, Drug and Cosmetic Act (FD&C Act) [24]. Every device is first assigned one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device: Class I (general controls), Class II (general and special controls), and Class III (general controls and premarket approval). Devices are further classified by medical specialty panels contained in 21 CFR 862-892, according to the description and intended use of the device. Each classified device has a 7-digit number associated with the medical specialty (e.g. 21 CFR 880.5440 - Intravascular administration set) and a three letter product code which is used on the Medical Device Listing form [25-27] (e.g. FPA - Intravascular administration set). While most medical devices can be appropriately classified according to the pre-existing product classes, some new and innovative products are more challenging to fit into this regulatory framework. New de novo classification is required for devices that have not been previously classified under the FD&C Act. The challenge with de novo applications is that they are automatically assigned a Class III designation, meaning the highest level of controls and regulatory requirements. Intraventricular drug administration is one of those areas where few appropriate classifications exist, and a new regulatory framework is needed.

For example, when searching for medical devices used to deliver pharmaceutical products to the brain, one would naturally gravitate to the Neurology medical specialty panel (21 CFR Part 882: Neurological Devices). Interestingly, there are no established classes for devices intended for drug administration in the Neurology panel [28]. In fact, to the authors’ knowledge, there is only a single product code, “PWH”, which was recently introduced by FDA for infusion components that contain NRFit” connectors. These connectors are specifically intended for neuraxial routes of administration and fall under the General Hospital specialty panel (21 CFR Part 880). Most administration sets fall under 21 CFR 880.5440 (Intravascular Administration Set) [29,30]. This means that administration of drugs with devices classified as above would constitute an off label use, if used in any route other than intravascular. Similarly, epidural administration sets are also not intended for intrathecal or intraventricular administration.
Additional testing required for medical devices intended for intraventricular administration

Differences exist between the testing required to obtain approval or clearance for medical devices intended for intraventricular compared to intravascular uses. Additional testing, including biocompatibility and endotoxin, and more stringent acceptance criteria have been established for devices that are intended for direct or indirect contact with the CSF.

**Endotoxin limits**: The Bacterial Endotoxin test (BET) is an assay to detect or quantify endotoxins from Gram-negative bacteria, generally conducted using amoebocyte lysate from the horseshoe crab (also known as the Limulus Amoebocyte Lysate (LAL) test). Endotoxin limits for drugs and medical devices that come into contact with the human body (direct or indirect) are typically established according to USP or AAMI standards [32-34]. Specifically, the endotoxin limit for parenteral drugs, defined on the basis of dose is calculated according to the formula below:

\[
\text{Endotoxin limit} = \frac{K}{M}
\]

- **K** = threshold pyrogenic dose of endotoxin per kg of body weight;
- **M** = maximum recommended bolus dose of product per kg of body weight.

The threshold (K) is 0.2 Endotoxin Units (EU)/kg for intrathecally administered drugs and 5 EU/kg body weight for all other routes of administration. Although endotoxin limits for drugs administered to the brain or ICV space are not specifically highlighted in USP <85>, presumably the same limit as intrathecally administered drugs applies to ICV drugs since they are delivered to the same contiguous biological fluid (cerebral spinal fluid (CSF)). If a drug is infused continuously, M is total dose administered in a single hour period [32].

For medical devices, the endotoxin limit for the finished device is Not More Than (NMT) 20 EU per device or 0.5 EU/mL for intravascular use, and NMT 2.15 EU or 0.06 EU/mL for devices in contact with cerebral spinal fluid (refer to USP <161>). As previously discussed, there are very few medical devices cleared for ICV delivery of drugs. Those devices that have general clearance, such as syringes or needles, are unlikely to be tested to the tighter endotoxin limits (2.15 EU/device) for CSF contact. Rather, they are most likely designed to meet limits for intravascular administration.

**Biocompatibility**: Medical devices that come into direct or indirect contact with the human body should be tested for biological compatibility with the body in order to determine the risk for potential adverse reactions. The degree of biocompatibility testing that is recommended in ISO-10993 and FDA’s Guidance on ISO-10993-1, depends on the intended use of the device, including the intended anatomical location, as well as frequency and duration of exposure [35,36]. For example, an infusion line for repeated intravascular administration of drugs may have no intended direct contact with blood. Such a device would be categorized as an external communicating device, indirect blood path and prolonged duration (>24 h to 30 d) as shown in Table 3. In this particular example, biological compatibility would be evaluated for the following endpoints: cytotoxicity, sensitization, irritation, acute systemic toxicity and hemocompatibility. This evaluation could be done by conducting biocompatibility testing and/or an assessment of existing knowledge and available literature.

In contrast, the same infusion line intended for administration to brain tissue would require additional testing including: subcutaneous/subchronic toxicity; genotoxicity and implantation, as shown in Table 3. Since there are no infusion lines actually cleared in the US with intended use for administration of drugs to the brain, the onus of bridging these gaps in biocompatibility testing rests with the manufacturer seeking to develop a drug intended for brain delivery. Similar conclusions can be drawn for administration sets, syringes, needles, filters or other devices cleared only for intravascular use or not evaluated for all biocompatibility endpoints.

