Module 4

Considerations for Parenteral Products

ICH Q3D Elemental Impurities

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Q3D: Large Volume Parenteral Section

Parenteral drug products with maximum daily volumes up to 2 liters may use the maximum daily volume to calculate permissible concentrations from PDEs. For products whose daily volumes, as specified by labeling and/or established by clinical practice, may exceed 2 liters (e.g., saline, dextrose, total parenteral nutrition, solutions for irrigation), a 2-liter volume may be used to calculate permissible concentrations from PDEs. (*Reference 4*)

4) Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. Pediatrics 1957;19:823-32.

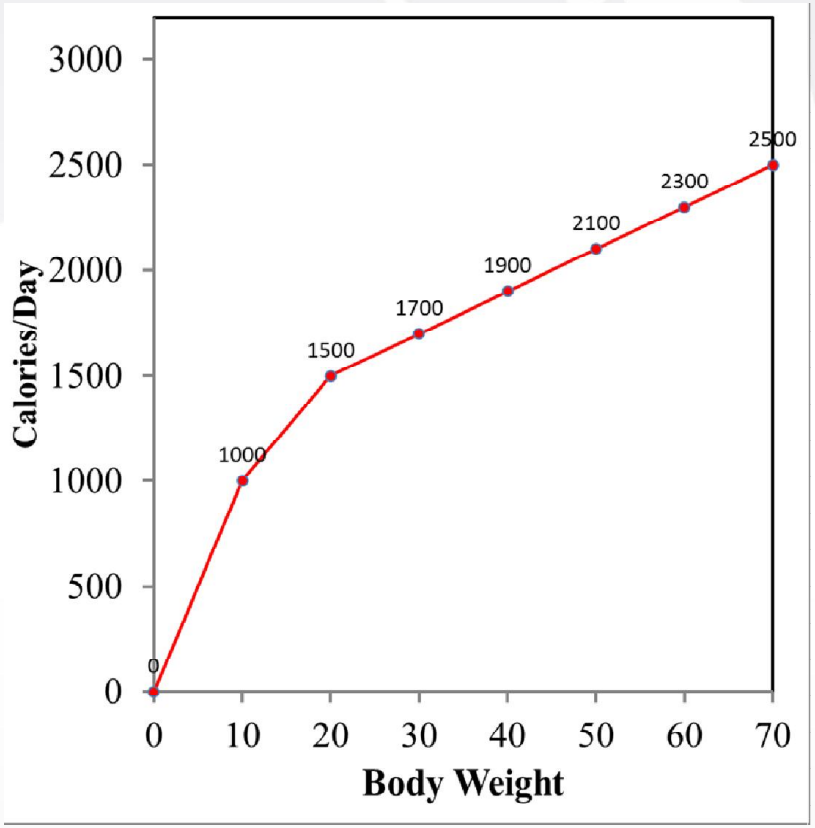
Maintenance Fluid Replacement

- In 1957, Holliday and Segar proposed a method for determining the average daily fluid replacement need for hospitalized patients. (Holliday, Segar [1957], ref. 1)
  - Summary, based on patient body weight
    - First 10 kg body weight: 100 ml/kg/day
    - Second 10 kg body weight: 50 ml/kg/day
    - Thereafter: 20 ml/kg/day
- This method is still considered the standard of care.
  - "The Holliday-Segar equation remains the standard method for calculating maintenance fluid requirements." (Meyers, [2009], ref. 2)

1. Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. Pediatrics 1957;19:823-32.
2. Meyers, RS. Pediatric Fluid and Electrolyte Therapy, Journal of Pediatric Pharmacology Therapeutics 2009;14:204-11

Holliday-Segar nomogram

- Summary: 1 ml of replacement fluid is required for every 1 Calorie expended. Caloric expenditure is correlated with body weight.
- A 50 kg patient requires about 2000 ml of fluid per day parenterally.
- Q3D established 2 liters as the reference volume for determining elemental impurity levels in parenteral products that may be delivered in large volume.
  - Q3D PDEs are based on 50 kg body weight
- On the basis of body weight, the Holliday-Segar nomogram confers an additional safety factor when volumes exceeding 2 liters are delivered to patients whose body weight exceeds 50 kg.



Example 1: 10% Dextrose Injection, USP

- **Product information**
  - Supplied in 1L PVC bags
  - Dose1: daily dose set at 2L
  - USP water for injection is used to produce the drug product
- **Risk assessment approach**
  - Risk assessment conducted using the drug product approach
    - During a review of the components of the drug product no potential elemental impurities were identified as likely to be present
    - Manufacturer conducted testing on samples from 3 representative commercial batches of the drug product to support the risk assessment (testing included class 1, 2A and 3 elements)
  - Leachable studies demonstrate that there are no significant elemental impurity contributions from the container closure system over the shelf life of the product.

