STUDY TITLE

PDE DETERMINATION FOR BENZYL PENICILLIN

CONTENTS

2. HAZARDS IDENTIFIED

Hazards	Yes	No	Unknown
Genotoxicant	--	X	--
Reproductive & Developmental Toxicant	--	X	--
Carcinogen	--	X	--
Sensitizing Potential	--	X	--

Since penicillin G potassium and Penicillin V potassium contain the same active moiety, the NOAEL defined for Penicillin V potassium, is applicable to Benzylpenicillin(Penicillin G).

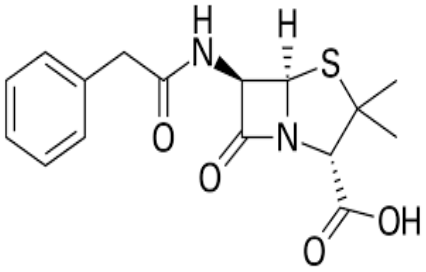
Genotoxicity studies conducted in bacteria, animal cell lines and animals have shown negative results. Whereas as shown an increase in micronucleus in mouse bone marrow at higher doses (600x). Based on the weight of evidence, Benzylpenicillin has got no propencity to elicit genotoxic response in human. Hence the benzylpenicillin can be classified as non-genotoxicant.

There is no reproductive and developmental study data available for benzyl penicillin in animal studies. Human experience with penicillins during pregnancy has not shown any positive evidence of adverse effects on the fetus. Humans treated with penicillin may experience Jarisch-Herxheimer reaction that induces early labor or cause fetal distress in pregnant women. Penicillins are excreted in human breast milk. Unless the infant is allergic to penicillins, breast-feeding is generally safe during maternal penicillin G therapy. Penicillins may cause diarrhea, candidiasis, and skin rash in the breast-feeding infant. The infant should be observed for potential effects.The pregnant women & human pregnancy category is 'B'(US FDA). Taking both animal & human data and based on the weight of evidence, Benzylpenicillin is not considered to be a reproductive & developmental toxicant.

Based on animal data, no carcinogenesis has been induced by benzyl penicillin. No information on long-term studies is available on the carcinogenesis, mutagenesis, or the impairment of fertility with the use of penicillins in human. Benzylpenicillin is a non-genotoxicant & not listed as a carcinogen by international agencies, hence is not classified as a carcinogen.

No animal high sensitizing potential data available for Benzylpenicillin. Penicillin is a substance of low toxicity but does have a significant index of sensitization. In humans, Benzyl penicillin may cause an allergic skin reaction, and allergy or asthma symptoms or breathing difficulties if inhaled. Adverse effects were reported only in a subset of population. Therefore, Benzylpencilln is not considered to possess sensitizing potential.

3. SUMMARY

Drug Name	Benzyl penicillin; *PubChem [CID 5904]*
Synonym	Penicillin G[5,6].
Dosage Form	Parenteral (IV/IM)
PDE – Adult	2.604mg/day
PDE –Paediatric	0.521mg/day
NOAEL Considered for PDE Calculations	250mg/kg/day for mice established in 13-week repeated dose toxicity study (section 6.2).
Justification	1. Selected NOAEL derived for mice from 13-week repeated dose toxicity study. 2. Gives lowest PDE value.
CAS Number	61-33-6; *[European Chemicals Agency (ECHA)]*
Molecular Formula	$C_{16}H_{18}N_2O_4S$; *PubChem [CID 5904]*
Molecular Weight	334.49g/mole; *PubChem [CID 5904]*
Structure	 *; PubChem [CID 5904]*
Drug Indication	For use in the treatment of severe infections caused by penicillin G-susceptible microorganisms when rapid and high penicillin levels are required such as in the treatment of septicemia, meningitis, pericarditis, endocarditis, and severe pneumonia[6].
Solubility Profile	Slightly soluble in water[6].

4. OBJECTIVE

To determine the health-based exposure limits for the residual active substance Benzyl penicillin, based on the calculation of the Permitted Daily Exposure (PDE). The calculated dose as per this document represents that Benzyl penicillin is unlikely to cause any adverse effect if an individual is exposed, by any route, at or below the calculated dose level every day for the lifetime.

5. INTRODUCTION

Benzylpenicillin (Penicillin G) is narrow spectrum antibiotic used to treat infections caused by susceptible bacteria. It is a natural penicillin antibiotic that is administered intravenously or intramuscularly due to poor oral absorption. Penicillin G may also be used in some cases as prophylaxis against susceptible organisms. Natural penicillins are considered the drugs of choice for several infections caused by susceptible gram-positive aerobic organisms, such as *Streptococcus pneumoniae*, groups A, B, C and G streptococci, nonenterococcal group D streptococci, *viridans* group streptococci, and non-penicillinase producing staphylococcus. Aminoglycosides may be added for synergy against group B streptococcus (*S. agalactiae*), *S. viridans*, and *Enterococcus faecalis*. The natural penicillins may also be used as first or second line agents against susceptible gram-positive aerobic bacilli such as *Bacillus anthracis, Corynebacterium diphtheriae, and Erysipelothrix rhusiopathiae*. Natural penicillins have limited activity against gram negative organisms; however, they may be used in some cases to treat infections caused by *Neisseria meningitidis* and *Pasteurella*. They are not generally used to treat anaerobic infections. Resistance patterns, susceptibility and treatment guidelines vary across regions[5,6].