Some of these gaps in biocompatibility evaluations may be bridged...
by existing chemical characterization data, clinical data, marketing experience, or a risk assessment to justify appropriate testing [35]. Experience from medical devices that have been on the market for extended periods, or evaluation of materials of construction that are commonly used in medical devices can be leveraged in lieu of testing, as described in ISO 10993.

Leachables and extractables: Compatibility, suitability, leachables and extractables testing for the container closure of a drug product is a requirement for any new drug approvals in the US [37-42]. However, testing of the medical devices used for administration of the drug has not historically been required. Recently, the FDA has become increasingly concerned with leachables associated with devices used for drug administration, such as infusion bags, tubing, filters, syringes, etc. This is evidenced by FDA warnings issued regarding drug-device incompatibilities. In 2002, FDA posted a Public Health Notification warning against the use of di(2-ethylhexyl) phthalate (DEHP)-containing devices for certain patient populations [43] and published a Safety Assessment Report on the subject in 2014 [44]. In 2015, FDA warned against using the chemotherapeutic drug Treanda® with administration devices containing polycarbonate or acrylonitrile-butadiene-styrene [45].

Concerns over drug-device compatibility are only enhanced in the case of drugs delivered directly to the brain or CSF. Indeed, levels of leachables and extractables for medical devices intended to be used for oral or vascular delivery may not necessarily be considered safe levels for intraventricular delivery. A toxicological risk assessment of leachables and extractables for intraventricular administration can be challenging. Often, there is no toxicology data available in the

### Table 3: Biocompatibility Evaluation Endpoints Table Adapted from FDA Guidance for Industry.

| Nature of Body Contact | Contact Duration | Biological effect |
|------------------------|------------------|-------------------|
|                        | A – limited (≤ 24 h) | Cytotoxicity | Sensitization | Inflammation/Interventricular Reaction | Acute Systemic Toxicity | Material-Mediated Pyrogenicity | Subchronic/Subacute Toxicity | Genotoxicity | Implantation | Hemocompatibility | Chronic Toxicity | Carcinogenicity | Reproductive/Developmental Toxicity | Degradation |
|                        | B – prolonged (>24 h to 30 d) | | | | | |
|                        | C - permanent (> 30 d) | | | | | |
| Surface device         | Intact skin       | X | X | X | | | | | | | | | | | |
|                        | Mucosal membrane  | X | X | | O | O | O | | | | | | | | |
|                        | Breached or compromised surface | X | X | X | O | O | | X | O | O | | | | | |
| External communicating device | Blood path, indirect** | X | | | | | | | X | | | | | | |
|                        | Tissue+/bone/ dentin## | X | X | X | O | X | X | | X | O | O | | | | |
|                        | Circulating blood | X | X | X | O | X | X | | X | X | O | O | | | |
| Implant device         | Tissue+/bone      | X | X | O | O | | | | | | | | | | |
|                        | Blood             | X | X | X | O | X | X | | X | X | X | O | | | |

X = ISO 10993-1:2009 recommended endpoints for consideration*  
O = Additional FDA recommended endpoints for consideration*  
Note * All X’s and O’s should be addressed in the biological safety evaluation, either through the use of existing data, additional endpoint-specific testing, or a rationale for why the endpoint does not require additional assessment.  
Note + Tissue includes tissue fluids and subcutaneous spaces  
Note ^ For all devices used in extracorporeal circuits  
Note # Reproductive and developmental toxicity should be addressed for novel materials, materials with a known reproductive or developmental toxicity, devices with relevant target populations (e.g., pregnant women), and/or devices where there is the probability for local presence of device materials in the reproductive organs.  
Note @ Degradation information should be provided for any devices, device components, or materials remaining in contact with tissue that are intended to degrade.  
** example of an infusion line for intravascular administration of drugs with no direct contact with blood.  
### Table: Biocompatibility Evaluation Endpoints Table Adapted from FDA Guidance for Industry.
public domain for neuraxial routes of administration, and using oral
toxicology data to extrapolate acceptable daily exposure limits for
the intraventricular route can under-predict toxicities which could
otherwise be a concern.

Going forward, sponsors developing drugs for intrathecal or
intraventricular administration will likely be required to conduct an
assessment of leachable and extractables from medical devices used in
the administration of the drug. There are no FDA guidance documents
on acceptable levels of leachables for drugs administered via the
intraventricular route. However, USP Chapter <661> has recently been
updated, and new chapters are being proposed for future revisions,
including USP <661.4> Plastic Medical Devices Used to Deliver or
Administer Pharmaceutical Products [38]. This new chapter will
provide a framework for the design and implementation of leachable
assessments for delivery systems.

