MODULE III

GENTAMICIN

USAID
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Manual for Procurement & Supply of
Quality-Assured MNCH Commodities

GENTAMICIN

INJECTION, 10 MG/ML IN 2 ML VIAL AND 40 MG/ML IN 2 ML VIAL

GENERAL PRODUCT INFORMATION

Gentamicin injection is the first-line drug recommended by WHO for the treatment of community acquired pneumonia (severe), complicated severe acute malnutrition, and sepsis in neonates and children. It is also considered an essential medicine for child health by the UN Commission on Life-Saving Commodities.

Gentamicin for injection is presented as an aqueous solution of gentamicin sulfate, mostly available in 2-mL vials or ampoules in two concentrations (10 mg/mL or 40 mg/mL). Gentamicin is also available in eye drops for ophthalmological infections, in ear drops for ear infections, and as a topical ointment for skin infections.

The scope of this manual includes only the presentation described in the WHO Essential Medicines List for Children (EMLc) that is gentamicin injection 10 mg/mL and 40 mg/mL (as sulfate) in 2-mL vial.

KEY CONSIDERATIONS IN PROCUREMENT

1. Procurement should be made from trusted sources. This includes manufacturers whose gentamicin injection has been approved by an SRA or accepted by the United Nations Children's Fund (UNICEF), and those with a proven record of quality products.

2. Procurers need to focus on product quality to ensure that it is safe for patient use as.

KEY QUALITY CONSIDERATIONS

Product specification

The product must comply with the quality specifications as detailed in the Annex.

Packaging and labeling

Gentamicin injection should be procured in vial presentations as per the WHO EMLc recommendation of 10 mg/mL and 40 mg/mL (as sulfate) in 2-mL vial. For typical neonatal dosages, approximately two doses could be obtained from a 10-mg/mL vial and up to eight doses from a 40 mg/mL vial. Note that some SRA-approved products may be presented in ampoules. For ampoules, any medicine not immediately used would have to be discarded, as it cannot be resealed.

The container-closure system (vial and rubber stopper) must be sufficient to preserve sterility during the shelf life of the product.

While pediatric ampoules exist for the intramuscular injections to newborns, the volumes are smaller if the 80 mg/2 ml ampoule is used (it is less painful for the patient). In this situation, syringes and needles of the right sizes for newborns should be considered in the procurement.

Note: Due to the calculations needed to determine the dose volume by weight of the infant, health workers at the primary care level may have difficulty accurately determining the correct amount of drug they should administer. A custom-marked syringe would be best as a 1-mL syringe with 0.2 increment markings most relevant for gentamicin administration, so it may be that a regularly marked 1-mL syringe can be used effectively by health care workers for this purpose. Based on a literature review, the syringe specifications shown in the table below are optimal for IM delivery of gentamicin in neonate[1].

[1] Viability of customized, marked syringes for gentamicin delivery for the outpatient treatment of neonatal sepsis. Available at http://www.path.org/publications/files/PATH_dt_cust_syringe_br.pdf

ITEM	OPTIMAL RANGE
Gauge	22–25 G
Needle length	16–25 mm
Gradations	< 0.1 mL
Volume	≥ 1 mL

Additional information about the packaging and labeling can be found in the Annex.

Storage, transportation, and distribution

Procurers need to verify from manufacturers there is satisfactory stability data to support shelf life and storage conditions.

Gentamicin injection does not need to be maintained in the cold chain, but should be stored below 25°C.

Procurers must ensure that the product is stored safely so that the vial cannot break or leak, which would compromise its sterility.

Additional information about the misoprostol finished product storage requirement can be found in the "Storage, Stability and Degradation" section.

Other considerations

Gentamicin injection must be manufactured in a sterile facility.