Permitted Daily Exposure (PDE) represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime. The definition for the PDE is based on (1) the International Society for Pharmaceutical Engineering (ISPE) under their document entitled "Risk-Based Manufacture of Pharmaceutical Products (Risk MaPP)"[1] and (2) European Medicines Agency "Guideline on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities"[2]. Furthermore, this document is prepared as per the 'Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities' Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-Operation Scheme, Inspection of Health-Based exposure limit (HBEL) Assessments and Use in Quality Risk Management, June 2020.

6. NON-CLINICAL STUDIES

6.1 ACUTE TOXICANT

Oral LD_{50} (rat): 8gm/kg; Oral LD_{50} (mice): >5gm/kg; Intraperitoneal LD_{50} (mice): 3500mg/kg; Intravenous LD_{50} (mice): 329mg/kg; Intracerebral LD_{50} (mice): 5700µ/kg; Intracerebral LD_{50} (dog): 1118µg/kg; Intracerebral LD_{50} (Rabbit): 653µ/kg; Oral LD_{50} (Hamster): 24mg/kg; Subcutaneous LD_{50} (Hamster): 96mg/kg[5].

Oral LD^{50} in rat is 8900 mg/kg. Neurological adverse reactions, including convulsions, may occur with the attainment of high CSF levels of beta-lactams. Neutropenia can occur if high doses are administered consistently for over 2 weeks[6].

The acute intraperitoneal toxicity study for calculating Benzyl penicillin G LD^{50} was carried out according to the OECD423 guideline and Kaber's method with modification. The doses of BPHCT used in oral and intraperitoneal acute tests were calculated according to the original concentration of BPG solution (480 mg 129 mL^{-1}). Mice were administered by gavage with the doses of 5 mg kg^{-1}, 50 mg kg^{-1}, 500 130 mg kg^{-1}, 1000 mg kg^{-1}, 1500 mg kg^{-1}, 2000 mg kg^{-1} and 5000 mg kg^{-1} or injected intraperitoneally with a dose level of 648.00 mg kg^{-1}, 777.60 mg kg^{-1}, 933.12 mg kg^{-1}, 1119.74 mg kg^{-1} and 1343.69 mg kg^{-1} of BPHCT. The negative control groups were given a 0.9% normal saline solution. After 14 days observation, mortality caused by oral administration or intraperitoneal injection was calculated. The surviving mice were sacrificed for organ necropsy[11]. There was no mortality found in the oral toxicity test. Regarding observational studies, mice exhibited static, huddled up behaviour, and showed asthenia. Interestingly, mice preferred water to food in the first hour and these clinical symptoms would last for a few hours and disappear before the following day, which was correlated in a dose-dependent manner. **A dose level of 1000 mg kg-1 was established as the no-observed-adverse-effect level (NOAEL), while the lowest-observed-adverse-effect level (LOAEL) was 1500 mg kg-1 for the Benzyl penicillin G acute oral toxicity.** In the acute intraperitoneal toxicity, the symptoms of BPHCT injected mice were similar with those in the acute oral toxicity study, but some mice in the high dose group had also showed dyspnoeic symptoms or shock. The calculated LD^{50} value was 933.04 mg kg-1 [b.w.] and the 95% confidence intervals were 856.72-1016.15 mg kg^{-1}. [11]

6.2 REPEATED DOSE TOXICANT

In chronic toxicity study of Benzylpenicilln G, a total of 80 mice were randomly allocated into 4 groups (10 females and 10 males 146 per group) and five mice were housed in each cage under the same conditions as described above. All mice were fed with the experimental diets every day. The weight of experimental diets provided was calculated based on the mice body weight. If the experimental diets were completely consumed before the end of a day, the normal diet would be supplied without restriction for the rest of the day. During the 6 months test period, body weight of mice was measured every 3 days in the first month and weekly during the rest of the study period[11].

Of the cohort, one female mouse and one male mouse were found crawling in circles around the cage continuously in the 60× and 600× dose group after 2 months feeding; this symptom lasted two weeks in the mouse in the 60× dose group, while it occurred in the mouse in the 600× dose group intermittently for the rest of the test. Mice in 600×dose group seemed abnormally active. At the end phase of the study, there was not a single mouse found to be dead due to drug induced toxicity. The was a significant decrease in body weight in the female test mice compared with those in the control group. In the male mice, the decreased body weight was only found in the 600× dose group while increased body weight was found in the 6× and 60× dose groups compared with those in the control group[11].

Since penicillin G potassium and Penicillin V potassium contain the same active moiety, the NOAEL defined for Penicillin V potassium, is applicable to Benzylpenicillin(Penicillin G). A 14-day repeated dose toxicity was conducted in rat through oral route, **2400mg/kg/day** was the **NOAEL** obtained for Penicillin V potassium [12].

A 14-day repeated dose toxicity was conducted in mice through oral route, **2400mg/kg/day** was the **NOAEL** obtained for Penicillin V potassium [12].

A 13-week repeated dose toxicity was conducted in rat through oral route, **750mg/kg/day** was the **LOAEL** obtained for Penicillin V potassium. Gastrointestinal system was the targeted organ[12].

A 13-week repeated dose toxicity was conducted in mice through oral route, **250mg/kg/day** was the **LOAEL** obtained for Penicillin V potassium. Gastrointestinal system was the targeted organ[12].

