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Determination of "F" Value for Solithromycin Capsules, 200 mg, Designing and Testing of Product Package for Child-Resistant and Senior-Friendly Requirements

Lovy Pradeep and David Pereira

Cempra, Inc., 6320 Quadrangle Drive, Suite 360, Chapel Hill, NC 27517, USA

2016 AAPS ANNUAL MEETING AND EXPOSITION
NOVEMBER 13–17, 2016
COLORADO CONVENTION CENTER, DENVER
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PURPOSE

Solithromycin is a fluoroketolide currently under FDA review for the treatment of Community-acquired Bacterial Pneumonia (CABP). These studies were carried out in preparation for market launch in order to (a) determine the "F" value of solithromycin capsules, (b) design product packaging based on the determined "F" value, and (c) evaluate the product package for child-resistant and senior-friendly requirements.

METHODS

The packaging for solithromycin capsules, 200 mg was designed per the packaging standards in 16 CFR § 1700.15 and subsequently tested per 16 CFR § 1700.20 to demonstrate that it is child-resistant while being senior-friendly.

The **Failure** ("F" value) for solid oral drugs in unit dose packaging is defined as the number of individual dose units (the 'harmful dose') that can cause serious illness or injury in a 25 lb. (11.4 kg) child. A 25 lb. child is a 2-year old (1.5 to 2.5 years) in the 50^{th} percentile based on the CDC growth chart. "F" value is used to guide the design of the product packaging; however, there is little or no guidance available on how to arrive at the 'harmful dose' for a child for purposes of "F" value determination.

The harmful dose is the lowest dose that may cause toxicity, but is rarely known in practice. Maximum Tolerated Dose (MTD) in adults, i.e., the largest dose a patient can tolerate, is generally used as a basis to determine "F" value but is often not available; instead, what is usually available is the Maximum Tested Dose. In addition, "F" value determination is rendered complex by the lack of known toxic drug concentrations based on animal and/or clinical experience in adults.

In the absence of pediatric data for solithromycin, a risk assessment for "F" value determination was carried out by evaluating acute and chronic animal toxicology data and adult clinical dose response data scaled to children.

50 children between the ages of 42 to 51 months, distributed between three age groups (42-44 months, 30%; 45-48 months, 40%; 49-51 months, 30%; 50% male and 50% female), were tested according to the Consumer Product Safety Commission's protocol (16 CFR § 1700.20). The children were tested in pairs and faced the tester with no visual barrier between them.

Removal of 4 (or more) placebo capsules from the package would constitute a failure. For a package to meet effectiveness criteria of 16 CFR § 1700.20, at least 94% of the children must be unable to open the package in the 1^{st} five-minute test period (before demonstration), and at least 90% of the children must be unable to open the package by the end of the 2^{nd} five-minute test period (accumulative) in a 50-child sequential testing. An opening demonstration was performed after the 1^{st} five-minute test period if either of the pair of children had not opened his or her package, following which each child was allowed to open his/her package for a 2^{nd} five-minute test period.

100 senior adults between the ages of 50 to 70 years, distributed into three age groups (50-54 years, 25%; 55-59 years, 25%; 60-70 years, 50%; 70% female and 30% male), were tested according to the Consumer Product Safety Commission's protocol (16 CFR § 1700.20).

Any adult unable to remove one placebo capsule from the package either within the 1^{st} five minutes and/or in the 2^{nd} test period (one minute) would count as a failure. For a package to meet effectiveness criteria of 16 CFR § 1700.20, at least 90% of the adults must be able to remove one placebo capsule from the package in the 1^{st} five-minute test period and in the 2^{nd} one-minute test period.

RESULTS

(A) Determination of "F" Value:

Studies that identify serious toxic effects and/or those derived from inadvertent overdosage of toddlers are relevant to "F" value calculations. Although adverse event data from clinical trials and results from pre-clinical toxicity studies (in species believed to be relevant to humans, for identifying potential adverse effects from overdosage) are useful and relevant, they are associated with uncertainties because (i) they may involve repeated rather than single dosing and (ii) they may require extrapolation from results in animals to results in humans.

Of the several repeat-dose studies conducted by oral and intravenous routes of solithromycin administration, treatment of Cynomolgus monkeys with 250 mg/kg/day solithromycin was selected for "F" value calculation. This is because an adverse effect relevant to human exposure (i.e., increase in serum liver enzymes) was observed after seven days of treatment. The "F" value was calculated as follows:

Study	Adverse Effect	Subject	Dose mg/kg	Dose mg/11.4kg child	"F" value (200 mg capsule)
Bridge Labs, 2008[a]	Elevation in serum liver enzymes	Cynomolgus monkeys	250 mg/kg/day for 7 days *(HED = 80.6 mg/kg/day)	919	4

* Dosage in Cynomolgus monkeys converted to Human Equivalent Dose (HED) by dividing by 3.1. (FDA, 2005)

An "F' value of 4 was determined for solithromycin capsules, 200 mg. This means that during child-resistant testing, per 16 CFR § 1700.20, if a child were to open four blisters containing solithromycin capsules of the 200 mg strength, the package would be deemed a failure and would require re-designing.

(B) Designing the Product Package:

A trade pack comprising 12 capsules was designed as a 12-count blister foil unit (BFU) inside a carton, for a 5-day CABP therapy with an 800 mg loading dose on Day 1 and 400 mg maintenance dose on Days 2-5. Every individual blister in the BFU has one 200 mg capsule with paper-backed lidding foil. Blisters are separated by perforations enabled by a unique peel-push feature to meet the "F" value of 4.

(C) Testing of the Product Package for Child-Resistance:

No children (0%) successfully gained entry to 4 or more capsules during the 1^{st} five-minute test period. Four children (8%) successfully gained entry to 4 or more capsules during the 2^{nd} five-minute test period in a mean time of 8 minutes and 42 seconds. Thus, four children (8%) successfully gained entry to 4 or more capsules during the ten-minute sequential testing, thereby demonstrating that the designed package met the criteria per 16 CFR § 1700.20.

(D) Testing of the Product Package for Senior-Friendliness:

99 adults successfully gained entry to one placebo capsule during the 1^{st} five-minute and during the 2^{nd} one-minute test periods, thereby demonstrating that the designed package met the criteria per 16 CFR § 1700.20.

CONCLUSION

In the absence of pediatric data, the "F" value for solithromycin capsules, 200 mg was determined by applying a weight-of-evidence approach. An "F" value of 4 was used to design the product package. The package was subsequently tested and determined to be child-resistant and senior-friendly, thereby meeting the effectiveness criteria per 16 CFR § 1700.20.

ACKNOWLEDGMENTS and REFERENCES

Acknowledgments: Lachman Consultant Services, Inc. ("F" value determination), Sharp Packaging Solutions (designing the package based on the "F" value), and CRR Inc. (child-resistance and senior-friendliness testing per 16 CFR § 1700.20.)

Reference: a. Bridge Laboratories, 2008. CEM-101: An oral (gavage) MTD and DRF toxicity study in Cynomolgus monkeys. Bridge Study Number: 1715-07145, March 25, 2008.