Name of the Medicinal Product

Gentamicin injection

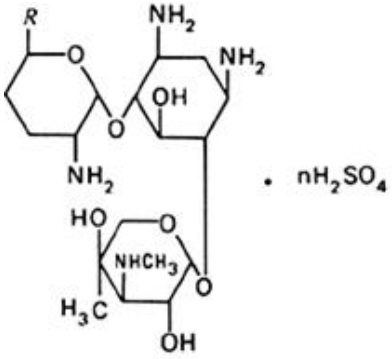
Chemical Name

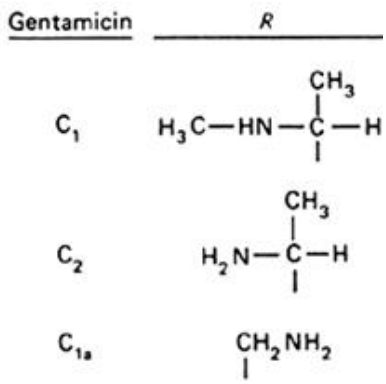
Gentamicin sulfate

Gentamicin sulfate is the sulfate salt of gentamicin fractions C_1, C_2, and C_{1a} produced by the growth of *Micromonospora purpurea.*

Chemical Structure

$C_{60}H_{125}N_{15}O_{25}S$





Pharmaceutical Form

Sterile solution for injection
A clear, colorless solution

Qualitative and Quantitative Composition

Gentamicin injection is a sterile solution of gentamicin sulfate in water for injection.

- Gentamicin injection 10 mg/mL: each vial (2 mL) contains gentamicin sulfate equivalent to 20 mg gentamicin base.
- Gentamicin injection 40 mg/mL: each vial (2 mL) contains gentamicin sulfate equivalent to 80 mg gentamicin base.

List of excipients[2]:

- Sodium chloride
- Water for injection
- Sulfuric acid and/or sodium hydroxide, for pH adjustment

Some formulations may contain the following excipients:

- Methylparaben (preservative)
- Propylparaben (preservative)
- Sodium metabisulfite (antioxidant)
- Edetate disodium (chelating agent)

Packaging and Presentation

The WHO EMLc includes two presentations: 10 mg/mL and 40 mg/mL in 2-mL vial presentation for gentamicin injection. However, some manufacturers sell it packaged in glass ampoules.

[2] Based on the formulation of an innovator product, Cidomycin®.

SUPPLY

Generally, products prequalified by the WHO PQP and/or approved by an SRA are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved, or ERP recommended products, medicines from trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment as described in Module II.

WHO-prequalified products

Gentamicin is not included in the WHO PQP. Therefore, no WHO-prequalified gentamicin products are available.

SRA-approved products

Table G-1. Examples of SRA-Approved Gentamicin Injection 10 mg; 40 mg (as sulfate)/mL in 2-mL Vial or Ampoule

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
Gentamicin sulfate EQ 40 mg base/mL EQ 10 mg base/mL	US FDA	Fresenius Kabi, USA	ANDA #062366	10 mg/mL: single-dose vials; 2 mL 40 mg/mL: multiple-dose flip-top vials; 2 ml	Not specified	Store at 20–25°C. [See USP, Controlled room temperature.]
Gentamicin sulfate EQ 40 mg base/mL EQ 10 mg base/mL	US FDA	Hospira, USA	ANDA #062420	Single-dose flip-top vials; 2 mL	Not specified	Store at 20–25°C. [See USP, Controlled room temperature.]
Gentamicin sulfate EQ 10 mg base/mL	US FDA	Hospira, USA	ANDA #062612	Single-dose vials; 2 mL	Not specified	Store at 20–25°C. [See USP, Controlled room temperature.]
Cidomycin® 80 mg/2 mL solution for injection	UK MHRA	Aventis Pharma (Sanofi-Aventis) Ltd, One Onslow Street, Guildford, Surrey, GU1 4YS, UK	PL 04425/0672	Colourless glass ampoules (type I) or colourless glass vials (type I) closed with chlorobutyl rubber stopper sealed with an aluminum capsule	3 years	Do not store above 25°C. Do not refrigerate or freeze.
Gentamicin 10 mg/mL solution for injection or infusion	UK MHRA	Wockhardt UK Ltd, Ash Road North Wrexham LL13 9UF, UK	PL 29831/0659	Type I glass ampoules; 2 mL	2 years	Do not store above 25°C. Do not refrigerate or freeze. Store in the original package in order to protect from light.
Gentamicin 40 mg/mL solution for injection or infusion	UK MHRA	Wockhardt UK Ltd, Ash Road North Wrexham LL13 9UF, UK	PL 29831/0660	Type I glass ampoules; 2 mL	2 years	Do not store above 25°C. Do not refrigerate or freeze. Store in original package in order to protect from light.