6.3 GENOTOXICANT

In polychromatic erythrocyte micronucleus formation assay done in femurs from female mice were observed using light microscope. Compared with the control group of (Benzyl penicillin G), no statistically significant increase in the micronucleus formation was observed in mice feed with experimental diets in 6× and 60× dose of BPHCT for 6 months. However, the rate of micronucleus formation was readily increased in the 600× dose BPHCT group compared with those in the control group[11].

Penicillin V potassium is negative *in vitro* bacterial mutagenicity (Ames test). It is positive with activation in *in vitro* cell transformation assay done in mouse lymphoma. Penicillin V potassium is positive without activation and negative with activation in sister chromatid exchange done in Chinese hamster ovary (CHO) cells.

6.4 REPRODUCTIVE AND DEVELOPMENTAL TOXICANT

In sperm aberration assay of Benzyl penicillin G, the epididymides from male mice were cut into pieces in PBS (pH 7.2) and smears were prepared. Several sperm abnormalities including hookless and amorphous were observed with a high frequency in the 60× and 600× dose groups, and at a lower frequency in the 6×dose group administered with BPHCT residue in HAFP orally for 6 months[11].

6.5 CARCINOGEN

A 2-year carcinogenicity was conducted in rat through oral route, **1000mg/kg/day** was the **NOAEL** obtained for Penicillin V potassium and no carcinogenic was reported[12].

A 2-year carcinogenicity was conducted in mice through oral route, **1000mg/kg/day** was the **NOAEL** obtained for Penicillin V potassium and no carcinogenic was reported[12].

6.6 SENSITIZING POTENTIAL

No pre-clinical data available.

7. PHARMACOLOGY

7.1 PHARMACODYNAMICS

Benzyl penicillin is a penicillin beta-lactam antibiotic used in the treatment of bacterial infections caused by susceptible, usually gram-positive, organisms. The name "penicillin" can either refer to several variants of penicillin available, or to the group of antibiotics derived from the penicillins. Penicillin G has in vitro activity against gram-positive and gram-negative aerobic and anaerobic bacteria. The bactericidal activity of penicillin G results from the inhibition of cell wall synthesis and is mediated through penicillin G binding to penicillin binding proteins (PBPs). Penicillin G is stable against hydrolysis by a variety of beta-lactamases, including penicillinases, and cephalosporinases and extended spectrum beta-lactamases[6].

Mechanism of action: By binding to specific penicillin-binding proteins (PBPs) located inside the bacterial cell wall, Benzyl penicillin inhibits the third and last stage of bacterial cell wall synthesis. Cell lysis is then mediated by bacterial cell wall autolytic enzymes such as autolysins; it is possible that penicillin G interferes with an autolysin inhibitor[6].

7.2 PHARMACOKINETICS

Pharmacokinetics describes how the body affects a specific xenobiotic/chemical after administration through the mechanisms of absorption and distribution, as well as the metabolic changes of the substance in the body and its excretion.

7.2.1 ABSORPTION

Rapidly absorbed following both intramuscular and subcutaneous injection. Initial blood levels following parenteral administration are high but transient. Oral absorption in fasting, healthy humans is only about 15-30% as it is very susceptible to acid-catalyzed hydrolysis[6].

When given intravenously, the drug is rapidly absorbed into blood stream, and its effect is immediate. When given intramuscularly, the absorption is slower, and the peak concentration is reached after 30 to 60 minutes. The bioavailability of benzylpenicillin after IM is approximately 37% to 76%[10].

7.2.2 DISTRIBUTION

Volume of distribution is 0.53–0.67 L/kg in adults with normal renal function. Bind to serum proteins (45-68%), mainly albumin[6].

After absorption, benzylpenicillin is distributed throughout the body. It has a low protein binding capacity, which allows it to penetrate into tissues and organs. It can also cross the blood-brain barrier, allowing it to reach the central nervous system. The volume of distribution of benzylpenicillin is around 0.3 to 0.4L/Kg[10].

7.2.3 METABOLISM

About 16-30% of an intramuscular dose is metabolized to penicilloic acid, an inactive metabolite. Small amounts of 6-aminopenicillanic acid have been recovered in the urine of patients on penicillin G. A small percentage of the drug appears to be hydroxylated into one or more active metabolites, which are also excreted via urine[6].

7.2.4 ELIMINATION

Benzyl penicillin is eliminated by the kidneys. Nonrenal clearance includes hepatic metabolism and, to a lesser extent, biliary excretion. In adults with normal renal function is reportedly 0.4–0.9 hours. Clearnce of benzyl penicillin is 560ml/min in healthy humans[6].

8. HUMAN STUDIES

8.1 THERAPEUTIC DOSAGE

Strength:

Injectable solution: 300000 units/mL, 600000 units/mL, 1.2 million units/mL, 2.4 million units/mL, and 5 million units/mL[10].

