drug concentration–time profiles derived from dermal OFM sampling [62]. Applying this known correlation of skin permeability and skin impedance data and preselect donors based on impedance data of the skin may offer the possibility to select donors with homogeneous permeation skin characteristics. Working with study populations that have homogeneous skin penetration characteristics can greatly improve the statistical outcome of any dermal study.

57.4.3.3 Reference-Scaled Average BE Statistical Approach

Because skin is highly variable, a fairly high number of study participants is still required when performing dermal PK measurements for BE evaluation of topical drug products [66, 67]. Such high participant numbers can be reduced by applying the reference-scaled average BE (SABE) statistical approach instead of the commonly applied average BE (ABE) statistical approach on dermal PK data. SABE scales the BE acceptance limits to the intra-subject variabilities of the reference product [68], and its use is recommended for reference products with an intra-subject standard deviation of more than 0.294.

Results from the clinical dermal OFM study on acyclovir [49] indicated that the variabilities of the dermal PK data for acyclovir can meet these criteria and that application of SABE may be appropriate. We further compared results from SABE and ABE and a power calculation revealed that SABE achieved a statistical power of at least 80% with a sample reduction of about 40% in the clinical study (unpublished data).

We additionally performed an ex vivo study using an identical study design as in [49], and assessed the PK profiles of the same acyclovir products as in the clinical study. This allows for the first time a direct comparison of dermal PK data obtained from a clinical study and an ex vivo study. BE evaluations applying SABE yielded similar results in the ex vivo and in the clinical study (unpublished data). Ex vivo data can thus provide preliminary PK parameters for subsequent clinical studies, and they might serve as test systems for clinical BE studies to compare the penetration behavior of topical drug products. Thus, results indicated that dermal OFM studies in combination with SABE are highly promising tools for BE evaluations of topical drug products.

57.5 OUTLOOK

57.5.1 Basic Research

For future basic research, dermal OFM studies can be used as valuable tools to investigate the skin microenvironment, allow assessment of skin pathology, and promote a mechanistic understanding of dermal drug action in various skin diseases.

57.5.1.1 Immune Cells

The active immune system of patients with commonly occurring chronic inflammatory skin diseases such as psoriasis or atopic dermatitis can be investigated by sampling immune competent cells from lesional skin and from healthy unaffected skin close to the lesions of psoriasis patients. Preliminary results from dermal OFM sampling experiments revealed that the immune cell populations between the different skin regions are notably different. This finding can foster further research efforts and might open doors to pursue novel, innovative approaches in drug target investigations.

57.5.1.2 Biomarker in Skin Cancer

Dermal OFM sampling can also be promising for biomarker research in skin cancer by monitoring interactions between cancer microenvironment in the skin and circulating cancer cells, microvesicles, and other compounds in the blood.

57.5.1.3 Protein Binding

The effect of a drug on numerous aspects of clinical PK/PD in the skin is, among other factors, influenced by the ratio between bound and unbound drug fraction at the site of action, which determines