PRODUCT NAME	SRA	MARKETING AUTHORIZATION HOLDER	REGISTRATION NUMBER	PACKAGING AND PRESENTATION	SHELF LIFE	STORAGE CONDITION
Gentamicin 40 mg/mL injection	UK MHRA	Hospira UK Ltd,	PL 04515/0037	Clear, type I glass vials; 2 mL	3 years	Do not store above 25°C.
Gentamicin 40 mg/mL solution for injection	UK MHRA	Amdipharm UK	PL 20072/0056	Colourless, type I glass ampoules; 2 mL	4 years	Do not store above 25°C. Do not freeze.
Gentamicin pediatric 20 mg/2 mL solution for injection	UK MHRA	Ennogen Pharma Ltd, UK	PL 40147/0042	Clear glass ampoules; 2 mL	2 years	Store below 25°C. Protect from light.
Gentamicin pediatric 20 mg/2 mL solution for injection	UK MHRA	Winthrop Pharmaceuticals UK Ltd, UK	PL 17780/0507	Vials; 2 mL	2 years	Do not store above 25°C. Do not refrigerate or freeze.
Gentamicin injection USP 10 mg/mL or	Health Canada	Teligent OU	2470462	Single-use ampoules;	Not specified	Store between 15–30°C. Protect from light.
40 mg/mL		Estonia		2 mL		
Gentamicin injection BP 80 mg/2 mL	TGA (Australia)	Pfizer Australia Pty Ltd, Australia	AUST R 11376	LDPE ampoules; 2 mL	2 years	Store below 25°C. Protect from light.
DBL gentamicin injection BP 80 mg/2 mL	TGA (Australia)	Hospira Australia Pty Ltd, Australia	AUST R 16337	Glass ampoules; 2 mL	Not specified	Store below 25°C.

It should be noted that the list of SRA-approved products provided above is not exhaustive. The list may be changed over time. When a manufacturer claims that its product is approved by an SRA, they should provide the following information/documents to prove the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, patient information leaflet, and the labeling by the reference SRA)
- A statement confirming the FPP—including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, product information—will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may cross check the submitted information with the corresponding NMRA websites:

- US FDA: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- Swissmedic: https://www.swissmedic.ch/swissmedic/en/home/services/authorized-medicines/human-and-veterinary-medicines.html
- Health Canada: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
- TGA, Australia: https://www.tga.gov.au/australian-register-therapeutic-goods

Trusted sources

Gentamicin injection from the following manufacturers are listed by UNICEF as approved sources for procurement[3]:

- Gland Pharma Ltd, India
- Intas Pharmaceuticals Ltd, India

It is recommended to check for updated information on the UNICEF website at the time of procurement.

Related Products

Other formulations of gentamicin on the market include:

- Gentamicin 1 mg/mL solution for injection
- Gentamicin 3 mg/mL solution for infusion
- Gentamicin eye/ear drops 0.3% w/v
- Gentamicin intrathecal 5 mg/mL solution for injection
- Implants—each chain consists of 10, 30, or 60 beads (each bead contains 7.5 mg gentamicin sulfate)

[3] Available at https://www.unicef.org/supply/index_27009.html

It is important to note that the WHO EMLc recommends gentamicin injection 10 mg/mL and 40 mg/mL (as sulfate) in 2-mL vial for the treatment of community-acquired pneumonia (severe), complicated severe acute malnutrition, and sepsis in neonates and children. Therefore, the procurement agency must focus on procurement of those presentations as per the WHO EMLs.

STORAGE, STABILITY, AND DEGRADATION

Gentamicin injection is stable at room temperature and does not require cold chain storage.

Shelf life: 2–4 years, depending on the manufacturer. It is recommended to check the product label before use.

Storage conditions: Do not store above 25°C. Do not refrigerate or freeze. Protect from light.

The shelf life and storage condition of each SRA-approved product can be found in Table G-1.

PRODUCT SPECIFICATIONS

The product must meet pharmacopoeial specifications, such as those of the US Pharmacopoeia and British Pharmacopoeia, depending on the quality assurance policy of the procurement agency, or the equivalent thereof. The testing parameters and acceptance criteria of the two pharmacopoeias are similar, except the assay limits and the composition of gentamicin sulfate (required only in the BP).