Strength of Penicillin G potassium [7]

- Intravenous Injection solution-50ml, 1000000U, 2000000U, 3000000U
- Intravenous Inj Pwd F/sol- 5000000U, 20000000U.
- Intramuscular Inj Pwd F/Sol- 5000000U, 20000000U.
- Intrapleural Inj Pwd F/Sol- 5000000U, 20000000U
- Intrathecal Inj Pwd F/Sol: 5000000U, 20000000U

Maximum Dosage:

Since penicillin G potassium and Penicillin V potassium contain the same active moiety, the data defined for Penicillin G potassium, is applicable to Benzylpenicillin(Penicillin G). The maximum dosage limit of penicillin G potassium are:

- **Adults:** 24 million units/day IV/IM is FDA-approved maximum; up to 30 million units/day IV/IM has been used off-label.
- **Geriatric:** 24 million units/day IV/IM is FDA-approved maximum; up to 30 million units/day IV/IM has been used off-label.
- **Paediatric:**
  - **Adolescents:** 300,000 units/kg/day IV/IM (Max: 24 million units/day) is FDA-approved maximum; up to 400,000 units/kg/day IV/IM (Max: 24 million units/day) has been used off-label.
  - **Children:** 300,000 units/kg/day IV/IM (Max: 24 million units/day) is FDA-approved maximum; up to 400,000 units/kg/day IV/IM (Max: 24 million units/day) has been used off-label.
  - **Infants:** 300,000 units/kg/day IV/IM is FDA-approved maximum; up to 400,000 units/kg/day IV/IM has been used off-label

Adult Dosage:

- **For Bacterial endocarditis – Intravenous:** 7.2-12 g or more, given daily in divided doses[8].
- **For Intrapartum prophylaxis against group B streptococcal infection in neonates- Intravenous:** Initially, 3 g, then 1.5 g 4 hrly until delivery[8].
- **For Meningococcal meningitis, Pneumococcal meningitis- Intravenous:** 2.4 g 4 hrly. Max: 18 g/day in meningococcal meningitis. Doses >1.2 g should be given at a rate not more than 300 mg/min[8].
- **For Susceptible infections- Parenteral:** 0.6-3.6 g daily in 4-6 divided doses, via IM, slow IV inj or infusion. Higher doses may be needed in more serious infections. IV doses >1.2 g should be given at a rate not more than 300 mg/min[8].

The adult dosage limit of penicillin G potassium are:

- **For the treatment of *streptococcal bacteremia* or pleural empyema- Intravenous or Intramuscular dosage:** Adults: 12 to 24 million units/day IV or IM divided every 4 to 6 hours.
- **For the treatment of *staphylococcal bacteremia* or pleural empyema- Intravenous or Intramuscular dosage:** Adults: 5 to 24 million units/day IV or IM divided every 4 to 6 hours.
- **For the treatment of meningococcal bacteremia: Intravenous or Intramuscular dosage:** Adults: 24 million units/day IV or IM divided every 2 hours.
- **For the treatment of bacteremia due to Pasteurella multocida- Intravenous or Intramuscular dosage:** Adults: 4 to 6 million units/day IV or IM divided every 4 to 6 hours for 2 weeks

- **For the treatment of botulism as adjunctive therapy to antitoxin- Intravenous or Intramuscular dosage:** Adults: 20 million units/day IV or IM in divided doses every 4 to 6 hours.
- **For the treatment of gas gangrene- Intravenous or Intramuscular dosage:** Adults: 2 to 4 million units IV every 4 to 6 hours. Alternatively, 20 million units/day IV or IM in divided doses every 4 to 6 hours. Penicillin plus clindamycin is recommended for necrotizing clostridial infections.
- **For the treatment of tetanus as adjunctive therapy to tetanus immune globulin : Intravenous or Intramuscular dosage:** Adults: 20 million units/day IV or IM in divided doses every 4 to 6 hours for 7 to 10 days.
- **For the treatment of inhalation anthrax infection caused by susceptible strains of Bacillus anthracis- Intravenous dosage:** Adults: 4 million units IV every 4 hours. Total treatment is for 60 days: switch to oral antibiotics as soon as clinically possible. Postexposure vaccination might permit the treatment duration to be shortened to 30-45 days, with concomitant administration of the anthrax vaccine at weeks 0, 2, and 4. The manufacturer recommends a minimum of 5-8 million units/day IV divided every 6 hours.
- **For the treatment of native valve endocarditis due to highly susceptible viridans group streptococci and nonenterococcal group D streptococci- Intravenous or Intramuscular dosage:** Adults: 12 to 18 million units/day IV divided every 4 to 6 hours or as a continuous IV infusion for 4 weeks as monotherapy or for 2 weeks plus gentamicin. The FDA-approved dose is 12 to 24 million units/day IV or IM divided every 4 to 6 hours.
- **For the treatment of native valve endocarditis due to relatively resistant viridans group streptococci and nonenterococcal group D streptococci- Intravenous or Intramuscular dosage:** Adults: 24 million units/day IV divided every 4 to 6 hours or as a continuous IV infusion for 4 weeks plus gentamicin for 2 weeks. The FDA-approved dose is 12 to 24 million units/day IV or IM divided every 4 to 6 hours.
- **For the treatment of native valve endocarditis due to group B, C, F, and G streptococci- Intravenous or Intramuscular dosage:** Adults: 24 million units/day IV divided every 4 to 6 hours or as a continuous IV infusion for 4 to 6 weeks plus gentamicin for at least 2 weeks. The FDA-approved dose is 12 to 24 million units/day IV or IM divided every 4 to 6 hours.
- **For the treatment of native valve endocarditis due to highly susceptible S. pneumoniae- Intravenous or Intramuscular dosage:** Adults: 12 to 18 million units/day IV divided every 4 to 6 hours or as a continuous IV infusion for 4 weeks. The FDA-approved dose is 12 to 24 million units/day IV or IM divided every 4 to 6 hours.
- **For the treatment of native valve endocarditis due to intermediate or highly penicillin-resistant *S. pneumoniae*- Intravenous or Intramuscular dosage:** Adults: 24 million units/day IV divided every 4 to 6 hours or as a continuous IV infusion for 4 weeks. The FDA-approved dose is 12 to 24 million units/day IV or IM divided every 4 to 6 hours.
- **For the treatment of native valve endocarditis due to *S. pyogenes*: Intravenous or Intramuscular dosage:** Adults: 24 million units/day IV divided every 4 to 6 hours or as a continuous IV infusion for 4 to 6 weeks. The FDA-approved dose is 12 to 24 million units/day IV or IM divided every 4 to 6 hours.
- **For the treatment of prosthetic valve endocarditis due to penicillin-susceptible Streptococcus sp- Intravenous or Intramuscular dosage:** Adults: 24 million units/day IV divided every 4 to 6 hours or as a continuous IV infusion for 6 weeks with or without