1. Package Insert Dosage: "As directed by a physician. Dosage is dependent upon the age, weight and clinical condition of the patient."

Example 1: 10% Dextrose Injection, USP

Lot number	As, µg/L	Cd, µg/L	Hg, µg/L	Pb, µg/L
20xx001	<0.50	<0.10	<0.25	<0.10
20xx002	<0.50	<0.10	<0.25	<0.10
20xx003	<0.50	<0.10	<0.25	<0.10
	As, µg	Cd, µg	Hg, µg	Pb, µg
Total daily level[1]	<1.0	<0.20	<0.50	<0.20
PDE	15 µg/day	2 µg/day	3 µg/day	5 µg/day
Control threshold	4.5 µg/day	0.6 µg/day	0.9 µg/day	1.5 µg/day

Lot number	Co, µg/L	V, µg/L	Ni, µg/L	Li, µg/L	Sb, µg/L	Ba, µg/L	Mo, µg/L	Cu, µg/L	Sn, µg/L	Cr, µg/L
20xx001	<0.20	<0.40	<2.0	<10.0	<2.0	<1.0	<10.0	<2.0	<3.0	<10.0
20xx002	<0.20	<0.40	<2.0	<10.0	<2.0	<1.0	<10.0	<2.0	<3.0	<10.0
20xx003	<0.20	<0.40	<2.0	<10.0	<2.0	<1.0	<10.0	<2.0	<3.0	<10.0
	Co, µg	V, µg	Ni, µg	Li, µg	Sb, µg	Ba, µg	Mo, µg	Cu, µg	Sn, µg	Cr, µg
Total daily level[1]	<0.40	<0.80	<4.0	<20.0	<4.0	<2.0	<20.0	<2.0	<6.0	<20.0
PDE	5 µg/day	10 µg/day	20 µg/day	250 µg/day	90 µg/day	700 µg/day	1500 µg/day	300 µg/day	600 µg/day	1100 µg/day
Control threshold	1.5 µg/day	3 µg/day	6 µg/day	75 µg/day	27 µg/day	210 µg/day	450 µg/day	90 µg/day	180 µg/day	330 µg/day

[1] (2L x observed level)

Example 1: 10% Dextrose Injection, USP

- **Conclusions**
  - All values for the potential elemental impurities of concern were observed to be less than the detection limit.
  - For each element, the limit of quantitation is less than the control threshold.

Example 2: 0.45% Sodium Chloride Injection, USP

- **Product information**
  - Supplied in 1L PVC bags
  - Dose1: daily dose set at 2L
  - USP water for injection is used to produce the drug product
- **Risk assessment approach – component approach**
  - An assessment of the water for injection revealed that the only potential elemental impurities to be considered were As, Cd, Hg, and Pb.
  - Literature revealed mean results for three grades of salt using validated methods (http://eusalt.com/salt-quality, As, Cd, Hg, Pb testing in salt)
  - Manufacturing equipment does not contribute elemental impurities due to mild conditions employed in the manufacture of the drug product
  - Leachable studies demonstrate that there are no significant elemental impurity contributions from the container closure system
  - Monitoring of the WFI quality demonstrates that there are no significant elemental impurity contributions.

[1] Package Insert Dosage: "As directed by a physician. Dosage is dependent upon the age, weight and clinical condition of the patient."

Example 2: 0.45% Sodium Chloride Injection, USP

	As, conc.	Cd, conc.	Hg, conc.	Pb, conc.
Maximum level in NaCl*	0.024 µg/g	0.011 µg/g	0.00062 µg/g	0.0808, µg/g
Water for injection	<0.50 µg/L	<0.10 µg/L	<0.25 µg/L	<0.10 µg/L
Impurity level per liter of drug product	<0.5108	<0.1495	<0.25279	<0.464
	As, µg	Cd, µg	Hg, µg	Pb, µg
Total µg/day (based on total 2L/day)	**<1.0216 µg**	**<0.299 µg**	**<0.50558 µg**	**<0.928 µg**
PDE	15 µg/day	2 µg/day	3 µg/day	5 µg/day
Control threshold	4.5 µg/day	0.6 µg/day	0.9 µg/day	1.5 µg/day

* NaCl data reported represent the maximum levels reported in the literature (see references)

Conclusions:

- **All potential elemental impurity levels are lower than the control threshold for each elemental impurity**

References

- **European Committee for the Study of Salt, ECSS/CN 287-1982, Statistical Study of Inter-Laboratory Analysis of Sodium Chloride (As, Cd, Hg, Pb)**
  - As: EuSalt/AS 011-2005
  - Hg: EuSalt/AS 012-2005
  - Pb: EuSalt/AS 013-2005
  - Cd: EuSalt/AS 014-2005