Table G-2. US Pharmacopoeia Specifications for Gentamicin

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification (TLC)	The intensities and Rf values of the three principal spots obtained from the test solution correspond to those obtained from the standard solution.	USP<621>
pH	3.0–5.5	USP<791>
Assay	90.0–125.0%	USP<81>
Bacterial endotoxins	Not more than 0.71 USP endotoxin unit/mg of gentamicin	USP<85>
Particulate matter	Meet the requirements for small-volume injections	USP<788>
Extractable volume	Comply	USP<1>
Sterility	Sterile	USP<71>

Table G-3. British Pharmacopoeia Specifications for Gentamicin

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Appearance	Clear, colorless solution, free from visible particulate matter	Visual inspection
Identification a) TLC	The three principal spots in the chromatogram obtained with solution (1) correspond to the three principal spots in the chromatogram obtained with solution (2).	Appendix III A
Identification b) Liquid chromatography	The retention times of the four principal peaks in the chromatogram obtained with solution (1) correspond to those of the four principal peaks in the chromatogram obtained with solution (2).	Appendix III D
pH	3.0–5.5	Appendix V L
Assay	The precision of the assay is such that the fiducial limits of error are not less than 95% and not more than 105% of the estimated potency. Calculate the content of gentamicin in the injection taking each 1,000 IU found to be equivalent to 1 mg of gentamicin. The upper fiducial limit of error is not less than 97.0% and the lower fiducial limit of error is not more than 110.0% of the stated content.	Appendix XI V
Composition of gentamicin sulfate (liquid chromatography)	The proportions are within the following limits: C1 25.0–50.0% C1a' 10.0–35.0% C2 plus C2a' 25.0–55.0%	Appendix III D
Bacterial endotoxins	Below 7.1 IU per mL	Appendix XI C
Sterility	Sterile	Ph.Eur. 2.6.1
Extractable volume	Comply	Ph.Eur. 2.9.17
Particulate matter	Comply	Ph.Eur. 2.9.19

GENTAMICIN ANNEX

PART 1: CLINICAL PARTICULARS

Therapeutic indications

Gentamicin is a first-line treatment for community acquired pneumonia (severe), complicated severe acute malnutrition, and sepsis in neonates and children.

Gentamicin injection is also indicated in urinary tract infections, chest infections, bacteremia, septicemia, severe neonatal infections, and other systemic infections due to sensitive organisms.

Posology, method, and duration of administration

Pneumonia[1]

Neonatal pneumonia

- 2.5 mg/kg IV every 8 hours (neonates <7 days: 2.5 mg/kg IV every 12 hours), together with amoxicillin 30 mg/kg IV every 12 hours for a total of at least 5 days

Pneumonia due to Staphylococcus aureus in children age 2 months–5 years

- 7.5 mg/kg IV in 1–3 divided doses daily, together with cloxacillin 25–50 mg/kg (maximum 2 g) orally every 6 hours for at least 3 weeks

Pneumonia in adults and children > 5 years

- Hospitalized patients
  - Adults: 5–7 mg/kg IV daily in divided doses, together with benzylpenicillin 2 million IU IV or IM every 4–6 hours for 7 days.
  - Children > 5 years: 7.5 mg/kg IV in 1–3 divided doses daily, together with benzylpenicillin 50,000–100,000 IU/kg (maximum 2 million IU) IV or IM every 4–6 hours for 7 days
- Patients with *atypical pneumonia* should *also* receive erythromycin 1 g (children: 10 mg/kg; maximum 1 g) IV every 6 hours for 14 days

Nosocomial pneumonia

- Adults: 5–7 mg/kg IV daily in divided doses for 7 days, supplemented by either cloxacillin 1–2 g IV every 6 hours or ceftazidime 1 g IV every 8 hours
- Children: 7.5 mg/kg IV in 1–3 divided doses daily for 7 days, supplemented by either cloxacillin 50 mg/kg (maximum 2 g) IV every 6 hours or ceftazidime 25 mg/kg (maximum 1 g) IV every 8 hours

[1] World Health Organization. 2001. *WHO Model Prescribing Information: Drugs used in Bacterial Infections*. Geneva: WHO. Available at http://apps.who.int/medicinedocs/en/d/Js5406e/16.19.html#Js5406e.16.19.