gentamicin for 2 weeks. The FDA-approved dose is 12 to 24 million units/day IV or IM divided every 4 to 6 hours.

- **For the treatment of prosthetic valve endocarditis due to relatively or fully penicillin-resistant Streptococcus sp- Intravenous or Intramuscular dosage:** Adults: 24 million units/day IV divided every 4 to 6 hours or as a continuous IV infusion for 6 weeks plus gentamicin. The FDA-approved dose is 12 to 24 million units/day IV or IM divided every 4 to 6 hours.
- **For the treatment of native valve endocarditis due to susceptible Staphylococcus sp- Intravenous or Intramuscular dosage:** Adults: Not recommended by guidelines. 5 to 24 million units/day IV or IM divided every 4 to 6 hours.
- **For the treatment of Erysipelothrix endocarditis: - Intravenous or Intramuscular dosage:** Adults: 12 to 20 million units/day IV or IM divided every 4 to 6 hours for 4 to 6 weeks.
- **For the treatment of endocarditis due to Listeria sp- Intravenous or Intramuscular dosage:** Adults: 15 to 20 million units/day IV or IM divided every 4 to 6 hours for 4 weeks.
- **For the treatment of meningococcal meningitis- Intravenous or Intramuscular dosage:** Adults: 24 million units/day IV divided every 4 hours for 7 days. The FDA-approved dose is 24 million units/day IV or IM divided every 2 hours.
- **For the treatment of staphylococcal meningitis- Intravenous or Intramuscular dosage:** Adults: 5 to 24 million units/day IV or IM divided every 4 to 6 hours.
- **For the treatment of beta-hemolytic streptococcal meningitis- Intravenous or Intramuscular dosage:** Adults: 12 to 24 million units/day IV or IM divided every 4 to 6 hours. Treat S. agalactiae with 24 million units/day IV divided every 4 hours for 14 to 21 days; consider the addition of an aminoglycoside.
- **For the treatment of meningitis due to *P. multocida*- Intravenous or Intramuscular dosage:** Adults: 4 to 6 million units/day IV or IM divided every 4 to 6 hours for 14 days.
- **For the treatment of listeriosis - Intravenous or Intramuscular dosage:** Adults: 15 to 20 million units/day IV or IM given in divided doses every 4 to 6 hours. Give for 2 weeks for meningitis and 4 weeks for endocarditis.
- **For the adjunctive treatment of diphtheria and to prevent establishment of carrier state- Intravenous or Intramuscular dosage:** Adults: 2 to 4 million units/day IV or IM divided every 6 hours for 14 days as an adjunct to diphtheria antitoxin.
- **For the treatment of rat-bite fever or Haverhill fever- Intravenous or Intramuscular dosage:** Adults: 12 to 20 million units/day IV or IM divided every 4 to 6 hours for at least 3 to 4 weeks.
- **For the treatment of actinomycosis- Intravenous or Intramuscular dosage:** Adults: 18 to 24 million units/day IV divided every 4 hours for 2 to 6 weeks, followed by oral therapy for 6 to 12 months. Shorter courses may be appropriate for less extensive infections. The FDA-approved dose is 10 to 20 million units/day IV or IM divided every 4 to 6 hours for thoracic/abdominal disease and 1 to 6 million units/day IV or IM divided every 4 to 6 hours for cervicofacial disease.
- **For the treatment of fusospirochetosis or Vincent's infection, including necrotizing ulcerative gingivitis, oropharynx infections, lower respiratory tract infections, and genital infections caused by Fusobacterium sp- Intravenous dosage:** Adults: 5-10 million units/day IV divided every 4-6 hours.

- **For the treatment of pneumonia, including community-acquired pneumonia (CAP)- Intravenous or Intramuscular dosage:** Adults: 5 to 24 million units/day IV or IM divided every 4 to 6 hours.
- **For the treatment of *streptococcal pericarditis*- Intravenous or Intramuscular dosage:** Adults: 12 to 24 million units/day IV or IM divided every 4 to 6 hours.
- **For the treatment of *staphylococcal pericarditis*- Intravenous or Intramuscular dosage:** Adults: 5 to 24 million units/day IV or IM divided every 4 to 6 hours.