Brineura® Case Study

Brineura is the first drug approved specifically for intraventricular
administration in the US. It is an enzyme replacement therapy
indicated for the treatment of CLN2 disease, a form of Batten disease, or
neuronal ceroid lipofuscinosis type 2 (CLN2). The administration is by
intraventricular infusion and requires pre-implantation of a ventricular
reservoir and catheter. Every two weeks, the product is administered
into the implanted reservoir through a port needle connected to a
syringe via a series of infusion lines and an in-line filter. The syringe
containing the drug is placed in a syringe pump to ensure slow and
continuous delivery of the therapy over a period of approximately four
hours. Brineura is supplied as a solution for intraventricular injection
with an electrolyte flushing solution, and a separately packaged
Administration Kit. The Administration Kit is approved under the
Brineura product license, and cross-labelled for use with Brineura.
The Administration Kit contains marketed devices in their original
packaging, including: two syringes, two syringe needles, an infusion
line with 0.2 μm in-line filter, an extension line and a port needle.

Brineura was originally developed as a drug, not a combination
product as defined in 21 CFR 3.2(e). It was not designed as a co-
packaged or cross-labelled biologic-device product, nor was it designed
as a convenience kit. Brineura became a combination product because
there are no commercially available infusion components specifically
clarified for intraventricular drug administration. Indeed, common
administration components are cleared under the “intravascular”
or “intrathecal” or “general hospital” umbrellas, and according to
FDA classification are not intended for the intraventricular route of
administration. As a result, Brineura was classified as a combination
product, per 21 CFR 3.2(e)(3). Being regulated as a combination
product meant that the drug developer, BioMarin Pharmaceutical Inc.
had to provide the necessary devices in an Administration Kit, register
as a device manufacturing facility, in addition to a drug manufacturing
facility, and also comply with Quality System Regulations, 21 CFR 820
as shown in Table 4 [27,46-48]. Devices included in the Administration
Kit were required to meet the additional testing criteria, as described
in the previous sections. FDA also required letters of authorization
to access the device manufacturers’ files (e.g. 510(k) Premarket
Notification).

Discussion

The challenges encountered for Brineura are interesting from a
regulatory perspective: despite a plethora of devices intended for
the intrathecal delivery of drugs, none are specifically cleared for the
intraventricular route. And although the CSF is contiguous between
the intrathecal and intraventricular space, these are separate routes of
administration from a U.S. regulatory perspective.

Perhaps changes to the regulatory framework are warranted in
the US for medical devices intended for intraventricular delivery
or other neuraxial applications (e.g. intrathecal, subarachnoid, epidural,
extra-, or peri-dural spaces, intratumoral, intraparenchymal).
Similarly, international standards are needed to bridge the gap between
intravascular and neuraxial applications. Recent updates to ISO 80369-
6:2016 - Connectors for neuraxial applications, are an attempt to
start bridging this gap. ISO 80369-6 is being implemented to prevent
inadvertent misconnections between incompatible systems. Medical
devices intended for neuraxial applications will have unique connector
design and performance standards (NRFit) [49]. NRFit devices will
start making their way to the marketplace in 2018 and California is
the first state requiring facilities to make the switch [50,51]. And while
implementation may be a slow process, guidelines have been drafted,
and medical device companies have started developing products with
neuraxial connectors [51-55]. This is a step in the right direction
and will hopefully provide drug developers more options for devices
intended for intraventricular administration.

Increasingly, innovative treatment and delivery approaches
are being investigated to tackle the daunting needs of patients with
gliomas and other brain cancers, Parkinson’s, Huntington’s and other
neurodegenerative diseases. Updates to the regulatory framework
are needed to keep pace with innovation for treating CNS diseases.
As described in the preceding sections, sponsors wishing to develop
drugs for intraventricular administration must consider challenges
associated with combination products. The paucity of appropriately
cleared devices for CNS delivery, the additional testing requirements
and heightened regulatory scrutiny contribute to the challenges in
gaining marketing approval in the U.S.

Proper planning prior to the initiation of clinical studies is critical
to identify adequate solutions for administration of the drug. A

| Key Provisions of Quality System Regulation to be Implemented if Following 21 CFR 210/211 (Current Good Manufacturing Processes For Pharmaceuticals) | Key Provisions of Drug GMPs to be implemented if Following 21 CFR 820 (Quality System Regulation for Medical Devices) |
|---|---|
| 1. 820.20 Management responsibility | 1. 211.84 Testing and approval/rejection of components, drug product containers & closures |
| 2. 820.30 Design controls | 2. 211.103 Calculation of yield |
| 3. 820.50 Purchasing controls | 3. 211.132 Tamper-evident packaging for over-the-counter (OTC) human drug products |
| 4. 820.100 Corrective and preventive action | 4. 211.137 Expiration dating |
| 5. 820.170 Installation | 5. 211.165 Testing and release for distribution |
| 6. 820.200 Servicing | 6. 211.166 Stability testing |
| 7. 820.220 Testing of components | 7. 211.167 Special testing requirements |
| 8. 820.400 Process control | 8. 211.170 Reserve samples |

Table 4: Regulatory Requirements for Combination Product Manufacturers.
proactive approach to development and design verification can help mitigate some of the additional requirements. Early and frequent interactions with the FDA prior to initiation of clinical studies and prior to submission of marketing applications can be helpful and are strongly recommended.

Disclosures
The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the FDA or any agency of the US government. Examples provided, and authors and do not necessarily reflect the official policy or position of the US government.

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