- In hospitals with a high prevalence of meticillin-resistant *Staphylococcus aureus*, vancomycin 1 g (children: 20mg/kg; maximum 1 g) IV every 12 hours for 10–14 days should be added to the above regimens.

Neonatal sepsis[2]

Gentamicin is delivered IV or by IM injection. The dosage of gentamicin is calculated based on patient weight to ensure the appropriate serum concentrations are obtained for safety and efficacy of the drug. Gentamicin has a narrow treatment window and incorrect usage can cause toxicity to the ears, kidneys, and neurological system. The recommended dose range for treatment of neonates is a total of–7.5 mg/kg/day, with one to three doses per day for seven to ten days. The WHO-recommended weight bands of gentamicin for inpatient treatment are summarized below.

WHO Recommended Gentamicin for Inpatient Treatment
(All doses to be drawn from a 10 mg/ml stock concentration)

INFANT WEIGHT	LOW BIRTH WEIGHT, FIRST WEEK OF LIFE (3 MG/KG IM OR IV ONCE DAILY)	NORMAL BIRTH WEIGHT, FIRST WEEK OF LIFE (5 MG/KG IM OR IV ONCE DAILY)	WEEKS 2–4 OF LIFE (7.5 MG/KG IM OR IV ONCE DAILY)
1 ≤1.5 kg	0.3–.5 mL	—	0.75–1.1 mL
1.5 ≤ 2 kg	0.5–0.6 mL	—	1.1–1.5 mL
2 ≤ 2.5 kg	0.6–0.75 mL	—	1.5–1.8 mL
2.5 ≤ 3 kg	—	1.25–1.5 mL	1.8–2.2 mL
3 ≤ 3.5 kg	—	1.5–1.75 mL	2.2–2. 6 mL
3.5 ≤ 4 kg	—	1.75–2.0 mL	2.6–3.0 mL
4 ≤ 4.5 kg	—	2.0–2.25 mL	2.0–3.3 mL

Other infections

Adults

- Serious infections: If renal function is not impaired, 5mg/kg/daily in divided doses at 6- or 8-hourly intervals. The total daily dose may be subsequently increased or decreased as clinically indicated.
- Systemic infections: If renal function is not impaired, 3–5 mg/kg/day in divided doses according to severity of infection, adjusting according to clinical response and body weight.
- Urinary tract infections: As for "Systemic infections," above. Or, if renal function is not impaired, 160 mg once daily may be used.

[2] PATH. 2015. *Gentamicin for Treatment of Neonatal Sepsis: A Landscape of Formulation, Packaging, and Delivery Alternatives.* Available at https://path.org/resources/gentamicin-for-treatment-of-neonatal-sepsisa-landscape-of-formulation-packaging-and-delivery-alternatives/

Pediatric patients

- The daily dose recommended in children aged 1 year and above and adolescents with normal renal function, is 3–6 mg/kg body weight per day as 1 (preferred) up to 2 single doses.
- The daily dose in infants after the first month of life is 4.5–7.5 mg/kg body weight per day as 1 (preferred) up to 2 single doses.
- The daily dose in neonates and preterm infants (aged 0–4 weeks old) is 4–7 mg/kg body weight per day. Due to the longer half-life, newborns are given the required daily dose in 1 single dose.

The elderly

- There is some evidence that elderly patients may be more susceptible to aminoglycoside toxicity, whether secondary to previous eighth-nerve impairment or to borderline renal dysfunction. Accordingly, therapy should be closely monitored by frequent determination of gentamicin serum levels, assessment of renal function, and signs of ototoxicity.

Renal impairment

- In impaired renal function, the recommended daily dose must be decreased and adjusted according to renal function.
- Gentamicin is excreted by simple glomerular filtration; therefore a reduced dosage is necessary where renal function is impaired.

Contraindications

Hypersensitivity to the gentamicin or to any of the excipients, pregnancy, and myasthenia gravis.

Special warnings and precautions for use

To avoid adverse events, continuous monitoring (before, during and after) of renal function (serum creatinine, creatinine clearance), control of function of vestibule and cochlea, and hepatic and laboratory parameters is recommended.