Paediatric Dosage:

- **For Meningococcal meningitis, Pneumococcal meningitis- Intravenous:** Newborn infants: 100 mg/kg daily in 2 divided doses; 1-4 wk 150 mg/kg daily in 3 divided doses; >1 mth to 12 yr 180-300 mg/kg daily in 4-6 divided doses[8].
- **For Susceptible infections- Parenteral:** Newborn infants: 50 mg/kg daily in 2 divided doses; 1-4 wk 75 mg/kg daily in 3 divided doses; >1 mth to 12 yr 100 mg/kg daily in divided doses, not exceeding 4 g/day[8].

The paediatric dosage limit of penicillin G potassium are:

- **For the treatment of *streptococcal bacteremia* or pleural empyema- Intravenous or Intramuscular dosage:** Infants, Children, and Adolescents: 100,000 to 300,000 units/kg/day IV or IM divided every 4 to 6 hours (Max: 24 million units/day).
- **For the treatment of *staphylococcal bacteremia* or pleural empyema- Intravenous or Intramuscular dosage:** Infants, Children, and Adolescents: 100,000 to 300,000 units/kg/day IV or IM divided every 4 to 6 hours (Max: 24 million units/day).
- **For the treatment of meningococcal bacteremia: Intravenous or Intramuscular dosage:** Infants, Children, and Adolescents: 100,000 to 300,000 units/kg/day IV or IM divided every 4 to 6 hours (Max: 24 million units/day).
- **For the treatment of native valve endocarditis due to highly susceptible viridans group streptococci and nonenterococcal group D streptococci- Intravenous or Intramuscular dosage:** Infants, Children, and Adolescents: 200,000 to 300,000 units/kg/day (Max: 24 million units/day) IV or IM divided every 4 hours for 4 weeks. The FDA-approved dose is 150,000 to 300,000 units/kg/day IV or IM divided every 4 to 6 hours.
- **For the treatment of native valve endocarditis due to relatively resistant viridans group streptococci and nonenterococcal group D streptococci- Intravenous or Intramuscular dosage:** Infants, Children, and Adolescents: 200,000 to 300,000 units/kg/day (Max: 24 million units/day) IV or IM divided every 4 hours for 4 weeks plus gentamicin for 2 weeks. The FDA-approved dose is 150,000 to 300,000 units/kg/day IV or IM divided every 4 to 6 hours.
- **For the treatment of native valve endocarditis due to group B, C, F, and G streptococci- Intravenous or Intramuscular dosage:** Infants, Children, and Adolescents: 200,000 to 300,000 units/kg/day (Max: 24 million units/day) IV or IM divided every 4 hours for 4 weeks plus gentamicin for 2 weeks for relatively resistant strains. The FDA-approved dose is 150,000 to 300,000 units/kg/day IV or IM divided every 4 to 6 hours.
- **For the treatment of native valve endocarditis due to highly susceptible S. pneumoniae- Intravenous or Intramuscular dosage:** Infants, Children, and Adolescents: Optimal therapy is not established. 150,000 to 300,000 units/kg/day IV or IM divided every 4 to 6 hours.

- **For the treatment of native valve endocarditis due to intermediate or highly penicillin-resistant *S. pneumoniae*- Intravenous or Intramuscular dosage:** Infants, Children, and Adolescents: Not recommended by guidelines. 150,000 to 300,000 units/kg/day IV or IM divided every 4 to 6 hours.
- **For the treatment of prosthetic valve endocarditis due to penicillin-susceptible Streptococcus sp- Intravenous or Intramuscular dosage:** Infants, Children, and Adolescents: 200,000 to 300,000 units/kg/day (Max: 24 million units/day) IV or IM divided every 4 hours for 6 weeks plus gentamicin for 2 weeks. The FDA-approved dose is 150,000 to 300,000 units/kg/day IV or IM divided every 4 to 6 hours.
- **For the treatment of prosthetic valve endocarditis due to relatively or fully penicillin-resistant Streptococcus sp- Intravenous or Intramuscular dosage:** Infants, Children, and Adolescents: 200,000 to 300,000 units/kg/day (Max: 24 million units/day) IV or IM divided every 4 hours for 6 weeks plus gentamicin. The FDA-approved dose is 150,000 to 300,000 units/kg/day IV or IM divided every 4 to 6 hours.
- **For the treatment of meningococcal meningitis- Intravenous or Intramuscular dosage:** Infants, Children, and Adolescents: 300,000 to 400,000 units/kg/day (Max: 24 million units/day) IV divided every 4 to 6 hours for 7 days. The FDA-approved dose is 250,000 units/kg/day (Max: 20 million units/day) IV or IM divided every 4 hours for 7 to 14 days.
- **For the adjunctive treatment of diphtheria and to prevent establishment of carrier state- Intravenous or Intramuscular dosage:** Infants, Children, and Adolescents: 100,000 to 250,000 units/kg/day (Max: 4 million units/day) IV or IM divided every 6 hours for 14 days as an adjunct to diphtheria antitoxin.
- **For the treatment of rat-bite fever or Haverhill fever- Intravenous or Intramuscular dosage:** Infants, Children, and Adolescents: 20,000 to 50,000 units/kg/day IV or IM divided every 6 hours for 5 to 7 days, followed by oral penicillin V for 7 days. For endocarditis, 150,000 to 250,000 units/kg/day (Max: 20 million units/day) IV or IM divided every 4 hours for at least 4 weeks.
- **For the treatment of congenital syphilis- Intravenous or Intramuscular dosage:** Infants and Children: 200,000 to 300,000 units/kg/day IV or IM divided every 4 to 6 hours for 10 days. FDA- labeling suggests a 10 to 14 day duration. Consider follow-up penicillin G benzathine after IV therapy. If more than 1 day of therapy is missed, the entire course should be restarted.
- **For the treatment of pneumonia, including community-acquired pneumonia (CAP)- Intravenous or Intramuscular dosage:** Infants, Children, and Adolescents: 150,000 to 300,000 units/kg/day IV or IM divided every 4 to 6 hours (Max: 24 million units/day).

