

for the reason of vial capping. At the time of package development, an aluminum/plastic cap has been chosen where the inner height of the skirt of the cap is capable of gripping the flange height of the stopper plus the height of the vial neck collar, and at the same time being well folded under the collar of the vial. If stopper flange thickness would be excessively high, crimping the cap under the collar could become difficult, while with too low flange thickness there could be an excess of folded aluminum which results in a cosmetically imperfect crimp, while in both cases, worst case, bad container/closure integrity (CCI) results.

### Flange markings

The functionality of flange markings (see Fig. 2) for all elastomeric closures can be described in terms of prevention of stopper clumping during storage, steam sterilization, and machining. This functionality is also valid for lyophilization closures; however, there is an additional functionality that is related to the final stoppering of the vials inside the lyophilization chamber at the end of the freeze-drying cycle. As explained above, the stoppers are pressed down by the shelf that is located above them. During this stage, a significant pressure is exerted on the stopper at the time it hits the vial neck. The pressure is transferred to the stopper flange that is in contact with the underside of the shelf, in other words, the stoppers are firmly pressed with the top of their flanges against a stainless steel plate that for reasons of good cleanability has only a low degree of surface roughness. These conditions are ideal to make the stoppers stick to the underside of the shelf. After pressing the stoppers down, the shelves are separated again. At this stage, it is absolutely undesired that the stoppers keep sticking to the shelf. If they do, then the shelf may pull the stopper slightly out of its seated position and thereby impair the integrity of the seal that at that time and until capping is between the plug of the stopper and the inner diameter of the vial neck. If the stopper is firmly stuck to the shelf and at the same time makes a good fit with the vial, then it may also come to the situation that the entire vial at first is lifted, and then, under the influence of gravity, falls down



**Fig. 2** Lyo stoppers with one, two, and three vent openings, and with different flange markings