Ototoxicity has been recorded following the use of gentamicin. Groups at special risk include patients with impaired renal function, infants, and possibly the elderly. Consequently, renal, auditory, and vestibular functions should be monitored in these patients and serum levels determined so as to avoid peak concentrations above 10 mg/L and troughs above 2 mg/L when administering gentamicin twice daily and 1 mg/L for a once-daily dose. As there is some evidence that risk of both ototoxicity and nephrotoxicity is related to the level of total exposure, duration of therapy should be the shortest possible compatible with clinical recovery. In some patients with impaired renal function, there has been a transient rise in blood urea nitrogen, which has usually reverted to normal during or following cessation of therapy. It is important to adjust the frequency of dosing according to the degree of renal function.

Gentamicin should be used in pregnancy only if considered essential by the physician (see section 1.6 of this annex, "Pregnancy and lactation").

Gentamicin should be used with care in conditions characterized by muscular weakness.

In cases of significant obesity gentamicin serum concentrations should be closely monitored and a reduction in dose should be considered.

Interaction with other medicinal products and other forms of interaction

Concurrent administration of gentamicin and other potentially ototoxic or nephrotoxic drugs should be avoided. Potent diuretics such as etacrynic acid and furosemide are believed to enhance the risk of ototoxicity, and amphotericin B, cisplatin and ciclosporin are potential enhancers of nephrotoxicity.

Any potential nephrotoxicity of cephalosporins, and in particular cephaloridine, may also be increased in the presence of gentamicin. Consequently, if this combination is used, monitoring of renal function is advised.

Neuromuscular blockade and respiratory paralysis have been reported from administration of aminoglycosides to patients who have received curare-type muscle relaxants during anesthesia.

Indomethacin possibly increases plasma concentrations of gentamicin in neonates.

Concurrent use with oral anticoagulants may increase the hypothrombinanemic effect.

Concurrent use of bisphosphonates may increase the risk of hypocalcemia.

Concurrent use of the botulinum toxin and gentamicin may increase the risk of toxicity due to enhanced neuromuscular block.

Antagonism of effect may occur with concomitant administration of gentamicin with either neostigmine or pyridostigmine.

Pregnancy and lactation

There are no proven cases of intrauterine damage caused by gentamicin. However, in common with most drugs known to cross the placenta, usage in pregnancy should be considered only in life-threatening situations where expected benefits outweigh possible risks. In the absence of gastrointestinal inflammation, the amount of gentamicin ingested from the milk is unlikely to result in significant blood levels in breast-fed infants.

Effects on ability to drive and use machines

Not known.

Undesirable effects

Side effects include vestibular damage or hearing loss, particularly after exposure to ototoxic drugs or in the presence of renal dysfunction. Nephrotoxicity (usually reversible) and acute renal failure, hypersensitivity, anemia, blood dycrasias, purpura, stomatitis, convulsions, and effects on liver function occur occasionally.

Rarely, hypomagnesiemia on prolonged therapy and antibiotic–associated colitis have been reported.

Nausea, vomiting, and rash have also been reported.

Central neurotoxicity, including encephalopathy, confusion, lethargy, mental depression, and hallucinations, has been reported in association with gentamicin therapy but is extremely rare.

Peripheral neuropathy: frequency not known.

Overdose

Hemodialysis and peritoneal dialysis will aid removal from the blood, but the former is probably more efficient. Calcium salts given intravenously have been used to counter the neuromuscular blockade caused by gentamicin.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies that plan to perform a full prequalification of gentamicin injection products. When assessing the complete quality/CMC documentation, assessors should consider the following particular information on gentamicin injection.

API

Gentamicin is not included in the WHO PQP. Therefore no WHO-prequalified gentamicin API exists.

Only two manufacturers of gentamicin sulfate API have obtained the certificate of suitability to monographs of the European Pharmacopoeia (CEP), confirming its suitable quality for use in medicinal product.

Manufacturers of Gentamicin API with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Gentamicin sulfate (monograph number 331)	LEK Pharmaceuticals D.D. SI 1526 Ljubljana, Slovenia	R1-CEP 2005-121-Rev 01	2/3/2016	Chemistry
Gentamicin sulfate (monograph number 331)	Fujian Fukang Pharmaceutical Co, Ltd, CN 350 002 Fuzhou, China	R1-CEP 1998-155-Rev 08	10/20/2017	Chemistry

Other manufacturers of gentamicin API should provide evidence for GMP compliance and API quality documentation as per WHO guidelines.[3]

Gentamicin API must meet pharmacopoeia specifications such as those of the International Pharmacopoeia, European Pharmacopoeia, and US Pharmacopoeia, depending on the quality assurance policy of the procurement agency, or the equivalent thereof.