8.2 DRUG-DRUG INTERACTION

- Concomitant use of high doses of parenteral penicillin G potassium with potassium-sparing diuretics (Amiloride, Hydrochlorothiazide, Spironolactone, Triamterene) can cause hyperkalemia[7].
- Avoid concomitant use of methotrexate with penicillins due to the risk of severe methotrexate-related adverse reactions. If concomitant use is unavoidable, closely monitor for adverse reactions[7].

- Prior or concomitant use of antibiotics with sodium picosulfate; magnesium oxide; anhydrous citric acid may reduce efficacy of the bowel preparation as conversion of sodium picosulfate to its active metabolite bis-(p-hydroxy-phenyl)-pyridyl-2-methane (BHPM) is mediated by colonic bacteria[7].
- Antibiotics which possess bacterial activity against salmonella typhi organisms may interfere with the immunological response to the live typhoid vaccine[7].
- Concomitant use of probenecid with benzyl penicillin may increase the plasma concentration[8].
- Benzylpenicillin can interact with aminoglycosides, leading to decreased effectiveness of both drugs[10].
- Benzylpenicillin can decrease the effectiveness of oral contraceptives, increasing the risk of unintended pregnancy[10].
- Benzylpenicillin can interact with warfarin, leading to an increased risk of bleeding[10].

8.3 CYP STUDIES

No data available.

8.4 REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Pregnancy Category B (US FDA)[8]

Human experience with penicillin G potassium during pregnancy has not shown any positive evidence of adverse effects on the fetus. Animal reproduction studies have also not revealed any evidence of impaired fertility or harmful fetal effects. However, there are no adequate and well-controlled studies in pregnant women showing conclusively that harmful effects of penicillins on the fetus can be excluded[7].

Because animal reproduction studies are not always predictive of human response, use penicillin G in pregnant women only if clearly needed. The Jarisch-Herxheimer reaction is an acute febrile reaction frequently accompanied by headache, myalgia, and other symptoms that usually occurs within the first 24 hours after any therapy for syphilis, most often among patients who have early syphilis. Antipyretics may be used, but they have not been proven to prevent this reaction. The Jarisch-Herxheimer reaction may induce early labor or cause fetal distress in pregnant women; this concern should not prevent or delay therapy[7].

Lactation: Penicillins are excreted in breast milk. Use caution when penicillin G is administered to a breast-feeding woman. Unless the infant is allergic to penicillins, breast-feeding is generally safe during maternal penicillin G therapy. Breast milk concentrations range from 0.015 to 0.37 mcg/mL with a milk: plasma ratio of 0.02 to 0.13. Penicillins may cause diarrhea, candidiasis, and skin rash in the breast-feeding infant. The infant should be observed for potential effects[7].

8.5 GENOTOXICITY AND CARCINOGENESIS

No information on long-term studies is available on the carcinogenesis, mutagenesis, or the impairment of fertility with the use of penicillins[13].

8.6 SENSITIZING POTENTIAL

Penicillin is a substance of low toxicity but does have a significant index of sensitization[13]. Benzyl penicillin may cause an allergic skin reaction, and allergy or asthma symptoms or breathing difficulties if inhaled[8,9].

The common side effects are allergic reactions rash, hives, itching, swelling, difficulty breathing), GI disturbances (diarrhea, nausea, vomiting)[10].

The less common/ rare side effects are neurological effects (confusion, seizures, encephalopathy), hematological effects (anemia, thrombocytopenia, leukopenia), superinfections (candidiasis), renal impairment, electrolyte imbalances, hypersensitivity reactions (fever, joint pain, eosinophilia), nephritis, thrombophlebitis, hemolytic anemia, pseudomembranous colitis, stevens-johnson syndrome, toxic epidermal necrolysis and jarisch-herzheimer reaction[10].

Overdosage of benzylpenicillin will cause neurological reactions like convulsions, neurotoxicity and nephrotoxicity[10,13]. Potentially fatal events are Anaphylaxis, pseudomembranous colitis[8].

The use of benzylpenicillin can lead to overgrowth of non-susceptible organisms, such as fungi, which can cause secondary infections[10]. Prolonged use of benzylpenicillin can lead to the development of resistant strains of bacteria, which can make the medication ess effective in the long run[10].

Cardiac arrhythmias and cardiac arrest may also occur. (High dosage of penicillin G sodium may result in congestive heart failure due to high sodium intake)[13].

9. PERMITTED DAILY EXPOSURE (PDE) CALCULATION

9.1 METHOD OF PERMITTED DAILY EXPOSURE (PDE) CALCULATION

PDE is calculated based on EMA guidance. A “parenteral” PDE is calculated that applies to intravenous, intramuscular, subcutaneous, or percutaneous routes of exposure as appropriate.