[3] World Health Organization. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. 46h report. WHO Technical Report Series, No. 970. Geneva: WHO.

Excipients

The typical excipients of gentamicin injection include sodium chloride, water for injection, and sulfuric acid and/or sodium hydroxide, for pH adjustment. There are no special concerns on the excipients. No excipient with the risk of transmitting TSE/BSE is used.

The quality of all excipients should be compliant with recognized pharmacopoeias (Ph.Int., Ph.Eur./BP, or USP).

Some formulations may contain methylparaben and propylparaben as preservatives when the product is intended for multiple-dose use. Where methylparaben and propylparaben are included in the formulation antimicrobial preservatives, their assays (preservative contents) should be included in the FPP specifications. If the lower limit for the proposed acceptance criterion for the assay of parabens is below 90.0%, its effectiveness should be established by appropriate studies (e.g., USP or Ph.Eur. general chapters on antimicrobial preservatives) using a batch of the FPP containing a concentration of methylparaben and propylparaben corresponding to the lower proposed acceptance criterion.

Where sodium metabisulfite is included in the formulation as an antioxidant, the effectiveness of the proposed concentration should be justified and verified by appropriate studies.

Manufacturing process

Gentamicin injection is a straightforward drug to manufacture, but the main quality concern is the sterilization process together with the sterility of the facility where it is made.

The manufacturing process of gentamicin injection is a standard process—conducted under appropriate aseptic conditions—including the steps of preparation of the solution with adjustment of pH, prefiltration and sterile filtration, and filling and sealing of the ampoules. Satisfactory operating parameters and in-process controls should be defined at each stage of manufacturing.

The filters used in sterile filtration should be validated with respect to pore size, compatibility with the product, absence of extractables, and lack of adsorption of the API or any of the components. The headspace of the vials should be replaced with nitrogen during the filling process to prevent oxidation of the API.

A manufacturing process validation protocol for the validation of the first three production-scale batches should be submitted. In addition, completed process validation reports for the sterile processes for three cycles/runs should be submitted. If the manufacturer is already manufacturing production-scale batches, the full validation data for the production of at least three (3) consecutive production-scale batches should be submitted.

Packaging

Neutral type I glass vials should be used.

Suitability of container should be demonstrated, including the following properties:

Safety

- Glass vials must meet compendial requirements such as USP<660> and USP<1660>.

- Rubber stoppers must meet compendial requirements such as USP<381> and USP<87>/<88>. Composition of the rubber stopper along with a declaration from the supplier that the material is free of 2-mercapto benzothiazoles (2-MCBT) and nitrosamines should be provided.
- Washing and sterilization/depyrogenation, if applicable, should be supported by process validation data.

Protection

- Container integrity regarding microbial contamination should be demonstrated by microbial or dye ingress or other methods:
  - One-time test reported as part of product development
  - Routine leak testing performed as part of product manufacture

Compatibility

- Extractables/leachables data of the rubber stoppers should be provided.
- Accelerated and long-term stability data on vials stored in inverted orientation should be submitted to further support absence of leachables as well as sorption.
- Compatibility of the FPP with diluents (such as 5% dextrose injection or 0.9% sodium chloride as per the label instruction), if relevant, over the proposed dilution range (label) in specified containers may also need to be demonstrated.

Bioequivalence requirements

A biowaiver can be requested as per WHO Technical Report Series, No. 992, which indicates that no bioequivalence study is necessary when the pharmaceutical product is to be administered parenterally (e.g., intravenously, subcutaneously, or intramuscularly) as an aqueous solution containing the same API in the same molar concentration as the comparator product and with the same or similar excipients in comparable concentrations as in the comparator product.

Appropriate comparator products are Cidomycin® (gentamicin injection 80 mg/2 mL solution for injection 40 mg/mL, Sanofi-Aventis), gentamicin sulfate injection 10 mg/mL, 40 mg/mL (Fresenius Kabi, USA), and gentamicin sulfate injection 10 mg/mL, 40 mg/mL (Hospira, USA). The composition of the proposed product should be the same as the comparator product.