The determination of health-based exposure limits for a residual active substance is based on the method for establishing the so-called Permitted Daily Exposure (PDE) as described in Appendix 3 of ICH Q3C (R4) “Impurities: Guideline for Residual Solvents” and Appendix 3 of VICH GL 18 on “residual solvents in new veterinary medicinal products, active substances and excipients (Revision)”. The PDE represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime.

Determination of a PDE involves (i) hazard identification by reviewing all relevant data, (ii) identification of “critical effects”, (iii) determination of the no-observed-adverse-effect level (NOAEL) of the findings that are considered critical effects, and (iv) use of several adjustment factors to account for various uncertainties.

Appendices 3 of the ICH Q3C[3] and VICH GL 18 guidelines[4] present the following equation for the derivation of the PDE (as per EMA):

$$\mathrm{PDE} = \frac{[\mathrm{NOAEL/LOAEL\ (mg/kg/day)\ X\ Bioavailability\ Adjustment\ (\alpha)\ X\ BW\ (kg)}]}{(\mathrm{F1\ X\ F2\ X\ F3\ X\ F4\ X\ F5})}$$

Where,

PDE	=	Permitted Daily Exposure (mg/day)
NOAEL/ LOAEL	=	No-Observed-Adverse-Effect-Level / Lowest-Observed-Adverse-Effect-Level (mg/kg/day)
BW	=	Body weight (kg)
F_1	=	A factor (values between 2 and 12) to account for extrapolation between species[3]
F_2	=	A factor of 10 to account for variability between individuals[3]
F_3	=	A factor (values between 1 and 10) to account for the variability in toxicity studies duration[3].
F_4	=	A factor (values between 1 and 10) that may be applied in cases of severe toxicity, e.g., non-genotoxic carcinogenicity, neurotoxicity or teratogenicity[3]
F_5	=	A variable factor that may be applied if the NOAEL was not established. When only LOAEL is available, a factor (values between 1 and 10) could be used depending on the severity of the toxicity[3].

9.2 PARENTERAL ROUTE

Parenteral (intramuscular, subcutaneous, and intravenous) PDE equation based on EMA Guideline.

$$\text{PDE} = \frac{[\text{NOAEL/LOAEL (mg/kg/day) X Bioavailability Adjustment } (\alpha) \text{ X BW (kg)}]}{[(\text{F1 X F2 X F3 X F4 X F5}) \text{ Total Safety Factors}]}$$

For Adult – 50Kg Body weight

$$\text{PDE} = \frac{[250\text{mg/kg/day (NOAEL) X 1 } (\alpha) \text{ X 50kg (BW)}]}{[(4800) \text{ Total safety factors}]}$$

Parenteral PDE for adult is 2.604mg/day.

For Paediatrics – 10Kg Body weight

$$\text{PDE} = \frac{[250\text{mg/kg/day (NOAEL) X 1 } (\alpha) \text{ X 10kg (BW)}]}{[(4800) \text{ Total safety factors}]}$$

Parenteral PDE for paediatric is 0.521mg/day.

Where,

Parameter	Value	Justification
NOAEL	250mg/kg/day	Established using 13-week repeated dose toxicity study in mice.
α	1	Bioavailability is 100%. α = Bioavailability/100
BW	50/10kg	Body weight in adult/paediatric
F_1	12	To account for extrapolation from mice to humans[3]
F_2	10	Based on human variability and drug precautions[3]
F_3	7	NOAEL established using 13-week repeated dose toxicity in mice[3].
F_4	5	Based on No genotoxicity, no carcinogenicity, no teratogenicity; and Human pregnancy category is 'B' (US FDA).
F_5	1	NOAEL is identified

10. CONCLUSION

PDE – Adult	2.604mg/day
PDE –Paediatric	0.521mg/day

The PDE value refers to the amount of Benzylpenicillin which is permitted as a cross contaminant in other drug products when multiple drugs are being manufactured in the shared facility.

11. REFERENCES

The data in the document were accessed from the below given references on 30th October 2023 .

1. ISPE (2010) – Risk-Based Manufacture of Pharmaceutical Products: A Guide to Managing Risks Associated with Cross-Contamination (Risk MaPP).
2. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/11/WC500177735.pdf
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11. https://www.biorxiv.org/content/10.1101/191346v2.full.pdf
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12. LIST OF ABBREVIATIONS AND SYMBOLS

Abbreviation / Symbols	
%	percentage
µ	micro
&	and
ml/mL	millilitre
mg	Milligram
L	Litre
Kg	Kilogram
g	Gram
ng	Nanogram
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area Under the Curve
BW	Body weight
CAS No.	Chemical Abstracts Service number
PO	Orally
GLP	Good Laboratory Practice
BPHCT	Benzyl penicillin G heated cooking temperature
HAFP	Heat-treated animal food products
PBS	Phosphate buffered saline

Abbreviation / Symbols	
hr/h	hour
ICH	International Conference on Harmonization
EMA	European Medicines Agency
FDA	Food and Drug Administration
ISPE	International Society for Pharmaceutical Engineering
IUPAC	International Union of Pure and Applied Chemistry
LOEL	Lowest Observed Effect Level
LD_{50}	Dose that results in 50% mortality
LOAEL	Lowest Observed Adverse Effect Level
MF	Modifying factor
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
ADE	Acceptable Daily Exposure
PDE	Permitted Daily Exposure
UF	Uncertainty Factor
PK	Pharmacokinetics
Risk MaPP	Risk-Based Manufacture of Pharmaceutical Products
VICH	Veterinary International Conference on Harmonization